Nektar Therapeutics Spotlight: Watch for NKTR-214 Results This Weekend at Society for Immunotherapy of Cancer Annual Meeting

Summary:

- NKTR-214 is a PEGylated version of IL-2 designed to selectively activate tumoricidal T cells and NK cells instead of suppressive regulatory T cells
- NKTR-214 appears most effective in combination with other immuno-oncology drugs and is being studied in clinical trials with PD-1 inhibitors
- Nektar is giving an oral presentation of updated PIVOT-02 trial results for NKTR-214 at the Society for Immunotherapy of Cancer (SITC) Meeting on November 11th

Investment Thesis:

There are a lot of exciting events happening now and throughout next year for Nektar Therapeutics (NKTR). For example, NKTR will be providing an update on its Phase 1/2b trial with its lead immuno-oncology asset, NKTR-214, this weekend. Investors were looking forward to data that was revealed this past June at ASCO, but due to the small patient numbers observed at early timepoints of treatment, the data were not strongly suggestive and the market was not very responsive. The update this Saturday at SITC could be a catalyst for NKTR's stock price if the data convincingly show that NKTR-214 is effective based on preliminary overall response rate (ORR) results, even though they are from the early stages of a Phase 1b/2 trial.

Company Overview:

Nektar Therapeutics (NASDAQ: NKTR) is a research, clinical, and commercial-stage biopharmaceutical company with many drugs in its pipeline. In the US, NKTR has partnered with AstraZeneca to sell Movantik to treat opioid-induced constipation in adults with chronic, non-cancer pain and Shire (formerly Baxalta) to sell Adynovate, a treatment for hemophilia A. For its Phase 3 assets, it has partnered with Bayer (NASDAQ: BAYN) for non-cystic fibrosis bronchiectasis treatment and Halozyme (NASDAQ: HALO) for pancreatic cancer. When looking at its wholly owned products, NKTR has a drug candidate for the treatment of moderate to severe chronic lower back pain (NKTR-181) that has drawn much attention because it is much less addictive than traditional opioids due to its slow release into the central nervous system. However, NKTR also has earlier-stage and pre-clinical immuno-modulating drugs such as NKTR-358, which it is developing through a strategic collaboration with Eli Lilly (NYSE: LLY). In the immuno-oncology setting, which is its core area of focus, NKTR has developed an exciting set of drug candidates led by NKTR-214, which we will highlight in this article.

Pipeline Highlight: NKTR-214

Background

NKTR-214 is a PEGylated version of IL-2 that selectively activates cytotoxic CD8+ T cells and natural killer (NK) cells compared to regulatory T cells (T_{regs}). Normally, the IL-

2 receptor is found in both a heterodimeric form consisting of the β (CD122) and γ (CD132) chains (IL2Rβγ) and a higher affinity heterotrimeric form made by the addition of α chain CD25 (IL2Rαβγ). The IL2Rαβγ complex is predominantly found on regulatory T cells (T_{regs}), a suppressive subset of immune cells that constitutively express CD25 and is implicated in the inhibition of anti-tumor responses. In contrast, the IL2Rβγ complex is predominantly expressed on unactivated cytotoxic CD8+ T cells, which become a key component of tumor infiltrating lymphocytes (TILs).

By adding six PEG chains to the region of IL-2 that binds to CD25, the IL-2 becomes inactive until four chains are slowly released at physiological pH. Once four chains are released, the PEGylated IL-2 is biased towards binding to CD122 and thus favors the IL2Rβγ complex. This feature extends the half-life of the cytokine to be more comparable to an antibody for sustained action over long periods instead of a very strong initial response that fades rapidly, which is a property of free, unaltered IL-2. Although the peak potency of NKTR-214 is weaker than free, unaltered IL-2, it has been effective in various mouse models as a monotherapy for bladder, liver and pancreatic cancer. In the initial publication that showed efficacy as a monotherapy in melanoma, NKTR-214 has also been shown to act synergistically with anti-CTLA-4 antibody treatment in mouse models of breast and colon cancer, providing better tumor reduction and maintenance of tumor-free mice than anti-CTLA-4 antibody in combination with free IL-2. This study also showed that hypotension and severe vascular leak were not observed with NKTR-214 at the maximum tolerated dose in non-human primates, side effects that have been a large hindrance to the use of free IL-2 in the clinic despite its efficacy as a monotherapy.

Current Trials
NKTR has various plans for NKTR-214, including an unpartnered Phase 1 trial with TECENTRIQ (atezolizumab) or KEYTRUDA (pembrolizumab) and in combination with its own TLR agonist (NKTR-262, a pre-clinical asset) in a first human trial scheduled to start early next year. However, the trials that are the furthest along are the Phase 1 monotherapy trial (EXCEL) and the Phase 1/2b PIVOT-02 trial using NKTR-214 in combination with the anti-PD-1 inhibitor nivolumab (Opdivo). The PIVOT trials are being conducted in partnership with Bristol-Myers Squibb (NYSE: BMY), which owns Opdivo. NKTR splits the costs equally for the trials while maintaining global commercial rights to NKTR-214.

AT SITC 2016, NKTR showed very preliminary data from the Phase 1 EXCEL trial demonstrating that NKTR-214 showed no signs of autoimmune adverse events or organ inflammation in a mixed population of 25 patients with melanoma, renal cell carcinoma (RCC), non-small cell lung carcinoma (NSCLC), bladder cancer, and triple negative breast cancer (TNBC). Grade 3 hypotension was observed in three patients, but it was rapidly reversed and the patients were able to continue treatment with NKTR-214. There were also no patients that experienced capillary leak syndrome.

These data were expanded upon at ASCO 2017, where NKTR presented more detailed data from 28 patients, with the largest number of patients in the melanoma (7) and RCC

(15) groups. These patients received NKTR-214 as a monotherapy, and for most, they had previously received some form of chemotherapy or immuno-oncology treatment. From this study, NKTR-214 treatment also showed no capillary leak syndrome and easily managed Grade 3 hypotension in 4 patients. The treatment in general had a favorable safety profile with only one patient discontinuing due to an infusion-related reaction, which the patient had a history of with other treatments. Among RCC patients, 4 that had not received prior immunotherapy and showed stable disease continued with sequential treatment with nivolumab. Upon the first scan available post-administration of nivolumab, there was a rapid change indicating partial response in 3 of 4 patients, with one patient having an unconfirmed PR that was later designated as stable disease at the next scan. These data could suggest that NKTR-214 helps prime the immune system for a response with other immuno-oncology therapies.

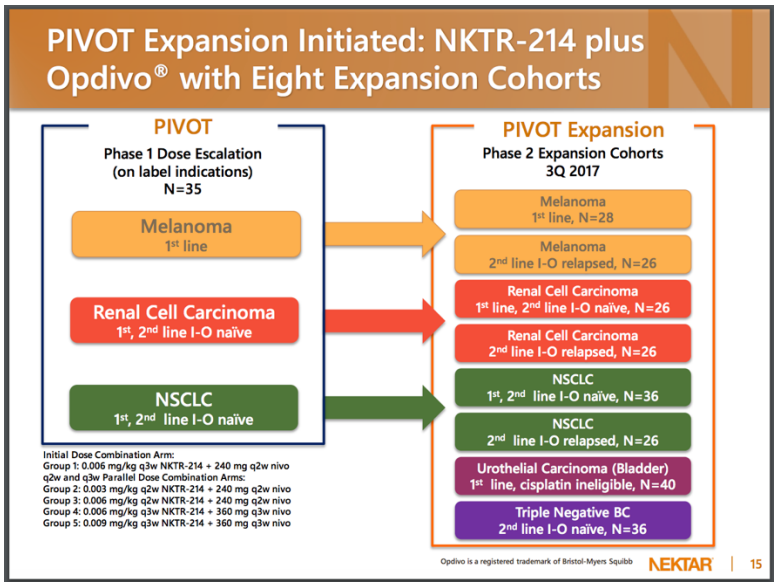

Figure 1. PIVOT Trial Designs for NKTR-214

NKTR also discussed preliminary data for the dose-escalation portion of the PIVOT trial via an investor presentation. For these data, NKTR showed 5 melanoma stage IV patients receiving NKTR-214 as a first-line therapy. 3/5 (all BRAF mutant positive) had at least a partial response (tumor reduction of at least 30% from baseline), and one patient has been tumor-free since week 5 of treatment at 22 weeks out. One patient (BRAF+) showed stable disease, and the other (BRAF-WT) was discontinued due to tumor progression. The one BRAF+ patient that did not show a response was only at week 5, and at a later timepoint it is possible that tumor would start shrinking as well (Figure 2).

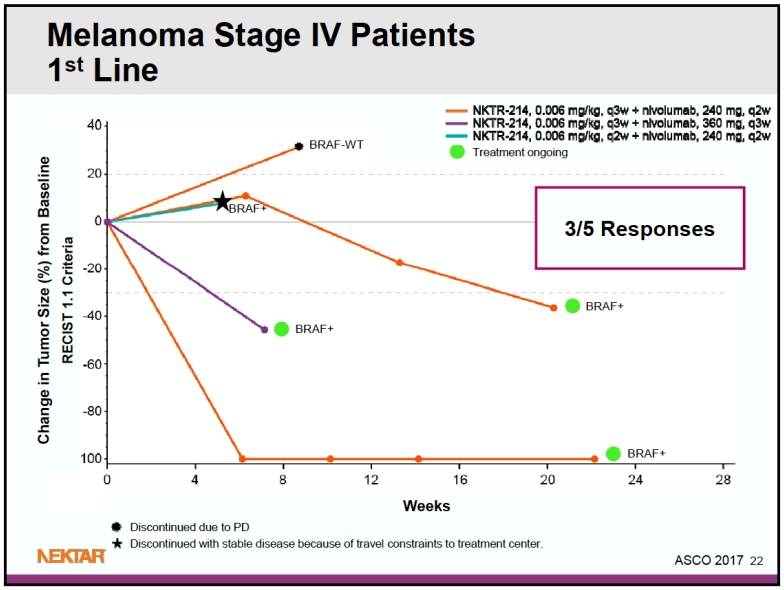

Figure 2. First-Line Treatment of Melanoma Patients with NKTR-214 (Slide 22)

There were also 6 RCC patients in early stages of treatment for the escalation portion of the PIVOT trial (4/6 were at week 7, one was at week 8, and the other was at week 15). The one patient at week 15 had a 38% tumor reduction, suggesting that for the other patients, we will need to wait until later timepoints to assess efficacy.

Based on these data, NKTR announced that they are moving into the expansion cohort phase of the PIVOT trials, where patients will simultaneously receive NKTR-214 and nivolumab. Primary outcomes will be safety, tolerability and overall response rate, with secondary outcomes including progression-free survival, overall survival, duration of response, and other factors. Dosing will be determined based on the results of the first part of PIVOT. Estimated completion of this study is October 2018.

Upcoming Data: What to Expect

Based on the press release by NKTR for its upcoming SITC oral presentation, published abstracts, and the scheduled investor call on Saturday, November 11th, investors are looking forward to more dose-escalation cohort PIVOT data in terms of more indications (NSCLC for the first time), later timepoints, and larger patient cohorts (all 38 patients). Potentially extended timepoint data for the NKTR-214 monotherapy treatments are also expected. The ultimate hope for nivolumab combination therapy with NKTR-214 is that the two treatments are at least additive if not synergistic in increasing overall response rates (ORRs) in various indications. Furthermore, investors will want to see that the safety profile of NKTR-214 continues to be favorable when administered as a combination therapy.

To understand what the expectations might be for the different tumor types and indications with NKTR-214 and nivolumab combo data thus far in the published SITC abstract (which was written based on a July 25, 2017 data cutoff), we have compiled

information about ORRs with current treatments. ORR in melanoma patients treated with nivolumab is usually around 28-41% (214-nivo combo 62.5%), while RCC patients have slightly lower ORR at 25% (214-nivo combo 50%) and NSCLC patients have a 20% ORR (214-nivo combo - no data) based on the CheckMate 017 and CheckMate 057 studies. For TNBC patients, recent data from ESMO 2017 show that ORR is 22-24% (214-nivo combo - no data) with nivolumab. Also, as discussed in a review of various indications, high-dose IL-2 treatment has had success in treating cancer even as a monotherapy, with 15% ORR in RCC patients and 13-16% in melanoma patients. For NSCLC patients, ORR was in the 14-16% range for IL-2 in combination with chemotherapies.

When considered together, people hope that the ORR for NKTR-214 + nivolumab will at least be additive, if not synergistic. Based on a 2005 study looking at 36 metastatic melanoma patients given a fixed dose of IL-2 and varying doses of anti-CTLA-4 antibody (MDX-010) based on weight, there was a 22% ORR for potential IL-2 + immune checkpoint blockade therapy. This result suggests that there is only an additive effect of the combined therapies, since other studies cited in the article have shown a 12.5% ORR for metastatic melanoma patients treated with anti-CTLA-4 and a 15% ORR for those treated with IL-2 monotherapy. However, this is done with free IL-2 that has the ability to also activate T_{regs}, and previous mouse studies show that NKTR-214 is more effective than free IL-2 in treatment. Furthermore, in the ongoing PIVOT study, NKTR-214 at the chosen dose for the expansion stage appears to be as well tolerated as nivolumab alone, which is a fundamentally better safety profile than unaltered, free IL-2.

Competitive Considerations
NKTR-214 is ahead of any competitive compounds with a similar mechanism of action of which we are aware. The most similar drug candidate that we are aware of is ALKS 4230, which selectively targets the same IL-2 receptors as NKTR-214 using a different mechanism. ALKS 4230 monotherapy is in a dose-escalation study currently in advanced solid tumor patients with 24 enrolled patients with data from the dose escalation cohort to be presented in 2018. However, as indicated herein, compounds like NKTR-214 and ALKS 4230 appear to be most effective as combination therapies, and we are not aware of any combination therapies yet initiated with ALKS 4230. Another competitive consideration specifically for melanoma is recent data on the combination of PD-1 inhibitors and IDO inhibitors, which we discussed in a recent Seeking Alpha article. For example, the ORR achieved with a combination of the PD-1 inhibitor KEYTRUDA and an IDO inhibitor in melanoma was about 60%, which appears to be better than the 42% ORR achieved with KEYTRUDA monotherapy. Thus, this combination therapy in melanoma appears to give similar efficacy results to the NKTR-214/anti-PD-1 combo therapy in melanoma based on the early results. It is possible that different subgroups of melanoma patients will respond better to different combination therapies. Either way, these treatments options bode well for melanoma patients. Furthermore, future data in RCC and NSCLC could differentiate these combination therapies in terms of efficacy.

Financials:
NKTR announced in its Q3 earnings call that it expects to have $350M in cash and short-term investments at the end of 2017. It lost $63M thus far in 2017, which we believe takes into account the $130M up-front payment received from LLY in Q3, 2017 related to the NKTR-358 deal. In its press release detailing more financial information, NKTR also stated that royalty revenue is continuing to increase, with revenue being $24M for the first 9 months of 2017 compared to $13M for the same period in 2016. NKTR continues discussions with potential partners for a NKTR-181 deal, which should include a large up-front payment. Therefore, given its current financial position and the reasonable probability of a NKTR-181 deal by the end of 2018, we do not anticipate that NKTR will need to raise money in a dilutive event through the end of 2018. However, if the stock price continues to rise, it is always possible that the company will decide to take advantage of the situation with a follow-on offering.

Summary:
We see NKTR as an attractive investment opportunity because of its strong partnered drug programs and its exciting clinical pipeline assets that span all stages. Its lead immuno-oncology asset, NKTR-214, has impressive biological effects and pre-clinical efficacy profiles. NKTR-214 is at an exciting stage of development where early human efficacy data is being generated at a rapidly expanding rate. The presentations by NKTR at a scientific meeting this weekend provides an important update for NKTR-214's human safety and clinical efficacy that is a possible further catalyst for this stock. Furthermore, we look forward to exciting events ahead as NKTR 1) submits its non-addictive pain treatment, NKTR-181, for regulatory approval with the FDA in the 1st half of 2018 and possibly announces a worldwide partnership for NKTR-181 in 2018, 2) provides further updates on its partnered assets, and 3) continues building its NKTR-214 program.

At AMP, we aim to differentiate ourselves with deeper analysis that leverages our years of scientific training and industry experience. We plan to continue to hold our core holding position in NKTR in our model portfolio.

Disclaimer: