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POC FOR CYTOKINES

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A body of clinical evidence is emerging that two different approaches to immune-stimulating cytokine therapies could increase efficacy of PD-1 inhibitors in both hot and cold tumors.

Oncologists who spoke to BioCentury said, taken together, data presented for Nektar Therapeutics' NKTR-214 at the American Society of Clinical Oncology (ASCO) meeting and data published on NantWorks LLC's N-803 suggest that cytokines that signal through a common heterodimeric receptor can increase responses to PD-1 inhibitors beyond what would be expected from the inhibitors alone.

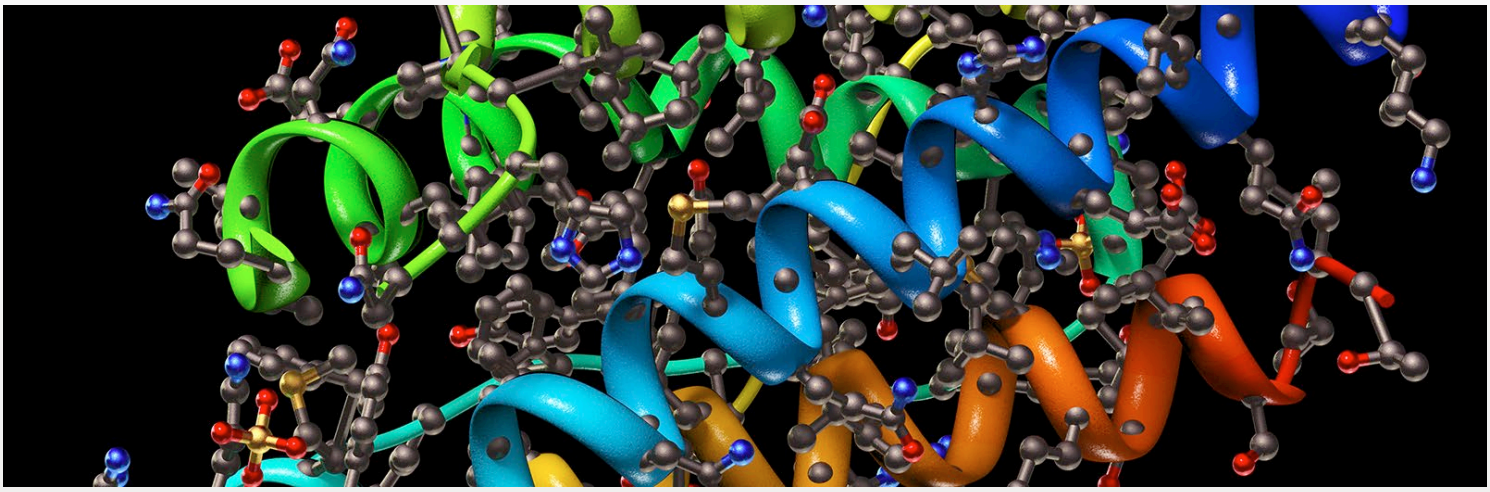
The doctors cautioned against reading too much into the apparent decline in response rates to NKTR-214 as the trial progresses, and pointed instead to multiple signs in the data that the product is having the biological effect expected of IL-2.

Both candidates signal through the intermediate-affinity IL-2 receptor, which comprises the IL-2 receptor beta chain (CD122; IL2RB) and gamma chain (CD132; IL2RG).

Selective activation of the intermediate-affinity receptor triggers activation and proliferation of CD8+ T cells and NK cells needed to carry out an anticancer response, but spares Treg expansion and toxicities mediated by the high-affinity IL-2 receptor.

NKTR-214 is an IL-2 that contains six conjugated PEG moieties that extend half-life and release over time in a way that biases the molecule to signal through the intermediate-affinity receptor instead of the high-affinity receptor.

N-803 is a mutant version of IL-15 complexed to an Fc fusion protein of IL-15 receptor alpha chain (IL-15RA). IL-15 signals through the intermediate-affinity IL-2 receptor only in the presence of IL-15RA. Fusing IL-15 to IL-15RA keeps the needed receptor close at hand and improves the construct's stability. NantWorks



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gained N-803 through last year's acquisition of Altor Bioscience Corp. for an undisclosed sum.

The oncologists did say that the bigger opportunity for these candidates may be in tumor types that have not typically responded well to PD-1 monotherapy. Early data showed the cytokines can flip tumors from PD-L1-negative to -positive, leading to responses comparable to those in tumors that were PD-L1-positive at baseline.

But Nektar and partner Bristol-Myers Squibb Co. will move into Phase III first in melanoma with NKTR-214 plus Opdivo nivolumab, followed by first-line renal cell carcinoma (RCC) and cisplatin-ineligible urothelial carcinoma. These are indications where checkpoint inhibitors are approved and produce substantial responses, which may make demonstrating an additive effect for the cytokine a high hurdle to clear.

N-803 is in Phase II development for non-small cell lung cancer (NSCLC), including a Phase II study in NSCLC that has progressed after responding to a PD-1 inhibitor. It also is in testing in combination with other immunotherapies in bladder, pancreatic, head and neck, breast, colorectal, liver, chordoma and hematologic cancer indications.

Posters with early data for Armo Biosciences Inc.'s pegilodecakin (AM0010) showed an alternative cytokine approach could also be effective in augmenting the efficacy of PD-1 inhibitors.

Pegilodecakin is a long-acting, pegylated form of recombinant IL-10 that stimulates a different population of cancer-fighting immune cells than are stimulated by cytokines that signal through the IL-2 intermediate-affinity receptor.

Armo is being acquired by Eli Lilly and Co. in a $1.6 billion deal expected to close this quarter.

While Armo's data for pegilodecakin plus PD-1 inhibitors also showed better response rates than would be expected for PD-1 inhibitor monotherapy, the oncologists who spoke with BioCentury wanted to see more data on how the molecule achieves its effects.

Because endogenous IL-10 has an immunosuppressive profile, they were unsure how to interpret the clinical results in cancer. In the absence of a full biological explanation for how AM0010 fights tumors, they had less confidence in its ability to potentiate checkpoint inhibitors without confirmation in larger studies.

Data for two Phase II studies of pegilodecakin in combination with anti-PD-1 mAbs are expected late this year.

Merck KGaA presented yet another alternative approach at ASCO that involved blocking rather than stimulating cytokine signaling (see "Two in One").

(BIO)LOGICAL RATIONALE

The oncologists thought IL-2-based therapy was among the most logical choices for combination with PD-1 inhibitors.

As a monotherapy, naked IL-2 has produced complete and durable responses in subsets of patients with RCC or melanoma, but is rarely used because few patients are healthy enough to tolerate its potentially fatal side effects.

"In terms of scientific rationale, there's probably no better immune stimulant than a gamma chain cytokine, like an IL-2- or IL-15-based agent," Vamsidhar Velcheti, associate director of the Center for Immuno-Oncology Research at the Cleveland Clinic Taussig Cancer Institute, told BioCentury.

"IL-2 is a T cell growth factor, and CTLA-4 is a negative checkpoint, just like PD-1. A negative checkpoint will not help if you don't have enough effector cells," he added.

In a similar vein, Chairman and CEO Patrick Soon-Shiong said NantWorks bought Altor because he believes IL-15 is a "master switch" that can break immune tolerance to cancer by simultaneously preventing Treg activation, while activating T cells and NK cells.

"Until you overcome inhibition, you can't activate the activators," he said.

While Nektar's June 2 presentation at ASCO disappointed investors, the doctors said it provided proof of concept. In the ongoing Phase Ib/II PIVOT study, responses to NKTR-214 plus Opdivo were higher than historical response rates to checkpoint monotherapy in first-line melanoma, urothelial carcinoma and NSCLC, and for Opdivo plus Yervoy ipilimumab in first-line RCC.

The combination met the criterion for advancement into Phase III in first-line melanoma, with more than 10 responders in stage 1 of the study; in cisplatin-ineligible urothelial carcinoma, with more than four responders in stage 1; and in first-line RCC with more than 10 responders in stages 1 and 2 combined.

PIVOT is powered at 90% to show 95% probability of superior response rates for NKTR-214 plus Opdivo compared with Opdivo monotherapy, based on assumptions of Opdivo monotherapy's efficacy in each tumor type.

After a dose-finding portion of the trial, PIVOT used a Fleming two-stage design in which stage 1 is fully enrolled before enrolling the stage 2 cohort. The eligibility criteria are the same for both stages.

Response rates were evaluated first in stage 1 patients, and then in the pooled population of stage 1 and stage 2 patients. If an indication met or exceeded the response rate threshold either in stage 1, or across stages 1 and 2, it would trigger the start of a Phase III study in that indication.

Investors seemed alarmed that the study showed declining response rates in stage 2 compared with stage 1, shaving $6.5 billion off Nektar's market cap on June 4, the first trading day after the presentation. Response rates were 85% in stage 1 in melanoma, but 50% across stages 1 and 2. In RCC, rates declined from 64% to 46%. The stage 1 urothelial carcinoma response rate was 60%; stage 2 is still enrolling (see "Emerging Evidence for Cytokines").

Part of the reason could be that the patients in stage 2 had not been treated as long as those in stage 1. Swimmer plots presented at a June 6 investor conference showed several melanoma and RCC patients with stable disease had not yet been treated for as long as some patients in stage 1 had taken to respond.

For example, in RCC the earliest responses tended to be recorded around day 50 — the first time the patients were scanned for responses — but two patients had their first response shortly after 100 days at the second scan, and four patients had a first response after day 150, corresponding to a third or later scan.

At the May 29 cutoff, three stable disease patients had not yet been treated long enough to receive a third scan.

"We'd expect that a portion of those patients would still be in the response range because we find that as patients stay on, they just have a higher and higher chance of responding over time," Nektar's SVP of Research and CSO Jonathan Zalevsky told BioCentury.

He added that unless patients decline rapidly on NKTR-214, "all our data suggest they are likely to benefit with deepening responses and increasing responses over time."

For instance, at the Society for Immunotherapy of Cancer (SITC) meeting in November, Nektar reported that 46% of patients in the RCC dose-escalation cohort had responded. That cohort's response rate had increased to 71% by the May 29 cutoff for ASCO.

TAKING IT ALL IN

Doctors who spoke to BioCentury looked at the totality of evidence, rather than focusing on the response rates.

They said it is unwise to compare response rates in such small study cohorts, where one or two patients could cause a change of 10% or more.

They also noted that response rates often decrease over the course of a clinical development program, and even a single clinical trial.

"The further you go on, the larger the sample size, the more likely it is that the responses get deflated. That's a very common phenomenon and why we don't overinterpret small Phase I or Phase II study data," said Heather McArthur, medical director of breast oncology at Cedars-Sinai Medical Center.

City of Hope Clinical Professor of Medical Oncology Kim Margolin added that enrollment of sicker patients could be a factor in the declining response rates, because investigators may be more likely to refer patients to a study if they hear it is testing an active regimen.

"They're a little more beat up, with more comorbidities, more disease burden, or higher LDH — all the things that can affect the outcome, even though they don't make the patients ineligible," she said.

> "ALL OUR DATA SUGGEST THEY ARE LIKELY TO BENEFIT WITH DEEPENING RESPONSES AND INCREASING RESPONSES OVER TIME."
>
> JONATHAN ZALEVSKY, NEKTAR

Margolin also noted that the fever and hypotension side effects seen in the trial, which were manageable, are signals of IL-2 activity.

"It has a little of that IL-2-like effect just to tell you that you're on target," she said.

In addition, paired biopsies showed that 53% of evaluable patients who were PD-L1-negative at baseline were PD-L1-positive three weeks later, which suggested that tumors were defending themselves against NKTR-214 in a way that PD-1 inhibitors could counteract.

Patients whose tumors became PD-L1-positive after treatment had responses similar to those whose tumors were PD-L1-positive at baseline.

Velcheti said PD-L1 up-regulation leading to responses was another form of proof of concept for the combination.

The doctors saw further proof of concept for the approach in Phase Ib data for N-803 in NSCLC that were published in *Lancet Oncology* on April 5.

That article reported that six of 21 patients (29%) had an objective response to N-803 plus Opdivo. Median progression-free survival (PFS) was 9.4 months and median overall survival (OS) was 17.4 months.

Eleven of those patients had progressed on a PD-1 inhibitor. Three patients had partial responses on the combination and seven had stable disease.

Three of 10 PD-L1-negative patients responded, as did three of four patients with >50% PD-L1 expression.

Velcheti said N-803's effects on the activity and levels of NK cells and CD8+ T cells, plus activity in PD-L1-negative patients, add to the body of evidence for gamma chain cytokines.

"I think this is as clear proof-of-concept data as you can get," he said.

Velcheti and Margolin have been investigators on clinical trials of N-803. McArthur does not have investigational experience with any of the cytokines discussed in this story.

WHAT NEXT?

Zalevsky said the Phase III melanoma study will enroll nearly 800 patients stratified by tumor stage, PD-L1 status and BRAF status. He said overall response rate (ORR), PFS and OS are co-primary endpoints, and the analysis plan includes an early look at ORR that could support an application for accelerated approval.

Atlas Venture's Michael Gladstone said Nektar could face an uphill battle trying to show superiority in melanoma. "Melanoma has the highest monotherapy response rates to PD-1, so it's particularly difficult to

EMERGING EVIDENCE FOR CYTOKINES

Four cytokine-based therapies had data at or just before this year's **American Society of Clinical Oncology** (ASCO) meeting in Chicago. Three are engineered forms of endogenous cytokines intended to stimulate growth of immune cells. A fourth from **Merck KGaA** (Xetra:MRK) sequesters an immunosuppressive cytokine. Presentations from the ongoing PIVOT study of NKTR-214 from **Nektar Therapeutics** (NASDAQ:NKTR) and partner **Bristol-Myers Squibb Co.** (NYSE:BMY) included updated data from the initial dose-escalation phase of the study in melanoma, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC) cohorts, as well as data from one or both of the study's subsequent two stages in melanoma, RCC and urothelial carcinoma. The urothelial carcinoma stage 2 cohort is still enrolling, while the NSCLC stage 1 cohort has not matured enough for evaluation. ORR = overall response rate; CR = complete response rate; PD-L1+ = expression ≥1%; PD-L1- = expression <1%; PFS = progression-free survival in months; OS = overall survival in months; NA = not applicable or not reported; (A) Includes unconfirmed complete responses; (B) PD-L1 > 50%; (C) PD-L1 1-49%; (D) Pooled data from Opdivo and Keytruda arms; *Source: ASCO presentations, Lancet Oncology*

Company	Product	Target	Trial	Combo partner	Indication/arm	ORR	CR (A)	PD-L1+ ORR	PD-L1- ORR	PFS	OS
Nektar Therapeutics (NASDAQ:NKTR)	NKTR-214	Intermediate-affinity IL-2 receptor comprising IL-2 beta chain (CD122; IL2RB) and gamma chain (CD132; IL2RG) receptors	PIVOT Phase Ib/II	Opdivo nivolumab	First-line melanoma, dose-escalation phase (n=11)	64%	27%	67%	60%	NA	NA
					First-line melanoma, study stages 1 & 2 (n=28)	50%	11%	62%	42%	NA	NA
					First-line renal cell carcinoma (RCC), dose-escalation phase (n=14)	71%	7%	80%	63%	NA	NA
					First-line RCC, study stages 1 & 2 (n=26)	46%	0%	29%	53%	NA	NA
					First-line cisplatin-ineligible urothelial carcinoma, study stage 1 (n=10)	60%	20%	60%	60%	NA	NA
					First- or second-line non-small cell lung cancer (NSCLC), dose-escalation phase (n=5)	60%	40%	NA	60%	NA	NA
NantWorks LLC	N-803 (ALT-803)	Intermediate-affinity IL-2 receptor	Phase Ib	Opdivo nivolumab	NSCLC (n=21)	29%	0%	75% (B); 0% (C);	30%	9.4	17.4
Merck & Co. Inc. (NYSE:MRK) / **Armo BioSciences Inc.** (NASDAQ:ARMO)	Pegilodecakin	IL-10 receptor	Phase I	Opdivo nivolumab	RCC (n=26)	39%	4%	NA	NA	10.1	NA
				Keytruda pembrolizumab	RCC (n=8)	50%	25%	NA	NA	16.7	NA
				Opdivo nivolumab	NSCLC (n=22)	41%	NA	80% (B); 67% (C) (D)	33% (D)	NA	NA
				Keytruda pembrolizumab	NSCLC (n=5)	40%	NA			11	32.2
Merck KGaA (Xetra:MRK)	M7824	PD-L1 and transforming growth factor (TGF) beta	Phase I	Monotherapy	NSCLC (n=80)	24%	1%	41%	NA	2.1	12.2
			Phase I	Monotherapy	HPV-associated cancers (n=17)	35%	12%	NA	NA	NA	NA
					HPV-positive subgroup (n=12)	42%	8%	NA	NA	NA	NA

TWO IN ONE

While the biggest cytokine story at the American Society of Clinical Oncology meeting focused on immune-stimulatory molecules, Merck KGaA presented data showing that blocking cytokine activity in the tumor environment along with PD-1 could give better response rates than PD-1 monotherapy.

The company reported that in a Phase I expansion cohort in second-line non-small lung cancer (NSCLC), M7824 at the recommended Phase II dose produced responses in 11 of 27 (40.7%) patients with ≥1% PD-L1 expression and five of seven (71.4%) patients with ≥80% PD-L1 expression.

M7824 is a fusion protein of an anti-PD-L1 mAb and two extracellular domains of TGF beta receptor II (TGFbeta-RII; TGFBR2). M7824 both blocks PD-1 signaling and prevents TGF beta signaling through sequestration.

Response rates to Keytruda pembrolizumab monotherapy are 18-19% in previously treated NSCLC patients with ≥1% PD-L1 expression. Merck plans to study M7824 in earlier lines of NSCLC therapy.

An oral abstract presented on Saturday, June 2 showed M7824 produced responses in six of 17 (35%) patients with HPV-associated cancers, and in five of 12 (42%) with HPV+ cancers. The data came from a retrospective analysis of an ongoing Phase I dose-escalation study of M7824 in patients with advanced solid tumors.

At the presentation, Chief of the NCI Genitourinary Malignancies Branch James Gulley said PD-1 monotherapies produce response rates around 16-21% in HPV-associated cancers. NCI is conducting a Phase II study of M7824 in HPV-associated cancers.

EVP and Global Head of R&D Luciano Rossetti said TGF beta it has multiple protumor and immunosuppressive effects. It promotes metastasis and angiogenesis, regulates the epithelial-to-mesenchymal transition, and may prevent other therapies from reaching tumors. He said the fusion protein modality allowed Merck to optimize the stoichiometry of the two moieties and ensures that both are acting near tumors.

City of Hope Clinical Professor of Medical Oncology Kim Margolin told BioCentury that animal models suggest that dual targeting is more effective than giving two agents against the same targets in combination.

"Almost always when two antibodies that block two molecules are combined, it's not as good as a bispecific that blocks both at the same time and same place," she said.

She added that keeping the TGF beta inhibitor portion within the tumor microenvironment could help prevent development of autoimmunity, a rare but potentially serious side effect of targeting TGF beta.

Merck plans to present additional data in NSCLC and other tumor types from the Phase I study in October at the European Society for Medical Oncology meeting.

— Emily Cukier

discern in that setting whether a second therapy is adding something," he said.

And the doctors thought that the combination could be more clinically valuable elsewhere.

Velcheti, who treats lung cancer, hopes to see it studied there. And McArthur hopes to be able to use it for her breast cancer patients.

PIVOT's cohorts in NSCLC and triple-negative breast cancer (TNBC) are ongoing, and had not met success or futility criteria at the May 29 cutoff.

The oncologists' hope is that in those indications NKTR-214 can convert tumors from PD-L1-negative to -positive. Velcheti said the NSCLC data were impressive in those patients, even though the numbers were small. Three of five patients in a dose-escalation cohort responded, including two complete responses. All five had PD-L1 expression <1%.

"We typically don't see such very deep responses in PD-L1-negative patients, and they seem to deepen over time," said Velcheti.

He also wanted to see the combination studied in tumors that become resistant to PD-1 agents. He said tumor cells can acquire resistance if they stop expressing major histocompatibility complex (MHC) — which NK cells expanded by NKTR-214 could sniff out and destroy.

Nektar plans to report updated data from the PIVOT cohorts at SITC this November or other scientific meetings.

IMMUNE ENIGMA

Armo's pegilodecakin works through a distinct and more selective immune mechanism, and also reported responses at ASCO.

In a Saturday poster presentation, Armo reported data from RCC patients receiving pegilodecakin with or without Opdivo or Merck & Co. Inc.'s Keytruda pembrolizumab in a Phase I trial. ORRs were 41% among 34 evaluable patients receiving either combination and 25% among 16 patients receiving pegilodecakin alone. Patients treated with combination therapy had received 0-5 prior lines of therapy, with a median of 2.

Opdivo's label notes the ORR for Opdivo monotherapy in second-line and later RCC is 21.5%. The label does not contain monotherapy data in first-line. But the ORR for Opdivo plus Yervoy in first-line RCC is 41.6%.

An ASCO abstract this year reported a 33.6% response rate for first-line clear cell RCC patients receiving Keytruda. In Armo's trial, 87% of RCC patients had the clear cell form.

On Sunday, the company reported data from the same trial in patients with NSCLC. ORRs were 41% among 27 evaluable patients receiving either combination. There were no responses in patients receiving

pegilodecakin alone. Patients treated with the combination had received 0-5 prior lines of therapy, with a median of 2.

In the second-line and later setting, Opdivo monotherapy led to an ORR of 19% in non-squamous NSCLC and 20% in squamous NSCLC. Keytruda monotherapy has produced response rates of 25% in treatment-naïve NSCLC and 18% in second-line NSCLC.

"UNTIL YOU OVERCOME INHIBITION, YOU CAN'T ACTIVATE THE ACTIVATORS."

PATRICK SOON-SHIONG, NANTWORKS

Uncertainty about pegilodecakin's potential to act as either immunosuppressant or immune activator left the doctors unable to comment on where it may find its niche.

"This is tantalizing, but not ready for any kind of prime time," said Margolin.

Though IL-10 was initially studied as an immunosuppressant due to its anti-inflammatory properties, Armo's founders developed a pegylated IL-10 with extended half-life that could induce tumor-specific immune responses and surveillance.

IL-10 receptor is expressed on activated and exhausted T cells, and continuous receptor activation via pegilodecakin can spur exhausted tumor-specific CD8+ T cells to proliferate and kill their targets.

Armo did not respond to requests for comment for this article. Lilly declined, citing a quiet period for its tender offer to acquire Armo.

Armo is testing pegilodecakin plus FOLFOX chemotherapy in the Phase III SEQUOIA trial to treat second-line pancreatic ductal adenocarcinoma (PDAC) and in the CYPRESS Phase IIb studies testing pegilodecakin plus Keytruda in first-line NSCLC with high PD-L1 expression and Opdivo in second-line NSCLC with low PD-L1 expression. bc

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Clinical Oncology (ASCO), Alexandria, Va.
Armo BioSciences Inc. (NASDAQ:ARMO), Redwood City, Calif.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Cedars-Sinai Medical Center, Los Angeles, Calif.
City of Hope, Duarte, Calif.
Cleveland Clinic, Cleveland, Ohio
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
European Society for Medical Oncology (ESMO), Lugano, Switzerland
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
NantWorks LLC, Los Angeles, Calif.
National Cancer Institute (NCI), Bethesda, Md.
Nektar Therapeutics (NASDAQ:NKTR), San Francisco, Calif.
Society for Immunotherapy of Cancer (SITC), Milwaukee, Wis.

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