Recent Advances in BEMPEG (NKTR-214) plus NIVOLUMAB Combination Strategies in Advanced Renal Cell Carcinoma

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ABSTRACT

In this roundtable discussion, renowned cancer experts analyze the potential immunomodulatory capabilities of bempegaldesleukin (BEMPEG; NKTR-214) in combination with an immune checkpoint inhibitor (CPI; anti-PD-1) in the therapeutic landscape of advanced renal cell carcinoma (aRCC) and other genitourinary cancers. The expert panel also shared their perspectives regarding the latest data from ongoing clinical trials which continue to show an encouraging efficacy and safety, risk/benefit of BEMPEG plus CPI combination.

KEYWORDS: Renal cell carcinoma, bempegaldesleukin, IL-2, immunotherapy, immune checkpoint, nivolumab, melanoma, bladder cancer, urothelial carcinoma.

INTRODUCTION

Despite the promising survival benefits achieved using PD-1/PD-L1 blockade based therapies across multiple cancers, a proportion of patients do not respond to anti-PD-1/PD-L1 therapies, and a subset of patients who initially respond to therapy will progress. Therefore, an unmet need remains for novel CPI (immune checkpoint inhibitors) combinations that achieve durable and deep responses in a broad population of patients with genitourinary cancers, without adding substantial toxicity. Combining an immune checkpoint inhibitor with an agent that modulates the tumor microenvironment (TME) may address some of their known limitations. Bempegaldesleukin (BEMPEG; NKTR-214) is an immunostimulatory IL-2 cytokine prodrug that preferentially binds to the heterodimeric IL-2βγ receptor complex (CD122/CD132) found on CD8+ Teff and NK cells to selectively stimulate an antitumor immune response.[1,2,3] The safety and clinical activity of the combination of BEMPEG plus nivolumab (NIVO) are being evaluated in many multicenter studies in multiple solid tumors.[3]

This roundtable discussion was chaired by a renowned expert, Robert A. Figlin, MD (*editor-in-chief, KCJ*). Reflecting insights and key perspectives from nation's leading oncologists on the panel: Drs. Nizar Tannir, MD and Arlene O Siefker-Radtke MD, the roundtable framed the discussion that would enable clinicians to better understand potential implications of promising novel therapeutics in a rapidly changing treatment paradigm of kidney cancers.

Below is an excerpt from the discussion edited for brevity and clarity.

Dr. Figlin:
Hello everyone. This is Robert Figlin, the Steven Spielberg Family Chair in Hematology-Oncology, Professor of Medicine and Biomedical Sciences, and Deputy Director of the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles. I am delighted to be joined for the Kidney Cancer Journal's roundtable program by Dr. Nizar Tannir, a professor in the Department of Genitourinary Medical Oncology at The University of Texas MD Anderson Cancer Center, Houston, where he holds the Ransom Horne, Jr. Professorship for Cancer Research. He has received many awards, including the Division of Cancer Medicine John Mendelsohn Lifetime Achievement Award in 2021. We also have Dr. Arlene O. Siefker-Radtke, who is a Professor in the Department of Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston. She is specialized in developing potential therapies for urothelial, bladder, and rare tumors. Nizar and Arlene, thank you so much for joining us.

This is really an exciting topic. As you are aware, we have a long-standing interest in interleukin-2 (IL-2) based therapies. Just to put that in perspective, I visited the FDA to review the first and second

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submissions for interleukin-2 almost 30 years ago in 1990 and 1992. Although it was difficult to deliver, the IL-2 therapy led to complete and durable responses in a subset of patients with metastatic cancers. It was for that reason IL-2 therapy as aldesleukin was first approved by the FDA for treating metastatic renal cell carcinoma (RCC) and melanoma in 1992 and 1998, respectively. Since then, it's been used moderately by selective physicians over the last few decades. We are very excited to learn that there might be a next-generation IL-2. Arlene, my first question is how does PEGylation affect IL-2's pharmacology and how does BEMPEG differ in its pharmacologic activities as compared to the -interleukin-2 that we have been using for decades?

Dr. Siefker:
This is a great question because bempegaldesleukin (NKTR-214/BEMPEG) is not our daddy's IL-2 which impacts its toxicity and clinical activity. The pharmacokinetics of IL-2 is not durable in the circulation following the intravenous administration as it is eliminated very quickly. Back in the day when IL-2 reigned as king for the treatment of renal cell carcinoma, we did see excessive toxicity and profound hypotension, cytokine type syndromes, and diffuse edema that led to frequent transfers to the intensive care unit. Therefore IL-2 was limited to a young and healthier patient population. With an average of six releasable polyethylene glycol (PEG) molecules conjugated to the IL-2 molecule, even though BEMPEG is given over a short interval, it remains in circulation for up to about a week as indicated by PK analysis. As a consequence, we observe prolonged stimulation of the lymphocytes resulting in an enhanced immune response in the circulation and patient's tumors, translating to the pharmacodynamics that we hope to achieve.

Dr. Figlin:
That's a wonderful summary and it takes me to the next question. How does the toxicity profile of the PEGylated molecule change the way the patient receives it, how we deliver it, and what the expected therapeutic index will be?

Dr. Siefker:
Once BEMPEG is infused into the circulation, PEG moieties from BEMPEG are gradually and sequentially released. This leads to the generation of active IL-2 conjugates and sustained activation of the IL-2 pathway as compared to a profound surge of cytokines following a high-dose IL-2 injection. Hence, PEGylated IL-2 can be delivered as an outpatient administration with less frequent dosing as compared to high-dose IL-2. We observed AEs that were transient and resolved spontaneously without intervention or by using standard treatment protocols. For example, although hypotension is still an issue, it happens usually within the first 3 days following BEMPEG's infusion and can be frequently managed by adequate hydration. So now we have a therapy that can be administered as an outpatient and doesn't cause profound toxicity effects similar to AEs obtained from high-dose of cytokines.

Dr. Figlin:
Well, just the idea that BEMPEG can be administered as an outpatient therapy that doesn't require hospitalization and Intensive Care Unit support is a big deal as compared to traditional IL-2 therapy. Dr. Tannir, let's turn our attention to you. Does BEMPEG have the same ability to produce deep and durable clinical remissions when administered alone or delivered in a combination for patients with kidney cancer? So, what are the responses that you've seen that have been reported with this molecule?

Dr. Tannir:
First, I appreciate Arlene's excellent summary. I'd like to add that BEMPEG, as compared to IL-2, preferentially signals through the dimeric βγ (CD122) of the IL-2 receptor pathway as opposed to the trimeric receptor (IL-2Rαβγ) found on Tregs. So BEMPEG is a CD122-preferential IL-2 pathway agonist that leverages the clinically validated IL-2 pathway. Now getting back to your question, the landscape of RCC, melanoma, and urothelial and other cancers has expanded with advent of the immune checkpoint inhibitors. Similar to immune checkpoint inhibitors, BEMPEG can produce a sustained and promising clinical activity to this competitive landscape. In the phase 1/2 PIVOT-02 study that Drs. Diab, Siefker, and I have participated in, we see an increased and sustained lymphocyte mobilization with each treatment cycle both in tumors and in peripheral blood.[5] BEMPEG induces proliferation and activation of lymphoid cells such as CD4+ and CD8+ T cells and NK cells accompanied by an increase in tumor-infiltrating lymphocytes. BEMPEG also increases PD-1 expression on lymphocytes and PD-L1 expression on tumor cells. Interestingly, BEMPEG in combination with the anti–PD-1 mAb nivolumab (NIVO) not only enhances the infiltration, proliferation, and activation of T cells but also increases the PD-1 expression on these T cells.

In this dual immunotherapy system, the PD-1 antibody or immune checkpoint inhibitor acts by releasing the brakes to go against the cancer cells, and BEMPEG on the other hand presses on the gas pedal. I would like to cite a recently published manuscript in JCO by Dr. Diab et al to give you an example of the efficacy of BEMPEG plus NIVO in solid tumors. In this study, the first-line therapy of BEMPEG plus NIVO showed an impressive 34.2% complete response (CR) rate and 52.6% overall response rate (ORR) with median progression-free survival (mPFS) of 30.9 months compared to 8% CR rate and 6.9 months for mPFS using single-agent PD1 antibody in a melanoma cohort at the primary analysis of the phase 3 CheckMate 067 trial.[4] This is already published data about

BEMPEG+NIVO in the melanoma cohort that I can share with your audience and I can also share the RCC cohort data from the PIVOT-02 trial once we publish the manuscript in the future. Arlene can speak about the urothelial/bladder cohort from the PIVOT-02 trial that she presented at GU ASCO.[6]

Dr. Figlin:
Arlene, our colleagues are excited about your combination trial data and are curious to know the details about how BEMPEG drives the recruitment of lymphocytes which turns cold tumors hot and then checkpoint inhibitors make that activity greater. Tell us a little bit about the phase I study experience involving this combination in urothelial tumors.

Dr. Siefker:
In the ongoing phase 1/2 dose-escalation and –expansion PIVOT-02 study, we are seeing exactly what you mentioned. We see the cold tumors, namely PD-L1 negative tumors that traditionally haven't responded to immunotherapy in the setting of urothelial carcinoma.[6] With treatment of BEMPEG and NIVO, we were able to convert these tumors to PD-L1 positive (≥1% by anti-PD-L1 immunohistochemistry assay) tumors. We're converting the tumor microenvironment from PD-L1 low to PD-L1 high.[6] When we looked at the early clinical data in the setting of bladder cancer, we saw a 44% objective response rate in cisplatin-ineligible patients. We also saw evidence that some of these responses are comparable to what we're seeing in the melanoma group, where they have 90% of patients who responded and haven't yet progressed at a median follow-up of 29.0 months.[6] So the hope is that these treatments will work in the PD-L1 negative group of patients where we've seen a lack of efficacy with immunotherapy. We've also seen activity in patients with visceral metastases with low response rates to immunotherapy as compared to the node-only group of patients. And yet, with BEMPEG plus NIVO, we're seeing similar response rates in both visceral and non-visceral metastases. We hope that this combination will overcome the limitation of immunologically cold tumors. It may help drive responses especially combined with other features associated with a cold tumor microenvironment and even enhance the activity of TKIs that may be used in a colder immune tumor environment.

Dr. Figlin:
Let's talk about what practicing physicians are always going to be worried about, that is immune-related adverse events. We have the history of interleukin-2, we have the history of IOs, and when we combine them, are you seeing anything unusual, or is it pretty much the expected toxicities associated with checkpoint inhibitors?

Dr. Siefker:
At this time, it does appear to be the expected and anticipated toxicity profile that we're observing with single-agent immunotherapy and combination immunotherapy strategies. Regarding treatment-associated adverse events, I do have a sense that hypothyroidism, hypoadrenalism, or low cortisol level do tend to come on a little faster in patients receiving this combination, which could be a result of a better and faster immune stimulation. These can be managed by respective replacement therapies. At the moment, it appears very similar to what's been observed with immune checkpoint inhibitors with a similar profile. We also see some of the IL-2 effects, but it's not as profound; we see hypotension that's controlled with fluids, and fever and myalgias usually controlled with Tylenol®. And most patients report these types of symptoms lasting a few days, up to a week, and then as they continue treatment, the effects do appear to improve.

Dr. Figlin:
When we think about combinations like IPI+NIVO, where both PD-1 and CTLA-4 checkpoints are blocked, there's a high frequency of steroids usage. How about for patients receiving the combination of BEMPEG + NIVO?

Dr. Siefker:
Based on my experience it is similar to the frequency of the immune-mediated adverse events such as pneumonitis, colitis, and myositis that are expected in response to stimulation of immune response by other checkpoint inhibitors. We have gotten better at recognizing these toxicities earlier and treating them more effectively. Overall, I would say, it has been a fairly similar use of steroids in the BEMPEG+NIVO cohort versus patients who were treated on other immune checkpoint inhibitors.

Dr. Figlin:
Nizar, let's turn our attention to the PIVOT-09 study. This randomized trial is evaluating the safety and efficacy of combinatorial agents compared to a TKI. Help us understand the design of the trial, the readouts of the primary and secondary endpoints, and also let us know what you're hoping to obtain with the phase 3 trial prospectively.

Dr. Tannir:
When we designed this international registrational trial four years ago in 2018, obviously we weren't aware that this landscape would quickly change with the approval of many immune checkpoint inhibitor-based regimens. For example, NIVO/ipilimumab (IPI) was approved for patients with intermediate- and poor-risk disease. Following that, three IO-TKI regimens were approved. However, in some countries, some of the IO-IO and IO-TKIs combinatorial regimens such as NIVO+IPI, PEMBRO+AXI, and NIVO+CABO were not approved. So, it was challenging to have a suitable comparator in all participating countries. The investigators from respective countries had to choose between sunitinib versus

cabozantinib for a comparator depending on the approval status in their country. Therefore, this trial was conducted using an investigator's choice TKI. For example, sunitinib was used as a comparator in those countries where sunitinib was approved. Cabozantinib was used as a comparator in those countries where cabozantinib was approved. We selected two co-primary endpoints, objective response rate (ORR) and overall survival (OS). The good news is we were able to enroll upwards of 600 patients in this international trial and we completed our target accrual by recruiting the last patient over a year ago. We hope we will have readouts this year and the combination will show promising results similar to what we saw from the single-arm study of PIVOT 02 with BEMPEG+NIVO.

I would like to add why BEMPEG+NIVO could be a promising approach in RCC. It's because the toxicity profile is so favorable. If you look at the CheckMate-214 study results, the percentage of patients who required high-dose corticosteroids was 35% and the discontinuation rate due to immune-mediated adverse events was 22%. In our experience with RCC, the actual utilization of high-dose corticosteroids with BEMPEG+NIVO combination was really low and discontinuation rates due to immune-mediated AEs (IMAEs) was low as well in patients with RCC. Therefore, I think BEMPEG+NIVO does bring an advantage over the other IO-based regimens with fewer IMAEs leading to a low discontinuation rate with less utilization of corticosteroids in patients with RCC. As compared to the NIVO+IPI combination, we certainly see a definite decrease in rates of discontinuation and IMAEs. So, if we can achieve the same efficacy with BEMPEG+NIVO that we achieved with NIVO+IPI or IO-TKIs, but with lower rates of discontinuation and adverse events, I think we would certainly bring a promising effective therapy that we all look forward to having in the clinic.

Dr. Figlin:
I want to circle back to your comments about turning cold tumors hot in the phase I study in the first-line setting. I'm intrigued to see how this can be implemented in a second or third-line setting where a person has received prior IO therapy and then gets the combination and obtains the benefit. Was there anyone in the phase I trial that had received prior immunotherapy and then benefited from the combination with BEMPEG?

Dr. Siefker:
It was not studied as part of our PIVOT-02 in GU tumors. Could there be scenarios in a post-immunotherapy or post TKI treated patient where the use of this combination could have clinical activity? I would have to say that the potential is there, although it hasn't yet been explored since the decision was made to try it in the upfront setting and we saw good early clinical activity in this group of tumors. Given the single-agent use of immunotherapy in the PD-L1 positive group of tumors but the lack of utility in PD-L1 negative tumors, the phase II trial in bladder cancer focused on the frontline PD-L1 negative group of tumors to see if BEMPEG+NIVO combination could provide a potential benefit compared to what had been observed historically with single-agent immunotherapy. Altogether, we hope this study will provide an alternative novel therapy for patients who might not be good candidates for systemic chemotherapy. I think it is very likely that this approach could enhance immune responses post TKI in combination with a TKI. I hope that these trials are positive and there is an incentive to continue studying this combination further.

Dr. Figlin:
Colleagues, let's bring this conversation to a close by asking each of you to summarize your experience for the people that will be listening and reading what they should be looking for over the next 1 to 5 years, as the readouts start to come from clinical trials. Because one of the challenges for these combinations is when oncologists hear the word IL-2, they sometimes get startled and wonder whether that's something that they can do. BEMPEG, as Nizar and Arlene nicely pointed out, is not 1990's interleukin-2, it's rather a 2022's PEGylated version of interleukin-2 with a better therapeutic index. So how would you summarize where the field is today and where it's going?

Dr. Tannir:
BEMPEG is a novel agent which signals preferentially through the βγ dimeric subunits of the IL-2 receptor. It has a 20-hour half-life compared to the 20-minute half-life with high-dose IL-2. It is given in the outpatient setting. When we gave it as monotherapy or in combination with an anti-PD1 like NIVO, we have not seen an increase in the rate of immune-mediated adverse events. In the phase I PIVOT-02 dose-escalation and -expansion trial, in analyzing biopsy and blood samples, we've seen an increased infiltration of T cells in the tumor microenvironment and lymphocytosis in the peripheral blood. Interestingly, we also noticed an increase in the PDL-1 expression in these cancers. As Arlene mentioned, there was a 70% conversion of PDL1 negative to PDL1 positive in bladder and in other tumors. Altogether, the potential of BEMPEG, I believe, can bring us a step forward to break the cure barrier. Regarding the prospective approaches using BEMPEG + NIVO in the next few years: currently, there are three registrational trials ongoing. First-line BEMPEG plus NIVO versus NIVO in melanoma, the PIVOT-09 of BEMPEG plus NIVO versus TKI of choice (cabozantinib or sunitinib),[7] and the PIVOT-10 trial (NCT03785925) of BEMPEG plus NIVO for the first-line treatment of cisplatin-ineligible patients with locally advanced or

metastatic UC and low tumor PD-L1 expression.[8] Both these trials have completed accrual and we hope to have the readouts soon. We hope that all three of these trials will be positive and we will be able to bring this combination to patients with RCC, melanoma, or bladder cancer. As you are aware the field is shifting from monotherapy to doublets and triplets. We have already started looking at triplets of BEMPEG plus NIVO plus a TKI in PIVOT IO 011. (NCT04540705) In my experience at MD Anderson Cancer Center where we treated several patients with the CABO plus NIVO plus BEMPEG triplet, this regimen can be delivered safely based on preliminary findings. So, I think it's an exciting time for the field of solid tumors as we see the utility of BEMPEG in combination with immune checkpoint inhibitors with or without TKI or chemotherapy in many solid tumors.

Dr. Figlin:
Arlene, in your experience, where do you hope these combination therapies will be going especially in urothelial tumors? We had such challenges with urothelial tumors for decades, and we've always used platinum-based therapies and tried to find ways to take care of people where we didn't feel like we were doing the best that we could. Now all of a sudden, we have immunotherapy, and now we have BEMPEG which could add to that. What are your hopes for the next several years for these patients with urothelial tumors in your experience?

Dr. Siefker:
I am hoping for the ability to apply the durability that was seen very early in the high-dose IL-2 era and now apply it to patients who were never candidates or never would have been candidates for an IL-2 directed therapy. The improved toxicity profile is real. Now we are able to give IL-2 in a new way, with six PEGylations on BEMPEG resulting in more tolerable outpatient therapy. We are now able to do it safely even in elderly and frail bladder cancer patients who are not candidates for cisplatin.

Dr. Figlin:
Let me just say Nizar and Arlene, it's a wonderful opportunity to chat with you and just hearing you talk about the next generation of a molecule that we know has profound effects, offering the patients an outpatient-based therapy, with an opportunity to transform their cold tumors to hot tumors with no additional immune adverse events to what we would have otherwise expected with our current checkpoint inhibitors. It continues to be an exciting time. I agree with you Nizar, whether it's in kidney or melanoma, or bladder cancer today, there is no reason to think that the portfolio of this combination could not be expanded to other immunologically responsive or nonresponsive tumors. Thank you both for your time and please be safe!

CONCLUDING REMARKS
Despite the promising utility of CPI therapy as an effective cancer treatment, an unmet need remains for developing novel therapeutic combinations that produce durable and deeper responses to a broad population of patients with genitourinary cancers, without adding substantial toxicity. In this panel discussion, renowned experts convened to examine the immunomodulatory potential of BEMPEG and also its synergistic potential when combined with CPI agents such as NIVO in the treatment landscape of aRCC. Panelists shared their perspectives about the ongoing PIVOT-02 trial with regards to safety andefficacy and on upcoming clinical studies, PIVOT-09 and PIVOT IO-011

CONFLICT OF INTERESTS
Dr. Tannir: Consulting/advisory relationship: Bristol-Myers-Squibb; Eisai Medical Research; Eli Lilly; Oncorena; Merck Sharp & Dohme. Research Funding: Bristol-Myers-Squibb; Nektar Therapeutics; Arrowhead Pharmaceuticals; Novartis. Honoraria: Eisai Medical Research; Bristol-Myers-Squibb; Intellisphere; Oncorena; Merck Sharp & Dohme; Deka Biosciences; Calithera; Neoleukin; Exelixis; Ono Pharmaceutical.
Scientific Advisory Committee: Nektar Therapeutics; Pfizer; Oncorena; Eli Lilly; Eisai Medical Research.
Dr. Siefker: Scientific advisory board: Astrazeneca; Basilea; Bristol Myers Squibb; Curio; Genentech; Ideaya; Immunomedics; Janssen; Loxo-Oncology; Merck Sharp & Dohme; Natera; Nektar Therapeutics; Taiho; and Seagen. Clinical Trial support: Basilea; Bristol Myers-Squibb; Janssen; Merck Sharpe & Dohme; Nektar Therapeutics. Non-promotional speaker: Janssen.
Dr. Figlin: No relevant conflicts to report for this roundtable.

CONTRIBUTIONS
The roundtable panelists (authors) were invited to participate in this discussion by the journal. All authors listed in the manuscript contributed significantly to KCJ roundtable. All authors have read and approved the final version. The final content and article is the sole work of the authors.

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ONLINE CONTENT
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