VIOLA ADVISORY

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Nektar Therapeutics (NKTR): Bempegadesleukin ("bempeg", NKTR-214) - potential 1st Line Treatment in Metastatic Melanoma

TABLE 1: Nektar Therapeutics (NKTR) – Key Valuation Metrics

Mkt. Cap (US$)	Symbol	Company	Mkt. Price 05/08/20	P/S	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
3.8B	NKTR	Nektar Therapeutics	20.77	23.0	-0.9%	Buy	30.00	77%	44%

Source: Yahoo Finance, Ycharts.com, Viola Advisory LLC

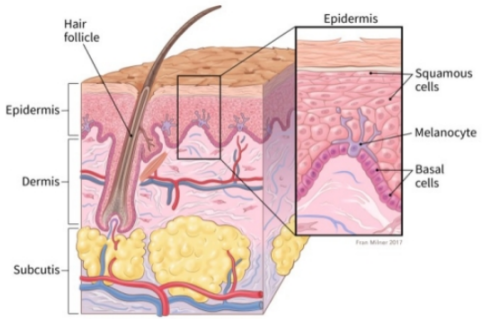
We believe the NKTR-214 plus Nivolumab combination therapy has a reasonable chance of being the next frontline therapy in advanced metastatic melanoma. NKTR-214 takes a cytokine approach to immunotherapy and is therefore different from the current standard of care immunotherapy which employs checkpoint inhibitors. Moreover, we believe that NKTR-214 is highly synergistic with nivolumab (PD-1 inhibitor) and could possibly produce better efficacy and safety signals. We believe this would be welcome news for oncologists and for patients with advanced metastatic melanoma whose disease is currently resistant to the standard of care treatment.

Summary of Contents

I. Melanoma Skin Cancer: Overview and Treatment Landscape

A. Where do Skin Cancers Start?

FIGURE 1: The 3 cell types in the epidermis



Source: American Cancer Society, melanoma

Melanoma is a type of skin cancer that develops when melanocytes (the cells that give the skin its tan or brown color) start to grow out of control. Most skin cancers start in the top layer of skin, called the epidermis (see Figure 1). There are 3 main types of cells in this layer:

- Squamous cells – these are flat cells in the upper (outer) part of the epidermis, which are constantly shed as new cells form.

- Basal cells – these cells are in the lower part of the epidermis, called the basal cell layer. These cells constantly divide to form new cells to replace the squamous cells that wear off the skin's surface. As these cells move up in the epidermis, they get flatter, eventually becoming squamous cells.
- Melanocytes – these are the cells that can become melanoma. They normally make a brown pigment called melanin, which gives the skin its tan or brown color. Melanin also protects the deeper layers of the skin from some of the harmful effects of the sun.

The epidermis is separated from the deeper layers of skin by the basement membrane. When a skin cancer becomes more advanced, it generally grows through this barrier and into the deeper layers.

Most melanoma cells still make melanin, so melanoma tumors are usually brown or black. But some melanomas do not make melanin and can appear pink, tan, or even white. Melanomas can develop anywhere on the skin, but they are more likely to start on the trunk (chest and back) in men and on the legs in women. The neck and face are other common sites.

Having darkly pigmented skin lowers your risk of melanoma at these more common sites, but anyone can get melanoma on the palms of the hands, soles of the feet, or under the nails. Melanomas in these areas make up a much larger portion of melanomas in African Americans than in whites. Melanoma is much less common than some other types of skin cancer. But melanoma is more dangerous because it is much more likely to spread to other parts of the body if not caught and treated early.

B. Changes in Melanoma Treatment Landscape: 2011 – Present

The treatment landscape for melanoma started to change when enhanced knowledge of the molecular pathogenesis of the disease led to the development of targeted therapies and immune-based therapies. Beginning in 2011, several BRAF/MEK inhibitors and checkpoint inhibitors were approved for the treatment of advanced melanoma (see Table 2).

TABLE 2: Changes in Melanoma Treatment Landscape: 2011-Present

	Approved Treatment	Brand	Manufacturer
2011	Ipilimumab (CTLA-4 inhibitor)	Yervoy	Bristol-Myers Squibb
	Vemurafenib (BRAF inhibitor)	Zelboraf	Roche
2013	Dabrafenib (BRAF inhibitor)	Tafinlar	Novartis
	Trametinib (MEK inhibitor)	Mekinist	GlaxoSmithKline
2014	Dabrafenib + Trametinib		
	Pembrolizumab (PD-1 inhibitor)	Keytruda	Merck
	Nivolumab (PD-1 inhibitor)	Opdivo	Bristol-Myers Squibb
2015	Ipilimumab + nivolumab		
	TVEC (oncolytic virus therapy	Imlygic	Amgen
	Cobimetinib (MEK inhibitor) + Vemurafenib	Cotellic	Roche
2018	Binimetinib (MEK inhibitor) + Encorafenib (BRAF inhibitor)	Mektovi Braftovi	Pfizer Pfizer

Note: IL-2 indicates interleukin 2; TVEC, talimogene laherparepvec.

Source: 16th Annual International Symposium on Melanoma and Other Cutaneous Malignancies, February 2020

Prior to 2011, the prognosis for patients with advanced melanoma was poor, with limited response to medical management. Dacarbazine was the treatment of choice for advanced/metastatic melanoma, but the efficacy of dacarbazine was low, with no confirmed survival benefit and transient responses observed in about 10% to 20% of patients. The shift to treatment with high-dose interleukin 2 was met with overall response rates of roughly 16% and a complete response rate of 6%.

Starting in 2011, progress in the treatment of advanced melanoma has markedly improved survival outcomes. The availability of new systemic therapies including ipilimumab (CTLA-4 inhibitor), nivolumab (PD-1 inhibitor) and pembrolizumab (PD-1 inhibitor), as well as BRAF and MEK inhibitors (dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) has transformed the treatment of this disease. Figure 2 shows the clinical trial results of the three BRAF/MEK inhibitor combos that are currently being used in advanced melanoma.

FIGURE 2: Clinical trial results of targeted therapies (BRAF/MEK inhibitor combos) in advanced melanoma

Agent(s)	Dab/Tram[1] (n = 352)	Vem[1] (n = 352)	Vem/Cobi[2,3] (n = 247)	Vem[2,3] (n = 248)	Enco/Bin[4,5] (n = 192)	Vem[4,5] (n = 191)
ORR (%)	64	51	68	45	64	41
PFS (median, mo)	11.4	7.3	12.3	7.2	14.9	7.3
HR; 95% CI; *P* value	0.56; 0.46-0.69; *P* <.001		0.58; 0.46-0.72; *P* <.0001		0.54; 0.41-0.71; *P* <.001	
OS (median, mo)	72%**	65%**	22.3	17.4	36.8	16.9
HR; 95% CI; *P* value	0.69; 0.53-0.89; *P* = .005		0.70; 0.55-0.90; *P* = .005		0.61; 0.47-0.79; *P* <.0001	

**12-month landmark survival.

[1]Robert C et al. *N Engl J Med*. 2015; [2]Larkin GV et al. *N Engl J Med*. 2014; [3]Ascierto PA et al. *Lancet Oncol*. 2016; [4]Dummer R et al. *Lancet*

Note: Dab = Dabrafenib (BRAF inhibitor); Tram = Trametinib (MEK inhibitor); Vem = Vemurafenib (BRAF inhibitor); Cobi = Cobimetinib (MEK inhibitor); Enco = Encorafenib (BRAF inhibitor); Bin = Binimetinib (MEK inhibitor).

Source: 16th Annual International Symposium on Melanoma and Other Cutaneous Malignancies, February 2020

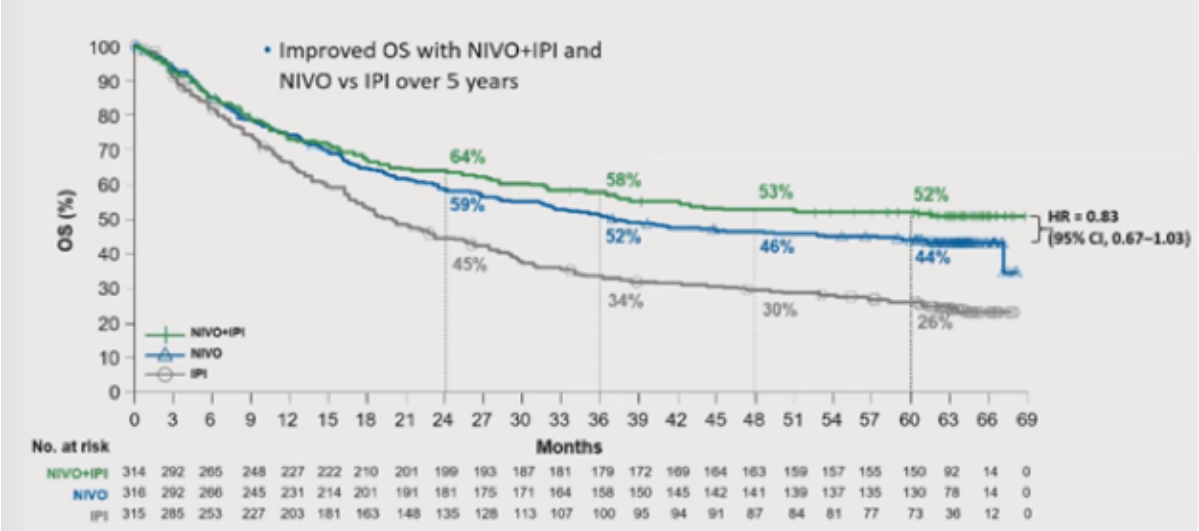
The BRAF/MEK inhibitor combo treatments show significant improvements across all survivor and efficacy metrics, compared to the older therapies that were in use prior to 2011. However, an interesting outcome of the trial results shows that there does not seem to be any comparable differences between the 3 targeted therapies in terms of their efficacies - ORR, PFS and HR. Therefore, in terms of selecting which treatment to recommend, clinicians may have to look at the differences in toxicity and delivery methods (how many pills per day and how often) of the three therapy treatments.

II. Bempegadesleukin (NKTR-214): Potential 1st Line Treatment in Metastatic Melanoma

A. Significant Advances in Immunotherapy

New systemic therapies in immunotherapy treatment, particularly with nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) have resulted in longer overall survival and progression-free survival outcomes. In a 5-year (60 months) follow-up analysis of the Phase 3 CheckMate 067 trial, a higher overall survival rate (OS) was produced by the immunotherapy treatment combo of nivolumab plus ipilimumab (52%) versus nivolumab (44%) or ipilimumab (26%) among patients with advanced melanoma (see Figure 3).

FIGURE 3: Five Year Overall Survival (OS): CheckMate 067 – Nivo+Ipi vs. Nivo vs. Ipi



Source: 16th Annual International Symposium on Melanoma and Other Cutaneous Malignancies, February 2020

Table 3 also shows additional data from the 5-year follow up study which shows significantly higher PFS and efficacy rates (ORR, CR) for the nivo+ipi combination therapy than just the single therapy agents of nivolumab and ipilimumab.

TABLE 3: Five Year Efficacy and Survival Rates: (OS, ORR, PFS): CheckMate 067 – Nivo+Ipi vs. Nivo vs. Ipi

Metric	Nivolumab + Ipilimumab	Nivolumab	Ipilimumab
	(n=314)	(n=316)	(n=315)
Overall Survival (OS):	52%	44%	26%
Progression Free Survival (PFS):	36%	29%	8%
Overall Response Rate (ORR):	58%	45%	19%
- Complete Response (CR):	22%	19%	6%
- Partial Response (PR):	36%	26%	13%
Hazard Ratio (HR):	0.52	0.63	--
Progressive Disease:	24%	38%	50%

Source: Larkin, J., et.al. Five-Year Survival with Combined Nivoluma and Ipilimumab in Advanced Melanoma, NEJM, Oct. 11, 2019

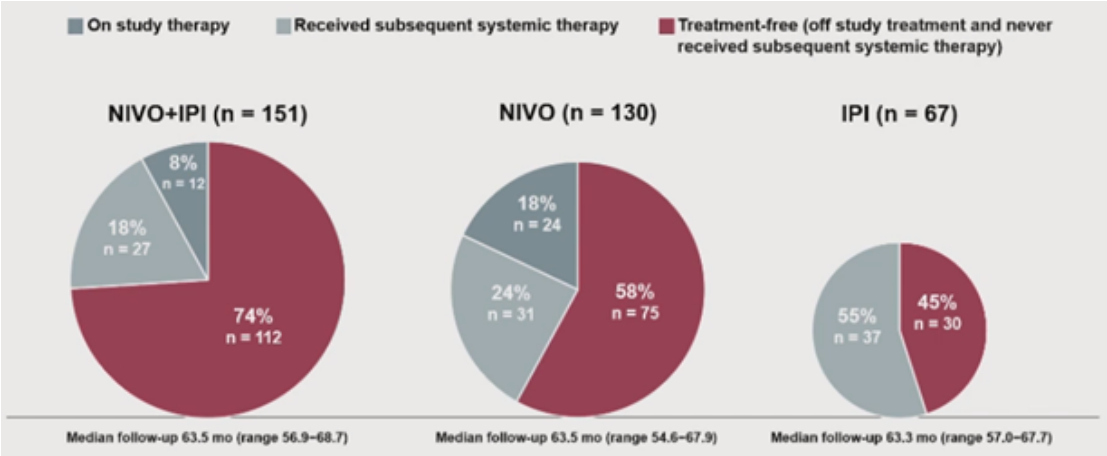
For example, 36% of patients on the nivo+ipi treatment arm were still alive with no signs of the advanced melanoma progressing (PFS) after 5 years versus 29% of patients receiving nivolumab as a single agent and 8% of patients being treated with just ipilimumab. Furthermore, 58% of patients receiving the nivo+ipi treatment combo saw their tumors decrease in size or completely disappear (ORR) with 22% of patients showing no detectable signs of advanced melanoma (CR) after 5 years of treatment. This stands in contrast to the 45% ORR and 19% CR rate of nivolumab and 19% ORR and 6% CR rate of ipilimumab as single therapy agents.

One last item to note is that despite advances in immunotherapy, metastatic melanoma remains a difficult disease to treat. Table 3 shows the percentage of patients with progressive disease in each of the 3 treatment arms. For example, 24% of patients in the nivo+ipi treatment group continued to show signs of disease progression after a 5 year follow-up, while 38% in the nivo treatment group and 50% in the ipi treatment group also showed no response (i.e., patients were refractory) to treatment.

Figure 4 shows how many patients in each treatment arm are treatment-free after the 5-year follow-up period. This is considered a QOL (quality-of-life) metric and is monitored by 3rd party payers and regulatory agencies who determine whether a treatment is covered under their formulary. It is also used by pharma companies to justify the high cost for their oncology drugs.

Figure 4 shows that for patients in the nivo+ipi treatment group whose average duration of treatment was 3.6 months, 74% were treatment-free after 5 years of follow-up. This patient group was no longer receiving clinical trial therapy and had never received subsequent systemic therapy (i.e., no treatment) after the initial treatment regimen. However, 18% of patients were receiving subsequent systemic therapy and 8% were still receiving trial therapy after 5 years.

FIGURE 4: CheckMate 067: More patients alive and treatment-free at 5 years with Nivo + Ipi combo treatment



Source: 16th Annual International Symposium on Melanoma and Other Cutaneous Malignancies, February 2020

In the nivo treatment group (average treatment duration = 7.6 months), 58% of patients were treatment-free and not receiving any treatment while 24% were still on subsequent systemic therapy and 18% were still on trial therapy after 5 years. In the ipi group (average treatment duration = 3.7 months), 45% were treatment free while 55% were still receiving subsequent systemic therapy. Figure 4 shows a clear QOL benefit for patients in the nivo+ipi treatment group as a higher proportion of these patients were alive and treatment-free at 5 years.

B. Bempegadesleukin (NKTR-214) plus Nivolumab (Opdivo) Combination

How NKTR-214 works. NKTR-214 is a type of immunotherapy, that is, it acts by boosting the immune response to encourage the patient's own body to fight cancer. The immune system is capable of identifying and destroying infected or abnormal cells, including cancer cells. One way it does this is by producing "tumor-infiltrating lymphocytes" (TILs), a type of immune cell capable of moving into a tumor and targeting the cancerous cells.

Two types of TILs are T-cells and natural-killer (NK) cells. NKTR-214 stimulates an increased immune response by expanding the numbers of activated T-cells and NK cells available to attack the tumor. TILs produce a protein called interleukin-2 receptor (IL-2R), which can send a signal to increase their production. This signal is sent when a particular cell signaling molecule, called interleukin-2 (IL-2), binds to IL-2R and activates it.

NKTR-214 is a "prodrug," as it is delivered to the body in an inactive form. The body breaks down the prodrug to produce a signaling molecule that is biased toward binding to and activating CD122, a subunit of IL-2R. When NKTR-214 binds to CD122, it triggers an increase in the number of TILs. This mobilization of TILs will heighten the immune response against a tumor and result in a reduction in tumor size. In addition, NKTR-214 also increases the levels of the PD-1 protein on T-cells and PD-L1 on cancer cells, which could boost the effectiveness of immune checkpoint inhibitors like nivolumab.

Safety. NKTR-214 is a cytokine resembling interleukin that is structured to side-step some of the toxicity problems found with interleukein-2 (IL-2). High-dose IL-2 is given to patients with melanoma and renal cell carcinoma. It is usually delivered in the intensive care unit and requires very intensive monitoring of the patient because of the high degree of toxicities found in these drugs.

NKTR-214 is structured with pegylation to minimize toxicity. The pegylation minimizes the activation of NKTR-214 with the alpha-subunit of the IL-2 receptor. It has been found that activation of that subunit causes some of the major toxicities seen with high-dose IL2. In addition, the pegylation also allows NKTR-214 to be given every 2 to 3 weeks which is more convenient for the patient.

PIVOT-02 Clinical Trial Results: NKTRA-214 plus Nivolumab vs. Nivolumab alone

The FDA granted a breakthrough therapy designation to the combination of NKTR-214 and nivolumab (Opdivo) for the treatment of patients with previously untreated unresectable or metastatic melanoma. The designation is based on results from a cohort of the ongoing Phase I/II PIVOT-02 trial, where the combination of NKTR-214 and nivolumab led to an overall response rate (ORR) of 53% by independent radiology review, which included a 34% complete response (CR) rate (see Table 4).

TABLE 4: PIVOT-02 Clinical Trial: NKTR-214 + Nivolumab vs. Nivolumab

Metric	Phase 1: dose escalation	Phase 2: dose expansion
	(n= 11)	(n= 41)
Overall Response Rate (ORR):		
- Overall:	64%	53%
- PD-L1 -negative:	60%	43%
- PD-L1 -positive:	67%	62%
- PD-L1 -unknown	n/a	33%
Complete Response (CR):	n/a	34%
Disease Control Rate (DCR):	91%	74%
Median Duration of Response (mDOR):	n/a	NR; but 80% had ongoing response at a median 12.7 mos. of follow-up
Median Time to Response:	n/a	2.0 months

Note: NR = not yet reached; n/a = not available.

Source: TargetedOncology, 8/1/19, www.targetedonc.com

Safety profile for Phase 2 PIVOT-02 trial

Grade 3/4 treatment-related adverse events: reported in 6 patients and included atrial fibrillation (4.9%), hyperglycemia (2.4%), and acute kidney injury, blood creatinine increase, dyspnea, hypernatremia, and hypoxia (n=1 each).

Grade 1/2 treatment-related adverse events: Flu-like symptoms (80.5%), rash (70.7%), fatigue (65.9%), pruritus (48.8%), nausea (41.5%), arthralgia (36.6%) and myalgia (31.7%). A total of 9.8% of patients discontinued therapy due to a treatment-related adverse event.

Phase 3 PIVOT-1O 001 Clinical Trial (ongoing): Positioning NKTR-214 + Nivolumab as 1st Line Treatment

Nivolumab (Opdivo) is currently the standard of care treatment for patients with unresectable or metastatic melanoma. In addition, nivolumab in combination with ipilimumab (Yervoy) is also front-line therapy for the treatment of patients with unresectable or metastatic melanoma. The ongoing Phase 3 PIVOT-1O 001 trial is evaluating NKTR-214 in combination with nivolumab versus nivolumab alone as front-line therapy for patients with advanced melanoma.

The Phase 3 trial intends to accrue 764 patients globally in a 1:1 unblinded randomized fashion. After 480 patients are randomized, researchers will examine the overall response rate. The co-primary endpoints are progression-free survival (PFS) and overall survival.

Success Criteria for Phase 3 PIVOT-1O trial. For the Phase 3 trial, investigators are hoping to increase the response rate by at least 21% compared with nivolumab alone. Investigators will consider the trial a success if the hazard ratio is met at 0.7, which means a 30% improvement on historical PFS with nivolumab by itself. Furthermore, investigators are also hoping that the NKTR-214 + nivolumab combination will offer more efficacy with less toxicity compared to the existing standard of care.

We believe an ORR of 65% or greater as the criteria for success set by the trial investigators is a bit on the high side given that the ORR for Nivolumab + Ipilimumab is 58% and the ORR for nivolumab alone is 45% (see Table 3). Still the NKTR-214 + Nivo combo did achieve an ORR of 64% in the Phase 1 dose escalation study.

However, we believe the ORR target of 65% could still be achievable depending on how the clinical trial is designed. If a higher proportion of trial patients express PD-L1-positive biomarkers, then hitting the 65% ORR target is realistic, considering the 67% and 62% ORR in the PD-L1-positive cohort for previous Phase 1 and Phase 2 trials (see Table 4). Moreover, the ORRs achieved by the targeted therapies (BRAF/MEK inhibitor combos) had a range of 64% to 68% in advanced melanoma (see Figure 2).

However, we also believe that safety signals are just as crucial as ORR signals when comparing treatments for advanced metastatic melanoma patients. We believe that NKTR-214 has a superior safety profile compared to other immunotherapy and targeted therapy treatments. Furthermore, patients also value convenience when deciding on which treatment to take. In the long term, more convenience translates to greater adherence by patients to their treatment schedule.

Disclosure Information

Analyst Certification

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