

# **Nektar Therapeutics (NKTR)**

*Doubling Down Against NKTR-214*

October 2018

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An e-mail reportedly circulated by Nektar Therapeutics in response to our initial report on NKTR-214 has been posted on the message boards of Seeking Alpha and Yahoo! Finance. While we were unable to obtain the actual email from Nektar despite requesting it through a third party, we have no reason to doubt its authenticity. If this is indeed from Nektar, it is easy to see why this was privately circulated rather than published as a press release—the points raised are flimsy and easily refuted, and it fails to address many arguments we raised in the initial report/presentation. Investors may review the presentation [here](#).

We will go through the entire e-mail section by section and reproduce the e-mail in its entirety at the end of this report. The e-mail begins:

*Hi [redacted],*

*Thank you for your inquiry on the “report” issued by Plainview. Please find below the company’s response. The report was lengthy and filled with what was positioned to be science but were actually inaccurate scientific inaccuracies and mis-calculations. Below, we chose to focus on the major inaccuracies to point out the author’s flaws in the central premise. My team and I are available for a call today if needed – please let me know if you need it.*

*With our partner Bristol-Myers Squibb, we are developing NKTR-214 with nivolumab in 9 tumor types in over 20 registrational trials. We have a melanoma Phase 3 trial that has already been initiated and several additional registrational trials that are planned to start in renal cell carcinoma and bladder cancer by the end of the year. Clearly, the commitment of our two companies to the long-term development of the combination underscores our conviction in the combination results and our belief in the potential value of NKTR-214 and Opdivo to patients and physicians in the fight against cancer.*

*As we stated on our last financial results call, we look forward to presenting mature data from the fully enrolled 38-patient Stage IV melanoma cohort from PIVOT at the upcoming SITC conference in November. The data will be presented in an oral presentation on Friday, November 9th in the Cytokines Reinvented session. As data from the PIVOT cohorts mature over the next six to 18 months, Nektar and Bristol are planning to present each of the data sets at various medical meetings, including tumor-specific conferences, in the lung, melanoma, GU and breast cancer specialty areas.*

*The report written and issued by Plainview has a flawed central premise, contains many scientific inaccuracies, and deliberately omits published data that did not support its premise. The author did not conduct diligence with the company or the authors of peer-reviewed published data on NKTR-214. While the report is long and cites a number of references, many references are omitted and those cited are selective. As a result, we focused on the most egregious inaccuracies and omissions found in the executive summary. Please don’t hesitate to reach out if you have any further questions.*

This is a typical blanket statement that contains vague assertions and no substance. Being short the stock, we are very pleased to read that Nektar is still on track to provide data on only 38 patients at SITC 2018 (28 previously reported at ASCO 2018, 10 new patients). There were 283 patients dosed on NKTR-214 as of May 7, 2018 and the “data is immature” card has expired. We cannot think of any reason for why Nektar would withhold so much data other than the obvious explanation: the data is bad.

The e-mail continues:

## Lymphocyte Effects

The writer uses as his premise in multiple areas that lymphocyte levels following treatment with NKTR-214 did not increase sufficiently. However, the writer ignores a more complete 2018 dataset presented for NKTR-214 to make this argument. Instead, he cites 2017 data from a handful of early patients enrolled in the dose-escalation stage of the PIVOT trial (ASCO 2017) and references only a 30-50% increase in lymphocyte levels. At ASCO 2018, the company presented comprehensive lymphocyte level data for over 200 patients who were treated with the recommended Phase 2 dose of NKTR-214. The data show an increase over baseline after first cycle of >100% (achieving a level of >200% of baseline) and in subsequent cycles with NKTR-214 lymphocyte levels range up to a 200% increase over a baseline (achieving a level of 300% of baseline) which is then sustained over 10 cycles of therapy (over 200 days):

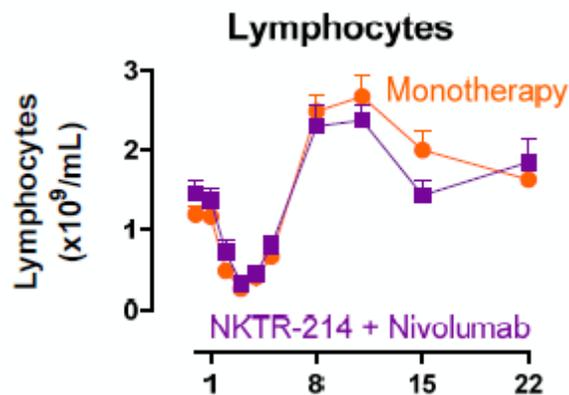
[graphics missing]

Source: ASCO 2018 --- graph notes added: A: ~200% of baseline, B: ~300% of baseline

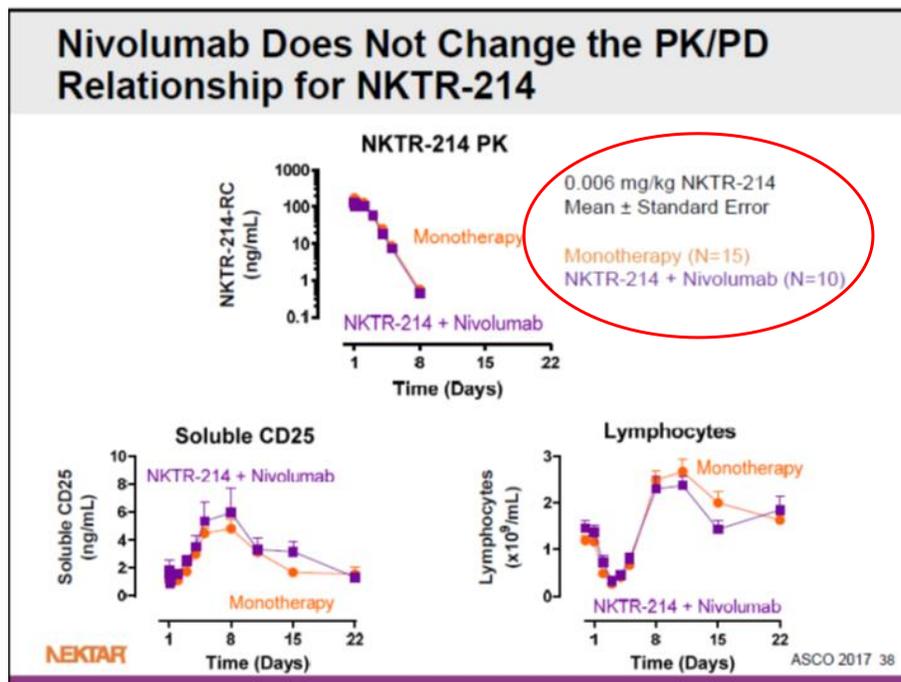
These ASCO 2018 results are concordant with what is known from the literature about lymphocyte increases following HD-IL-2. Contrary to the author's conclusion, the pharmacodynamic effect for NKTR-214 is in fact consistent with modeling expectations for HD-IL-2.

However, NKTR-214 maintains an essential difference to HD-IL-2 in that it is very-well tolerated and allows for continuous dosing (note the 10 cycles of therapy shown in the chart above). This provides a longer duration of sustained IL-2 receptor agonism and sustained increased lymphocyte levels, much longer in duration than the short increase provided by one to two cycles of HD-IL-2.

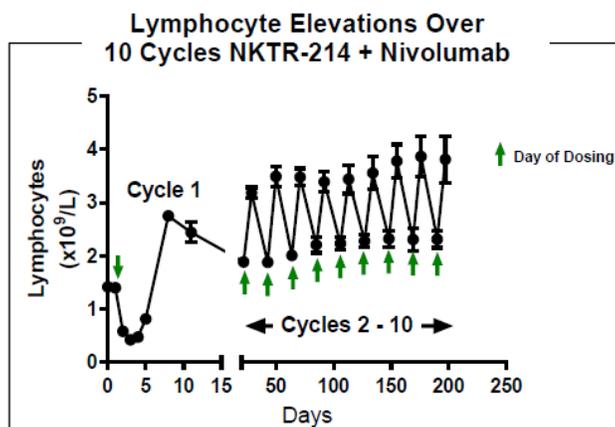
As a refresher, the e-mail is referring to this graph from our initial report, which we took from slide 38 of Nektar's ASCO 2017 presentation where we stated that NKTR-214 only increases lymphocytes by a fraction of the level required to induce a response (50% peak increase compared to 300% peak increase required for a response and 33% sustained increase compared to 200% sustained increase required for a response):



The e-mail wants investors to disregard this graph because the patients were in the dose-escalation stage of the trial. The problem with that excuse is that the slide explicitly says that all the patients were dosed at 0.006 mg/kg—so while they may technically have been measured during the dose escalation phase, the patients were all being dosed at MTD. See below for the full slide:



The e-mail asks investors to instead focus on a graph from slide 51 of the ASCO 2018 presentation (reproduced below):



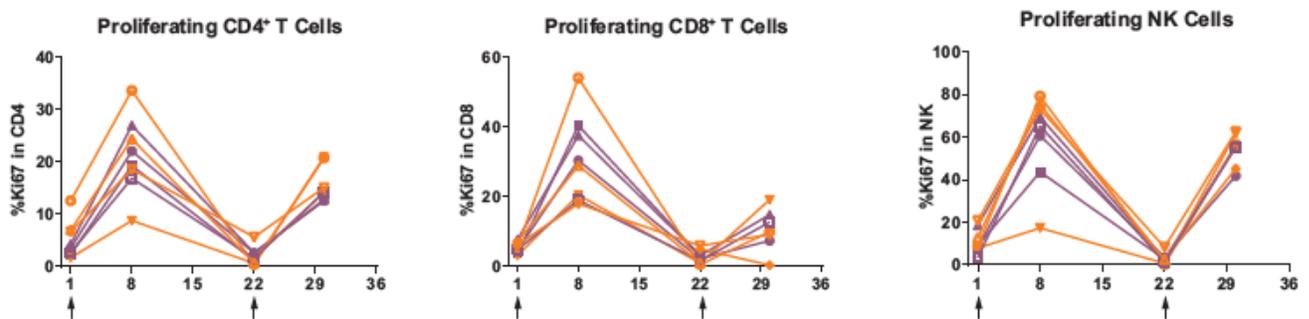
Note below the graph reads: “Lymphocyte values obtained from hematology analyses. Rich sampling in Cycle 1, limited sampling in other cycles. Green arrows indicate NKTR-214 + nivolumab administration. Data is shown as mean +/- standard error. N = a maximum of 200 patients over the first few cycles, N = 10-50 patients for the later cycles.”

There are four problems with this:

- 1) This is still nothing like IL-2’s pharmacodynamics. Based on the studies we cited, responding to IL-2 requires either a 300% peak increase in lymphocytes or a 200% sustained increase in lymphocytes. A 300% peak increase would put lymphocytes at  $\sim 6 \times 10^9/L$ . A 200% sustained increase would put the trough level at  $\sim 4.5 \times 10^9/L$ . Even in this depiction (which we find highly misleading for the following three reasons), **NKTR-214 does not come close to hitting the benchmark for efficacy-- ever**. The e-mail phrases lymphocyte change in a way that artificially inflates the effect: “achieving a level of 200% of baseline” = a 100% increase & “achieving a level of 300% of baseline” = a 200% increase—which never even happens! The highest peak reached is still  $\sim 3.9 \times 10^9/L$ ,

which is a <100% increase from the trough prior to that point. The trough levels never increase beyond ~50% from baseline—not significantly different from the 33% figure from the other graph which we cited in our report. The change from trough to peak following a dose of NKTR-214 never exceeds 100% (it’s in the 50-100% range at each dose—again, very similar to the 50% increase from the graph we cited), and even if you compare the final peak with the initial baseline, the increase is only 160%— still far away from the 305% peak change seen among responders in [Phan et al 2001](#). Recall that in Phan et al 2001, even the non-responders saw a peak increase of 262% and a peak level of  $4.9 \times 10^9/L$ —far above the highest point ever reached by NKTR-214. In [Lissoni et al 1994](#), the three-week lymphocyte increase among responders was 2.6 or 217% of baseline—far beyond the 0.5/33% increase seen in this chart.

- 2) This graph is unreliable for assessing the effect of NKTR-214 because the total patient pool changes with each new point. This creates a host of problems, especially survivorship bias: how do you know that the patients at later points did not have higher baselines at the initial point? The patient population is changing at every single time point. The peak and sustained levels are not necessarily increasing at all—they may very well have been the same and the apparent increase is merely a product of the changing patient pool
- 3) Nektar’s biomarker data contradicts the idea that NKTR-214’s effect increases with repeated dosing and instead indicate that **NKTR-214’s effect becomes weaker the more times it is administered to patients**. It makes sense—cytokine systems adjust to NKTR-214 and the drug becomes less effective over time. For instance, NKTR-214’s vaunted change in Ki67<sup>+</sup>CD8<sup>+</sup> is significantly diminished following a second dose ([Bernatchez et al 2016](#)):



- 4) Suspending reality and assuming that NKTR-214’s effect does in fact increase over time, one would also assume that IL-2 improves over time as well. In that case, by comparing the graph shown above with the initial change in patients on IL-2, you’d be making an apples-to-oranges comparison because you’re comparing the worst data for IL-2 (initial treatment data) with the best data for NKTR-214 (the final treatment data for patients who were doing well enough on therapy to make it that far and may have had significantly higher baseline lymphocyte levels)

The e-mail continues:

#### *Overall Response Rate for Monotherapy HD-IL-2 vs NKTR-214*

*The body of selected data listed in report with high-dose IL-2 is in first-line previously untreated patients. ORR reported in the older literature vary but the studies were conducted prior to the availability of TKI therapies, BRAF therapies and checkpoint inhibitors. As is well-known, the IL-2 response rates were achieved at the expense of safety in these relatively healthy first-line patients. As an example, the author omits Phase 1 clinical data in second-line RCC patients where high-dose IL-2 was evaluated and had no responses. An important retrospective analysis by Dr. Daniel Cho (Journal of Immunotherapy 2009), highlights 28 patients who received high-dose IL-2*

*following treatment with TKI therapy/bevacizumab therapy. Only 3 of 28 or 11% experienced stable disease and there were no PRs or CRs (unconfirmed or otherwise). Only 1 of 23 patients could receive a second cycle of high-dose IL-2 and 26% of patients experienced severe cardiovascular toxicities, including cardiac arrest and acute pulmonary edema.*

*NKTR-214 was evaluated in a dose-ranging monotherapy trial in 28 patients with advanced, pre-treated cancer with a median number of prior therapies of 2 (and a range of 1-12). The breakout for pre-treatment was as follows: 16 (57.1%) had received targeted therapy; 16 (57.1%) had received an immune checkpoint inhibitor; and 6 (21.4%) had received an immune checkpoint inhibitor in addition to other immunotherapy. Tumor shrinkage was observed in 32% or 9 out of 28 patients (ranging from 2-30% tumor shrinkage), with a best response of stable disease in 50% or 14/28 patients. One patient experienced an unconfirmed partial response (a patient with advanced renal cell carcinoma who was treated with a prior TKI regimen). Another patient with pre-treated renal cell carcinoma had a 40% reduction on the right adrenal gland at the first on-treatment scan (the overall response was stable disease). Durable, stable disease > 1 year was also seen in 2 patients who continued on therapy for over one year. One patient with metastatic melanoma, previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of NKTR-214 and had durable stable disease (SD) for 15 months. A second patient with metastatic RCC, who had progressed on HD-IL-2 and was refractory to single-agent OX40 and nivolumab, was treated with 19 cycles of NKTR-214 and had durable SD for 13 months. Every patient evaluated showed evidence of immune activation and these effects were reproduced with repeated administration. Only 21% of patients experienced a G3 toxicity but these were reversible and short-lived; there were no G4/5 AEs reported. (SITC 2016, ASCO 2017 and SITC 2017)*

In this section, the email is suggesting that investors should ignore the nine studies we cited with total N=2,728 and instead focus on a specially hand-picked n=23 [retrospective study](#) (not a prospective trial, and not n=28 as the e-mail says) where IL-2 was used as salvage therapy for patients. 22/23 of patients only received one cycle of IL-2. None of the patients responded, and the e-mail presents this as though it were definitive evidence that IL-2 never works as monotherapy (just like NKTR-214). The anecdotes from the EXCEL trial prove nothing and do not change the fact that Nektar saw zero responses in the trial.

The toxicity profile was also discussed. We agree that NKTR-214's toxicities are very minor at the clinical dose. This is not a specially-designed benefit though: it is a product of NKTR-214's weak clinical profile. NKTR-214 never exceeds 2% of the peak concentration of IL-2. This is also the reason why NKTR-214 is too weak to work. The e-mail continues:

*Finally, the author quotes a paper from 2005 by Maker et al in order to disparage the combining of an IL-2 mechanism with a checkpoint inhibitor and its clinical benefit. However, the writer omits the conclusions from a later paper published by Prieto et al in 2012 which analyzed the same patients cited in the Maker study in a longer-term follow-up and highlighted the long-term clinical benefit of the combination, namely a high rate of durable complete responses achieved in these patients.*

The e-mail cites [Prieto et al 2012](#) as "highlighting long-term clinical benefit of the combination [checkpoint inhibitor and IL-2]". **Prieto et al 2012 does not make any statements endorsing the combination.** Prieto et al 2012 merely suggested testing the combination of IL-2 and ipilimumab in a randomized trial. We also note that Prieto et al 2012 showed that patients receiving ipilimumab monotherapy demonstrated a substantial mean increase in peripheral lymphocytes even without IL-2, providing further evidence against the idea that there would be synergies combining NKTR-214 with checkpoint inhibitors:

*Since it has been shown that IL-2 alone can cause lymphocytosis and that this lymphocytosis is associated with the development of an OR to IL-2 (20), we analyzed posttreatment ALC in patients in protocols 1 and 3 who did not receive IL-2 in conjunction with ipilimumab. For these patients, the change in ALC after one dose of ipilimumab (defined as ALC measured approximately 3 weeks after the first dose of ipilimumab minus pretherapy ALC) was associated the development of an OR. Responders had a higher mean increase in ALC (513 +/- 73 counts/uL; range, -349 to 1,176 counts/uL) than nonresponders (313 +/- 42 counts/mL; range, -612 to 2,816 counts/uL)*

This side effect of ipilimumab is nearly the same as the principal effect of NKTR-214. Converting units to match Nektar's change in lymphocytes, the reported change three weeks after treatment in responders is  $0.5 \times 10^9/L$  and the change in non-responders is  $0.3 \times 10^9/L$ —NKTR-214 reported a  $\sim 0.5 \times 10^9/L$  increase in patients taking the drug three weeks after dosing.

The next section of the e-mail discusses NKTR-214's receptor bias:

#### *Exposure Comparisons of NKTR-214 Active Drug and HD-IL-2*

*The author mis-casts the receptor-bias inherent to NKTR-214 by pulling a partial figure from a published peer-reviewed publication (2017 Charych et al PLOS ONE). If the full figure is viewed, it is clear that NKTR-214 exhibits a biased receptor occupancy favoring the IL-2 beta-gamma receptor. As a result of its bias, direct comparison of exposure (AUC) from PK evaluation of NKTR-214 active drug vs HD-IL-2 is not relevant.*

This section is saying that AUC is not relevant because NKTR-214 is biased and IL-2 is not. **This is not true at all.** AUC is critical to figuring out what a drug's end therapeutic effect is: you must know AUC in order to calculate total target receptor binding in order to gauge the magnitude of the drug's effect. We showed that a standard cycle of IL-2 has a significantly higher (5-14x) AUC compared to NKTR-214-AC. This has a huge impact on the therapeutic effect.

We don't dispute that NKTR-214 has a bias to CD122—we never did. What we do dispute is that having that bias yields any benefit. If all things else were equal, then a CD122 bias could increase target receptor binding time. The problem with NKTR-214 is that all other things are not equal: its PEG polymers that prevent it from binding with  $IL2R\alpha\beta\gamma$  also obstruct its ability to bind with  $IL2R\beta\gamma$  (CD122)—so even though it is technically biased towards  $IL2R\beta\gamma$ , it binds to  $IL2R\beta\gamma$  much less than IL-2 would with identical AUC.

The purpose of clipping the table was to enable the reader to focus on relevant information. As we showed in the report, even with its bias, NKTR-214 yields 73% less target receptor binding than IL-2 when the AUC of NKTR-214-AC is the exact same as the AUC of IL-2. We reproduce the full table below:

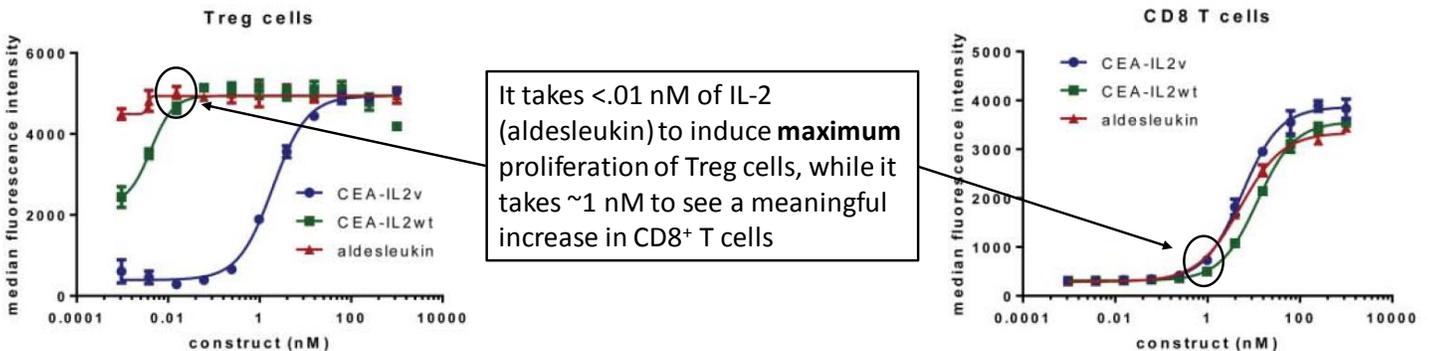
AUC of receptor occupancy for aldesleukin at 3 dosing regimens compared to single dose NKTR-214 at IL2R $\alpha\beta\gamma$ and IL2R $\beta\gamma$				
[%receptor occupancy*hr]				
Receptor	Aldesleukin, 0.8 mg/kg, single dose	Aldesleukin, 0.8 mg/kg, qdx5, 2 cycles <sup>1</sup>	Aldesleukin, 0.8 mg/kg at equivalent AUC to NKTR-214 <sup>2</sup>	NKTR-214, 0.8 mg/kg, single dose
IL2R $\beta\gamma$	33.4	357.4	2598.7	695.8
IL2R $\alpha\beta\gamma$	212.6	2265.8	20336.9	118.2
Ratio of IL2R $\beta\gamma$ to IL2R $\alpha\beta\gamma$	0.16	0.16	0.13	5.9

<sup>1</sup>Therapeutic aldesleukin regimen typically used in animal tumor models

<sup>2</sup>Theoretical "sustained delivery formulation" of aldesleukin that provides an AUC comparable to NKTR-214. The aldesleukin concentration was artificially kept constant, such that the AUC<sub>0-10d</sub> of IL2 was the same as the actual AUC<sub>0-10d</sub> of NKTR-214-AC after a single 0.8 mg/kg dose of NKTR-214.

The target receptor thought to drive expansion of NK/CD8<sup>+</sup> T cells is IL2R $\beta\gamma$ . As this table shows, at an equivalent AUC, NKTR-214-AC only produces 695.8/2,598.7 = 26.8% of the IL2R $\beta\gamma$  receptor binding of IL-2

At the same AUC, aldesleukin binds to both receptors significantly more than NKTR-214, and binds to the target receptor 3.7x (2,598.7/695.8) as much as NKTR-214. Combining this with our AUC range (7-20%), we find that NKTR-214's total target effect is 2-5% of IL-2—and that is spread out over a longer period of time with a much weaker C<sub>max</sub>. The difference in binding to IL2R $\alpha\beta\gamma$  is largely irrelevant because as the Roche study [Klein et al 2017](#) showed, maximum proliferation of Treg cells occurs at a tiny fraction of the dose required to elicit any measurable change in CD8<sup>+</sup> and both drugs quickly reach that level of binding (reproduced from initial report below):



Nektar's clinical results confirmed that it was not preventing Treg proliferation as evidenced by the 18-25 fold increases in Tregs (%CD4) reported in its trials.

The e-mail continues:

*Further, HD-IL-2 clears rapidly and requires TID dosing. NKTR-214 has a prodrug design with a long half-life and q3 week dosing. Given the difference in mechanisms, an analysis of PD changes, notably the increases in lymphocyte levels after drug administration (or the desired effects of dosing) is the more important measure of adequate dose administration. Nektar has highlighted achievement of this desired effect in data presented at ASCO 2018 (refer to above section on Lymphocyte Effects).*

As we have already shown in the initial report and again in this report:

- 1) The long half-life is a bug, not a feature. It significantly increases the minimum safety threshold, which has resulted in a much lower dose and pegylation also backfired by completely blocking drug activity for 76% of the

AUC and continuing to interfere during the active state-- reducing target receptor binding by 73% compared to IL-2 according to [Charych et al 2017](#)

- 2) The lymphocyte changes for NKTR-214 are not even close to IL-2. Our explanation of AUC and target receptor binding in the initial report/presentation were written as a courtesy to help investors understand why the change in lymphocytes was so much lower for NKTR-214 compared to IL-2

The e-mail continues:

*Modified T Reg Increase in the Peripheral Blood and Not in the Tumor*

*NKTR-214 was designed to avoid Treg accumulation in the tumor microenvironment. Our earliest preclinical studies demonstrated the ability to promote transient Treg elevations in the peripheral blood, but not the tumor. Inherent to its design, it is necessary to preserve some binding to IL-2R-alpha because that receptor is needed for T-cell priming reactions in the lymph node.*

This does not even make sense. There is no viable explanation for why NKTR-214 would have the same impact on peripheral Tregs as IL-2 but magically prevent those Tregs from entering in the tumor microenvironment—unless Tregs simply don't accumulate in the tumor microenvironment, in which case IL-2 also does not cause a Treg increase in the tumor microenvironment and NKTR-214 is not actually adding any value.

The e-mail continues:

*TIL Increases with NKTR-214*

*The statements made around TIL increases with NKTR-214 are inaccurate; in the monotherapy trial, substantial increases in intratumoral CD8+ T cells were reported with no intratumoral CD4+ T regulatory expansion (SITC 2016, ASCO 2017 and SITC 2017). These data have been published at numerous congresses.*

*As stated above, NKTR-214 causes elevations in lymphocytes. These elevations are seen in blood and in tumor. The fact is that substantial lymphocyte increases with NKTR-214 were observed in the periphery so this can't be used to refute the reported TIL increases with NKTR-214 in the published data as the author attempts.*

*In the tumor, we have observed high concordance of TIL increases with monitoring using multiple methods; immunohistochemistry (IHC), fresh tissue flow cytometry, and T cell DNA analysis (a method that compares T cell-specific DNA vs non T cell-specific DNA to quantify the mass of T cells in tumor tissue) and all three methods have produced concordant results (manuscript in preparation). The use of several methods is critical as it important to observe concordance across these methods to increase confidence in the results.*

*The author uses older SITC 2016 data rather than referring to more recent publications. At ASCO 2018, Nektar reported IHC data on TIL elevations from 33 tumor biopsies in PIVOT patients at the RP2D. IHC is the most common method used in the historical literature for other agents and allows for comparison to nivolumab. The author uses a TumeH paper to support an argument that TIL increases are observed with nivolumab. However, the author declines to point out that the TumeH paper only demonstrates that select patients with elevated baseline TILs were able to experience a small 2-fold or less increase in TILs following nivolumab. The reality is that a 10-fold increase in TILs was observed following treatment with NKTR-214 even in patients with low*

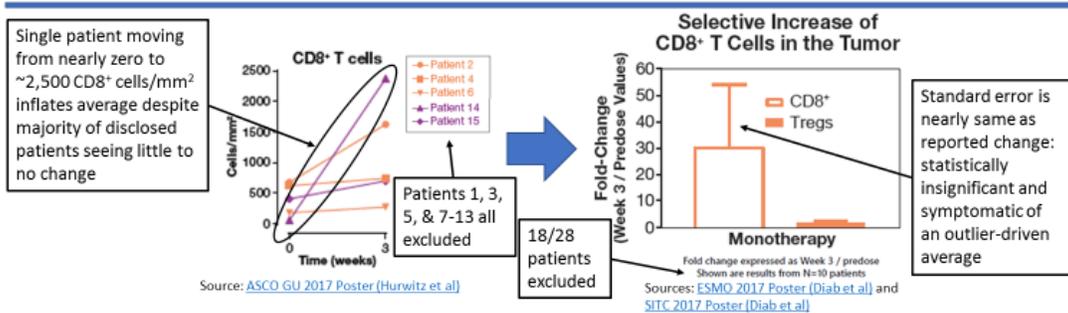
baseline TILs which has not been shown with nivolumab. This is consistent with the mechanism of action of NKTR-214.

In a revealing move, the e-mail does not dispute any of the actual allegations in our initial report. To refresh, we alleged:

- 1) NKTR-214 does not actually have a substantial impact on TIL CD8<sup>+</sup> and the oft-cited 10- and 30-fold average changes in TIL CD8<sup>+</sup> are driven by single outliers
- 2) The initial SITC 2016 data showed that 3/9 patients saw a decline in TIL CD8<sup>+</sup>-- basically what you'd expect to see from a placebo and certainly not what you'd expect to see from a drug that claims to drive a 10-fold or 30-fold average increase in TIL CD8<sup>+</sup>

Instead, the e-mail merely states that the report focuses on SITC 2016 data and does not refer to more recent 2017 and 2018 publications, which is not true: we discussed those publications in detail. Our main complaint was that the recent data appears to be manipulated to portray NKTR-214 as having a strong effect when it actually doesn't. See below for the slide discussion Nektar's 2017 claims:

### CD8<sup>+</sup> Data Presentation Creates Biased Appearance of Efficacy



- 28 patients were enrolled in NKTR-214 monotherapy trial. Only 10/28 (36%) were included in the 30-fold calculation
- Patient-stratified data limited to an even smaller subgroup of patients
- There is high variance in change in CD8<sup>+</sup> due to tumor-specific factors that have nothing to do with NKTR-214, and it is right-skewed with fold-change bound between 0 and infinity, making it highly inappropriate to assess using averages.
- None of the 28 enrolled patients actually responded to NKTR-214 monotherapy (0% ORR), indicating that the patient who saw TIL CD8<sup>+</sup> increase from 0 to 2,500 cells/mm<sup>2</sup> was likely a product of variance or poor data collection

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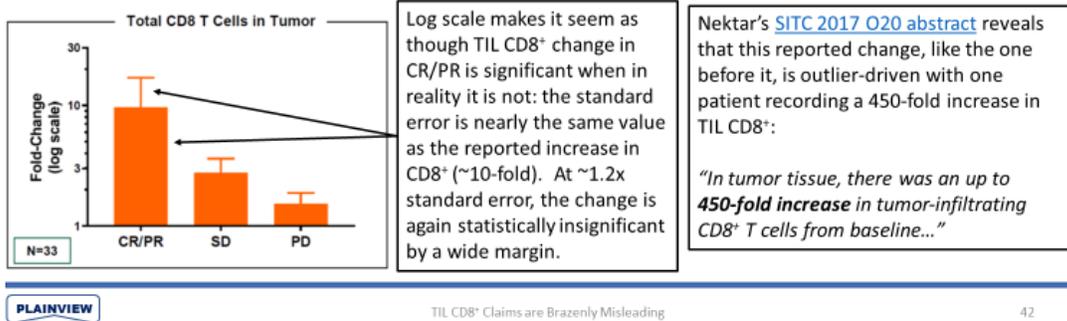
TIL CD8<sup>+</sup> Claims are Brazenly Misleading

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And here's the slide from our presentation where we describe how Nektar pulled the exact same stunt with its data at ASCO 2018:

## ASCO 2018 Data Also Outlier-Driven

- At ASCO 2018, Nektar again [presented](#) average data (instead of median or patient-stratified data) on change in CD8<sup>+</sup> in NKTR-214/nivolumab combination therapy patients. Again, the average was outlier-driven and was significantly lower than the prior monotherapy data despite 1) segregating patients by response and 2) the fact that PD-1 inhibitor monotherapy has been proven to increase TIL CD8<sup>+</sup> by itself

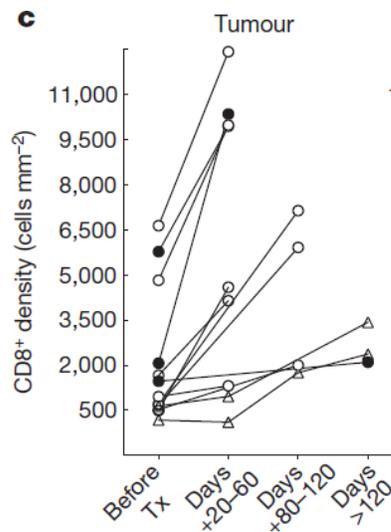


The paragraph about TumeH 2014 is especially baffling:

*However, the author declines to point out that the TumeH paper only demonstrates that select patients with elevated baseline TILs were able to experience a small 2-fold or less increase in TILs following nivolumab. The reality is that a 10-fold increase in TILs was observed following treatment with NKTR-214 even in patients with low baseline TILs which has not been shown with nivolumab.*

This paragraph is two completely unrelated thoughts:

- 1) "Plainview did not point out that TumeH showed that patients with elevated baseline levels of TIL CD8<sup>+</sup> were limited in their increases." We did not point it out because it's not true—TumeH showed several multi-fold increases from elevated baselines. See below:



- 2) "NKTR-214 showed high increases in patients with low baseline TIL CD8<sup>+</sup> levels." **This is exactly what we are alleging—that NKTR-214's purported increases are a result of patients with low baseline levels recording large**

multi-fold increases which skewed the averages and could easily have been driven by tumor-related factors/variance in measurements and been completely unrelated to NKTR-214.

The e-mail continues:

*Comparison to epacadostat*

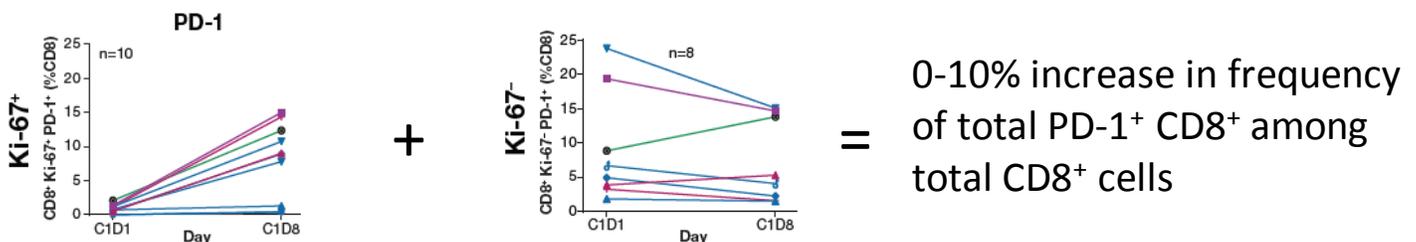
*Unlike the epacadostat open label single arm trials, the PIVOT trial of NKTR-214 and Opdivo has independent blinded central data review for ORR. Nektar and BMS have stated there is a high concordance between the investigator-assessed and independent review. As the separate tumor cohorts are independently presented, such as at the upcoming SITC meeting, Nektar and BMS plan to present the investigator and independent ORR side-by-side for full transparency. The NKTR-214 and nivolumab PIVOT trial is enrolling Stage IV patients and did not enroll Stage III patients as the epacadostat studies did.*

The PIVOT trial technically *had* independent blinded central review, but the results reported to the public are from the investigator-assessments. Nektar says “there is high concordance”—we find it highly unlikely that the investigators involved in Nektar’s trial are uniquely able to avoid bias in investigator-assessments while investigators in other trials are not.

*Nektar has demonstrated translational data from NKTR-214 monotherapy and the nivolumab combination studies that clearly differentiates from the mechanism of IDO inhibition. NKTR-214 promotes TIL increases, proliferation of lymphocytes (Ki67+ expressing), increases in PD-1 and ICOS expression, and increases in PD-L1 in the tumor. The MOA of NKTR-214 changes the immune system and the tumor microenvironment in a beneficial way that is non-overlapping and complementary with anti-PD1 checkpoint antibodies. We’ve observed high response rates with NKTR-214 and nivolumab in baseline PD-L1 negative patients, deepening of responses over time, and a low immune-mediated AE profile which is critically important in an I-O combination therapy.*

Best,  
Jennifer  
Jennifer Ruddock  
SVP, Investor Relations & Corporate Affairs  
Nektar Therapeutics | 455 Mission Bay Boulevard South, San Francisco, CA 94158

The e-mail ends with the “change in biomarkers” schtick that Nektar has long been using to convince people that NKTR-214 works. We showed in the initial report why Nektar’s reported average TIL CD8+ increases are unreliable and why Nektar’s reported change in Ki67+ expression means little to nothing with regard to actual proliferation of CD8+. Nektar’s NKTR-214 has little to no effect on PD-1, as we see by adding up Ki67+ and Ki67- PD-1 changes from [Bentebibel et al 2017](#):



Ki-67+ PD-1+ + Ki-67- PD-1+ = total PD-1+; if a cell is not Ki-67+ then it must be Ki-67-

The PD-L1 concept just doesn't make sense. Imagine you had a drug that could instantly turn all tumors PD-L1 positive: that would be a bioterrorism agent, not a medicine. PD-L1 expression is a bad thing—it is a problem that PD-1 inhibitors are designed to solve. When a tumor cell expresses PD-L1, it has the ability to downregulate the immune responses; how could creating that problem help? It's not as though PD-1 inhibitors do other magical things once a tumor reaches a certain level of PD-L1; they simply block PD-1 from binding with PD-L1/2. If PD-L1 is not the initial problem for a patient, making it a problem and then fixing it doesn't achieve anything.

Further, like most tumor biomarkers, PD-L1 expression is highly variable and heterogeneous and we strongly doubt that NKTR-214 had any actual effect on it. NKTR-214 was not designed to increase PD-L1 expression—it is simply a pegylated version of IL-2 which previously failed to show synergies with a checkpoint inhibitor in Maker 2005.

## Full E-mail

Hi [redacted],

Thank you for your inquiry on the “report” issued by Plainview. Please find below the company’s response. The report was lengthy and filled with what was positioned to be science but were actually inaccurate scientific inaccuracies and mis-calculations. Below, we chose to focus on the major inaccuracies to point out the author’s flaws in the central premise. My team and I are available for a call today if needed – please let me know if you need it.

With our partner Bristol-Myers Squibb, we are developing NKTR-214 with nivolumab in 9 tumor types in over 20 registrational trials. We have a melanoma Phase 3 trial that has already been initiated and several additional registrational trials that are planned to start in renal cell carcinoma and bladder cancer by the end of the year. Clearly, the commitment of our two companies to the long-term development of the combination underscores our conviction in the combination results and our belief in the potential value of NKTR-214 and Opdivo to patients and physicians in the fight against cancer.

As we stated on our last financial results call, we look forward to presenting mature data from the fully enrolled 38-patient Stage IV melanoma cohort from PIVOT at the upcoming SITC conference in November. The data will be presented in an oral presentation on Friday, November 9th in the Cytokines Reinvented session. As data from the PIVOT cohorts mature over the next six to 18 months, Nektar and Bristol are planning to present each of the data sets at various medical meetings, including tumor-specific conferences, in the lung, melanoma, GU and breast cancer specialty areas.

The report written and issued by Plainview has a flawed central premise, contains many scientific inaccuracies, and deliberately omits published data that did not support its premise. The author did not conduct diligence with the company or the authors of peer-reviewed published data on NKTR-214. While the report is long and cites a number of references, many references are omitted and those cited are selective. As a result, we focused on the most egregious inaccuracies and omissions found in the executive summary. Please don’t hesitate to reach out if you have any further questions.

### **Lymphocyte Effects**

The writer uses as his premise in multiple areas that lymphocyte levels following treatment with NKTR-214 did not increase sufficiently. However, the writer ignores a more complete 2018 dataset presented for NKTR-214 to make this argument. Instead, he cites 2017 data from a handful of early patients enrolled in the dose-escalation stage of the PIVOT trial (ASCO 2017) and references only a 30-50% increase in lymphocyte levels. At ASCO 2018, the company presented comprehensive lymphocyte level data for over 200 patients who were treated with the recommended Phase 2 dose of NKTR-214. The data show an increase over baseline after first cycle of >100% (achieving a level of >200% of baseline) and in subsequent cycles with NKTR-214 lymphocyte levels range up to a 200% increase over a baseline (achieving a level of 300% of baseline) which is then sustained over 10 cycles of therapy (over 200 days):

Source: ASCO 2018 --- graph notes added: A: ~200% of baseline, B: ~300% of baseline

These ASCO 2018 results are concordant with what is known from the literature about lymphocyte increases following HD-IL-2. Contrary to the author’s conclusion, the pharmacodynamic effect for NKTR-214 is in fact consistent with modeling expectations for HD-IL-2.

However, NKTR-214 maintains an essential difference to HD-IL-2 in that it is very-well tolerated and allows for continuous dosing (note the 10 cycles of therapy shown in the chart above). This provides a longer duration of sustained IL-2 receptor agonism and sustained increased lymphocyte levels, much longer in duration than the short increase provided by one to two cycles of HD-IL-2.

### **Overall Response Rate for Monotherapy HD-IL-2 vs NKTR-214**

The body of selected data listed in report with high-dose IL-2 is in first-line previously untreated patients. ORR reported in the older literature vary but the studies were conducted prior to the availability of TKI therapies, BRAF therapies and checkpoint inhibitors. As is well-known, the IL-2 response rates were achieved at the expense of safety in these relatively healthy first-line patients. As an example, the author omits Phase 1 clinical data in second-line RCC patients where high-dose IL-2 was evaluated and had no responses. An important retrospective analysis by Dr. Daniel Cho (Journal of Immunotherapy 2009), highlights 28 patients who received high-dose IL-2 following treatment with TKI therapy/bevacizumab therapy. Only 3 of 28 or 11% experienced stable disease and there were no PRs or CRs (unconfirmed or otherwise). Only 1 of 23 patients could receive a second cycle of high-dose IL-2 and 26% of patients experienced severe cardiovascular toxicities, including cardiac arrest and acute pulmonary edema.

NKTR-214 was evaluated in a dose-ranging monotherapy trial in 28 patients with advanced, pre-treated cancer with a median number of prior therapies of 2 (and a range of 1-12). The breakout for pre-treatment was as follows: 16 (57.1%) had received targeted therapy; 16 (57.1%) had received an immune checkpoint inhibitor; and 6 (21.4%) had received an immune checkpoint inhibitor in addition to other immunotherapy. Tumor shrinkage was observed in 32% or 9 out of 28 patients (ranging from 2-30% tumor shrinkage), with a best response of stable disease in 50% or 14/28 patients. One patient experienced an unconfirmed partial response (a patient with advanced renal cell carcinoma who was treated with a prior TKI regimen). Another patient with pre-treated renal cell carcinoma had a 40% reduction on the right adrenal gland at the first on-treatment scan (the overall response was stable disease). Durable, stable disease > 1 year was also seen in 2 patients who continued on therapy for over one year. One patient with metastatic melanoma, previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of NKTR-214 and had durable stable disease (SD) for 15 months. A second patient with metastatic RCC, who had progressed on HD-IL-2 and was refractory to single-agent OX40 and nivolumab, was treated with 19 cycles of NKTR-214 and had durable SD for 13 months. Every patient evaluated showed evidence of immune activation and these effects were reproduced with repeated administration. Only 21% of patients experienced a G3 toxicity but these were reversible and short-lived; there were no G4/5 AEs reported. (SITC 2016, ASCO 2017 and SITC 2017)

Finally, the author quotes a paper from 2005 by Maker et al in order to disparage the combining of an IL-2 mechanism with a checkpoint inhibitor and its clinical benefit. However, the writer omits the conclusions from a later paper published by Prieto et al in 2012 which analyzed the same patients cited in the Maker study in a longer-term follow-up and highlighted the long-term clinical benefit of the combination, namely a high rate of durable complete responses achieved in these patients.

### **Exposure Comparisons of NKTR-214 Active Drug and HD-IL-2**

The author mis-casts the receptor-bias inherent to NKTR-214 by pulling a partial figure from a published peer-reviewed publication (2017 Charych et al PLOS ONE). If the full figure is viewed, it is clear that NKTR-214 exhibits a biased receptor occupancy favoring the IL-2 beta-gamma receptor. As a result of its bias, direct comparison of exposure (AUC) from PK evaluation of NKTR-214 active drug vs HD-IL-2 is not relevant.

Further, HD-IL-2 clears rapidly and requires TID dosing. NKTR-214 has a prodrug design with a long half-life and q3 week dosing. Given the difference in mechanisms, an analysis of PD changes, notably the increases in lymphocyte levels after drug administration (or the desired effects of dosing) is the more important measure of adequate dose administration. Nektar has highlighted achievement of this desired effect in data presented at ASCO 2018 (refer to above section on Lymphocyte Effects).

### **Modified T Reg Increase in the Peripheral Blood and Not in the Tumor**

NKTR-214 was designed to avoid Treg accumulation in the tumor microenvironment. Our earliest preclinical studies demonstrated the ability to promote transient Treg elevations in the peripheral blood, but not the tumor. Inherent to its design, it is necessary to preserve some binding to IL-2R-alpha because that receptor is needed for T-cell priming reactions in the lymph node.

### **TIL Increases with NKTR-214**

The statements made around TIL increases with NKTR-214 are inaccurate; in the monotherapy trial, substantial increases in intratumoral CD8+ T cells were reported with no intratumoral CD4+ T regulatory expansion (SITC 2016, ASCO 2017 and SITC 2017). These data have been published at numerous congresses.

As stated above, NKTR-214 causes elevations in lymphocytes. These elevations are seen in blood and in tumor. The fact is that substantial lymphocyte increases with NKTR-214 were observed in the periphery so this can't be used to refute the reported TIL increases with NKTR-214 in the published data as the author attempts.

In the tumor, we have observed high concordance of TIL increases with monitoring using multiple methods; immunohistochemistry (IHC), fresh tissue flow cytometry, and T cell DNA analysis (a method that compares T cell-specific DNA vs non T cell-specific DNA to quantify the mass of T cells in tumor tissue) and all three methods have produced concordant results (manuscript in preparation). The use of several methods is critical as it important to observe concordance across these methods to increase confidence in the results.

The author uses older SITC 2016 data rather than referring to more recent publications. At ASCO 2018, Nektar reported IHC data on TIL elevations from 33 tumor biopsies in PIVOT patients at the RP2D. IHC is the most common method used in the historical literature for other agents and allows for comparison to nivolumab. The author uses a Tumeh paper to support an argument that TIL increases are observed with nivolumab. However, the author declines to point out that the Tumeh paper only demonstrates that select patients with elevated baseline TILs were able to experience a small 2-fold or less increase in TILs following nivolumab. The reality is that a 10-fold increase in TILs was observed following treatment with NKTR-214 even in patients with low baseline TILs which has not been shown with nivolumab. This is consistent with the mechanism of action of NKTR-214.

### **Comparison to epacadostat**

Unlike the epacadostat open label single arm trials, the PIVOT trial of NKTR-214 and Opdivo has independent blinded central data review for ORR. Nektar and BMS have stated there is a high concordance between the investigator-assessed and independent review. As the separate tumor cohorts are independently presented, such as at the upcoming SITC meeting, Nektar and BMS plan to present the investigator and independent ORR side-by-side for full transparency. The NKTR-214 and nivolumab PIVOT trial is enrolling Stage IV patients and did not enroll Stage III patients as the epacadostat studies did.

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Best,

Jennifer

Jennifer Ruddock

SVP, Investor Relations & Corporate Affairs

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