VIOLA ADVISORY

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1Q19 Nektar Therapeutics (NKTR) Summary: HOLD @ PT $30.00

TABLE 1: NKTR – Key Valuation Metrics

Mkt. Cap			Mkt. Price 6/7/19	Fwd. P/E	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
5.75B	NKTR	Nektar Therapeutics	33.00	(11.9)	-3.6%	Hold	30.00	179%	-9%

Source: Yahoo Finance and YCharts.com

Summary: **We believe the collaboration between Bristol-Myers Squibb (BMY) and Nektar Therapeutics (NKTR) may be in jeopardy as a result of the recent merger between Bristol Myers and Celgene Corp. and the less than stellar data readouts of the recent Pivot-02 clinical trial study.**

BMY recently announced that the current Chief Science Officer Tom Lynch, who supported the BMY-NKTR collaboration, will be leaving in 4 months having been replaced by Celgene's former R&D head Rupert Vessey. Moreover, BMY also announced the hiring of Samit Hirawat, former head of Novartis' Oncology Development, to be the new Chief Medical Officer in charge of BMY's drug development. Presumably, the new CSO and CMO heads of BMY could now prioritize a pipeline of research projects that they were developing at Celgene and Novartis, respectively.

Furthermore, we also believe that given the less than stellar data readout of the bempe + Opdivo combo study in the Pivot-02 clinical trial at ASCO 2019, there could be less of an incentive for BMY to continue its collaboration with NKTR. At most, the new management at BMY could limit the scope of the current clinical study to just a few indications instead of the several indications currently being pursued in the Pivot-02 study. The lack of support by BMY could hurt NKTR's chances of discovering a novel breakthrough blockbuster drug in the solid tumor space.

I. What makes NKTR's leading drug candidate, Bempegaldesleukin (NKTR-214), a novel therapy?

Nektar's leading drug candidate, bempegaldesleukin (aka "bempe," formerly NKTR-214) belongs to a class of drugs known as cytokines. Cytokines are messenger molecules that help control the growth and activity of immune system cells, as well as blood cells. Types of cytokines include interleukins (ILs) which help immune cells grow and divide more quickly and interferons (IFNs), which boost the ability of certain immune cells to attack cancer cells.

Cytokine therapies generated a lot of excitement last year as the combination of interleukin-2 (IL-2) based therapeutics and checkpoint inhibitors (PD-1/PD-L1 and CTLA-4) brought the possibility of turning non-responsive cancer treatments back to immunogenic (i.e., capable of stimulating an immune response). This promise of turning "cold" tumors back to "hot" tumors earned Nektar Therapeutics a $1.85 billion up-front payment from Bristol-Myers Squibb (BMY), who bought the rights for NKTR-214 in early 2018, a project working specifically to stimulate cell signaling via the cytokine interleukin-2 (IL-2) pathway.

BMY's leading checkpoint inhibitor, Opdivo (nivolumab), a PD-1 inhibitor, was slowly losing share to Merck's leading PD-1 inhibitor, Keytruda (pembrolizumab). BMY's strategy was to combine Nektar Therapeutics' bempe with Opdivo on several studies investigating various solid tumors. This currently serves as the

underlying basis for Nektar Therapeutics' Pivot-02 clinical trial which is investigating combo (bempe/Opdivo) and triplet (bempe/Opdivo/Yervoy) therapies in melanoma, renal cell carcinoma, non-small cell lung cancer, urothelial carcinoma, or triple-negative breast cancer.

II. Reasons for our Bearish Sentiment

1. Pivot-02 clinical trial results have been less than stellar

When the first Pivot-02 trial data for bempe + Opdivo was presented in SITC 2017, the results looked very promising. The objective response rate (ORR) came in at an impressive 64% as 7 out of 11 subjects showed either a partial or a complete response (see Table 2). However, given the small number of participants (11), the ORR was expected to decline once the size of the clinical trial grew.

TABLE 2: Pivot-02 Trial in 1st-line Melanoma (bempe + Opdivo)

Presentation	Data cut	No. of patients	Objective response rate	Complete response rate	ORR in PD-L1 negative
SITC 2017	Nov. 2, 2017	11	7 (64%)	2 (18%)	3/5 (60%)
ASCO 2018	May 29, 2018	28	14 (50%)	3 (11%)	5/11 (45%)
SITC 2018	Oct. 1, 2018	38	20 (53%)	9 (24%)	6/14 (43%)
ASCO 2019	Mar. 29, 2019	38	20 (53%)	13 (34%)	6/14 (43%)

Source: Company Presentation, VantageDaily 6/3/19

The second data cut at ASCO 2018 was a complete disappointment as the trial size more than doubled from 11 to 28 patients, but the ORR dropped to 50% and complete response rate (CRR) fell from 18% to 11%. Moreover, the ORR in the patient subgroup that were shown to be PD-L1 negative also fell from 60% to 45%, casting doubt as to whether bempegaldesleukin can turn cold tumors into hot tumors – a key principle behind the project.

The most recent Pivot-02 data presented at ASCO 2019 has so far failed to convince investors about the drug's overall efficacy. While the patient size has grown to 38, the ORR is still roughly at the same level at 53% (see Table 2). The bullish view is that 4 partial responders converted to complete responders bringing the CRR up to 34%. However, skeptics argue that the lack of new remissions has shown no improvement in the ORR where it remains at 53%.

Perhaps the most interesting data is the cross-trial comparison between the bempe + Opdivo combo and the Opdivo + Yervoy combo shown on Table 3. The ORR for both combos is roughly the same with 53% for the former and 58% for the latter. This is probably not the best data to support a continued collaboration between BMY and NKTR. Both Opdivo and Yervoy are BMY checkpoint blockade products that appear to perform better together than with NKTR's bempe checkpoint inhibitor.

TABLE 3: Cross-trial Comparison in 1st-line Melanoma

Product	Follow-up (years)	Objective response rate	Complete response rate
Keytruda	5	52%	25%
Opdivo	4	45%	18%
Opdivo + Yervoy	4	58%	21%
Bempegaldesleukin + Opdivo	1	53%	34%

Source: Leerink note, Vantage Daily 6/3/19

However, it should be noted that the two products cannot be compared directly since both studies have major differences. First, the Opdivo-Yervoy study enrolled 945 patients and had a follow-up period of 4 years. The bempe + Opdivo study only had 38 patients and a follow-up period of around 1 year. Second, the bempe + Opdivo study is a single-arm trial with no control (placebo) group. BMY and NKTR started a Phase 3 bempe + Opdivo study for untreated melanoma and is in the process of enrolling 764 subjects. The CRR for this new study may decrease further as the size of the patient population goes up.

2. New changes in BMY management could signal a shift in a BMY-NKTR collaboration

The merger between BMY and Celgene Corp. (CELG) is due to close in 2H19. On June 5, 2019, BMY announced new management changes post the Celgene acquisition. BMY's Chief Science Officer Tom Lynch will be leaving in four months and will be replaced by Celgene's R&D executive Rupert Vessey. Furthermore, BMY recruited Samit Hirawat, former head of Novartis' Oncology Development group to be the new Chief Medical Officer in charge of BMY's drug development group.

BMY's former CSO, Tom Lynch, was brought in to fix BMY's pipeline and to bring needed changes to BMY's research and development program as BMY started to lose market share to Merck in the PD-1 field – particularly in lung cancer. While Merck found a winning strategy in combining Keytruda with chemo, BMY pursued an approach using their lead CTLA-4 checkpoint inhibitor Yervoy, as well as focusing on high tumor mutational burdens in identifying the best patient population for their drug. That strategy failed and Merck continues to widen its lead with Keytruda.

To bring much needed changes to BMY's current R&D program, the new Chief Science Officer and Chief Medical Officer could begin to prioritize a pipeline of research projects that they were developing at Celgene and Novartis, respectively. This would jeopardize the status of the current BMY-NKTR clinical program or at best, limit the wide-ranging scope of investigations to just 1 or 2 indications with the highest possible chances of success. The narrowing of the scope of investigation may be justified by the less than stellar data readout of the bempe + Opdivo combo study in the Pivot-02 clinical trial at ASCO 2019.

Disclosure Information

Analyst Certification

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