Reinventing the Paradigm of IL-2 Therapy: Pivotal Trial Could Change the Landscape of Combination Strategies in Advanced RCC


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Objectives of the Roundtable Discussion

This roundtable discussion held on January 15, 2020 explores the potential impact and innovative clinical strategy of the PIVOT-09 trial involving bempegaldesleukin (BEMPEG: NKTR-214) combined with nivolumab as a novel combination therapy for renal cell carcinoma (RCC). In this discussion, three RCC cancer experts analyze the landscape of interleukin-2 (IL-2) therapy, and they also outline how a novel re-designed IL-2 molecule, comprising a PEGylated version of IL-2 (bempegaldesleukin; BEMPEG; NKTR-214), may deliver promising immunomodulatory capabilities. One of the goals of the PIVOT-09 trial is to evaluate the synergistic effect of BEMPEG with the checkpoint inhibitor (CPI) nivolumab (NIVO) in IMDC intermediate- or poor-risk patients and IMDC all-risk patients with previously untreated advanced renal cell carcinoma (aRCC). The discussion is led by Robert A. Figlin, MD, Editor-in-Chief of *Kidney Cancer Journal*. The panel members are Nizar Tannir, MD, Professor, Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, and Arif Hussain, MD, Professor of Medicine, University of Maryland Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland.

The Development of NKTR-214 (BEMPEG) Therapy: A Historical Perspective

Dr Figlin: Please describe the development of NKTR-214 and the properties that make it different from the historical IL-2 therapies that were developed in the 1990s.

Dr Hussain: Before we consider the development of NKTR-214, it is important to first review the background of IL-2 therapy and how it relates to recent treatment advances. The clinical treatment landscape of advanced RCC with a component of clear cell histology has been evolving dramatically over the last 14 years, since the approval of the first targeted therapies which target angiogenesis factors or further downstream factors at the level of the mammalian target of rapamycin (mTOR) complex. The approval of these newer agents was based on the findings from randomized phase 3 trials that included various primary endpoints such as progression-free survival (PFS; e.g. sorafenib, sunitinib) or overall survival (OS; e.g. temsirolimus). The subsequent progress has been steady, both for initial treatment of patients presenting de novo with advanced disease, and those progressing after initial systemic therapies. These additional therapies have continued to build upon further targeting of receptor kinases (primarily vascular endothelial growth factor receptor [VEGFR], but potentially other targets as well such as MET, AXL, among others), demonstrating that progression on one tyrosine kinase inhibitor (TKI) does not preclude responses to other tyrosine kinase-targeting agents. In the last few years, an additional approach has also been incorporated into the treatment landscape of RCC with the demonstration of a positive impact of immune checkpoint inhibitor (CPI)-based therapy: a) in patients failing TKI-based treatments (nivolu-mab), or b) in patients as first-line therapy (nivolumab + ipilimumab). Furthermore, recent trials have also established a role for combination therapies in the first-line RCC setting that include TKI plus CPI (e.g. axitinib + pembrolizumab, axitinib + avelumab).

The role of IL-2 in RCC needs to be put in context with the current evolving treatments for metastatic renal cell carcinoma (mRCC) or aRCC, keeping in mind that HD intravenous IL-2 was in fact the first FDA-approved therapy for RCC (approved in 1992). The basis for use of HD IL-2 was a phase 2 pooled study in which approximately 12% of mRCC patients achieved a partial response, with 9% achieving complete response (CR).[1] Further, some of the responding patients could be converted into long-term cancer-free survivors upon resection of residual disease. Although the high incidence of significant side effects, including those related to capillary leak syndrome (CLS), necessitates close inpatient monitoring of high-dose interleukin-2 (HD IL-2) treatment, treatment by experienced providers and appropriate medical support can allow for successful administration of HD IL-2. The potential advantage of this approach is that if one is destined to respond, they do so

after 1–3 courses of therapy; such responding patients likely may not require other long-term systemic treatments, thus limiting prolonged treatment-related adverse events (TRAE)s. By contrast, with targeted therapies and perhaps also immune CPIs, longer-term treatments are generally required, which can be associated with their own set of potentially prolonged AEs.

With HD IL-2 therapy there appears to be a plateau in terms of the proportion of patients with RCC achieving objective response and CR. Although to date there are no head-to-head comparisons, ORRs are often higher with single-agent TKI therapies, but CR rates lower than with HD IL-2. However, this paradigm may be shifting. For instance, TKI plus immune checkpoint blockade as upfront therapy (axitinib + pembrolizumab, axitinib + avelumab) demonstrates ORR of 50–59% and CR rates of 3–6%.[2] Interestingly, double immune checkpoint blockade with nivolumab plus ipilimumab in the first-line setting has resulted in ORR of 42% and CR rate of 9%. Thus, it appears that immune modulation in advanced aRCC is relevant to achieving clinical CR, and perhaps durable CR, albeit the proportion of patients achieving this remains low.[3]

An important question now is whether IL-2 can be integrated with some of the newer approaches to further improve treatment outcomes of RCC patients, given its purported immunomodulatory mechanisms of action, including enhanced expansion of antigen-specific clonal T cells and cytotoxic CD8 cells, stimulation of large granular lymphocytes (natural killer [NK] cells) and stimulation of B cells to secrete antibodies. The intense treatment schedule of HD IL-2, and the significant associated toxicities, have made it difficult to readily incorporate and test HD IL-2 with other treatments in combination therapies. Although lower-dose IV IL-2 and subcutaneous IL-2 have also been used to treat RCC, their anti-tumor activities are even more modest than HD IL-2. The challenge therefore has been to develop other formulations of IL-2 that: a) can recapitulate the clinical efficacy associated with HD IL-2, b) have lower side effects, c) be given in an outpatient setting, and d) be safely combined with other treatments to potentially improve anti-tumor activity.

BEMPEG incorporates recombinant human IL-2 into a polyethylene glycol moiety that favorably alters some of the pharmacokinetic and pharmacodynamic properties of HD IL-2. The gradual release of bound IL-2 from pegylated chains after IV administration allows for IL-2 to reach peak serum concentrations more gradually over 24–48 hours after administration compared with the rapid kinetics and short half-life of HD IL-2.[2] BEMPEG consequently has a 500-fold increase in AUC vs HD IL-2.[4] These properties allow for less frequent dosing, and mitigate the rapid release of cytokines and hence cytokine release-associated AEs that often occur with HD IL-2 administration. Further, BEMPEG preferentially activates the intermediate affinity IL-2 receptors (IL-2R beta/gamma) over the high-affinity IL-2 receptors (IL-2R alpha/beta/gamma), leading to preferential activation and expansion of the desirable $CD8^+$ T cells and NK cells rather than the immunosuppressive $CD4^+$ T-regulatory (T_{reg}) cells. It is the location of PEG chains at the IL2/IL2Ra interface that interferes with binding to high-affinity IL2Ra (CD25), while leaving binding to low-affinity IL2Rb (CD122). Its receptor-binding properties also lead to decreased activation of the high-affinity IL-2R on endothelial cells, and thus less likelihood of capillary leak syndrome. Altogether, these properties suggest that BEMPEG can be more readily incorporated into combination therapies.

Dr Tannir: HD IL-2 was approved by the FDA in 1992 based on seven single-arm phase 2 trials showing consistent ORRs of approximately 20% and CR rates of 7-10%, with approximately 85% of the CRs being durable.[1] Two major limitations of HD IL-2 therapy have limited its wide application: 1) significant toxicity, which in the early years was associated with a 4% fatality rate and 2) need for high-level training of healthcare providers to administer this therapy in an inpatient setting with close monitoring to manage challenging complications such as capillary leak syndrome, refractory hypotension requiring IV fluids, vasopressors, and intensive care unit monitoring, liver and/or renal dysfunction, neurotoxicity, sepsis, and gastrointestinal toxicity.[5] The approvals of targeted therapies (VEGF-directed agents, mTOR inhibitors) have supplanted cytokine therapy, including HD IL-2, although few centers continue to administer HD IL-2 to selected patients who are candidates for this therapeutic approach. The recent approval of immune CPI- based therapies (e.g. nivolumab + ipilimumab, pembrolizumab + axitinib) as first-line therapies further eroded the use of HD IL-2.

The limitations of HD IL-2 have spurred the development of a more tolerable IL-2 therapy, which can harness the benefits of the immune system while minimizing the toxicity. BEMPEG was developed with these aims in mind. The inactive 6-PEG prodrug compound yields two active moieties after irreversible release in the circulation and shifts signaling preferentially through the IL-2R beta and gamma components, essentially acting as a CD122 agonist, away from the IL-2R alpha signaling that is responsible for much of the toxicity of HD IL-2. Additionally, the serum half-life of BEMPEG is 20 hours compared with 20 minutes for HD IL-2. The more favorable toxicity profile and longer half-life of BEMPEG allow for outpatient administration; the recommended dose of BEMPEG is on a three-week schedule.

Delineating the Pharmacologic Properties of BEMPEG

Dr Figlin: What are the results from the phase 1 monotherapy trials that delineate the pharmacologic properties, the AE profile, and how BEMPEG allows for intermittent dosing in cancer?

Dr Tannir: BEMPEG has been evaluated in solid tumors as a single agent in the phase 1 and phase 2 settings to establish dosing and safety, and to assess initial activity. It has been tested on an every-3-week schedule given IV; five dose levels were evaluated ranging from 0.003–0.012 mg/kg, with the maximal tolerated dose identified as 0.009 mg/kg and the phase 2 dose defined as 0.006 mg/kg every 3 weeks. The dose-escalation phase included 28 patients.[6] Among these, only one patient experienced

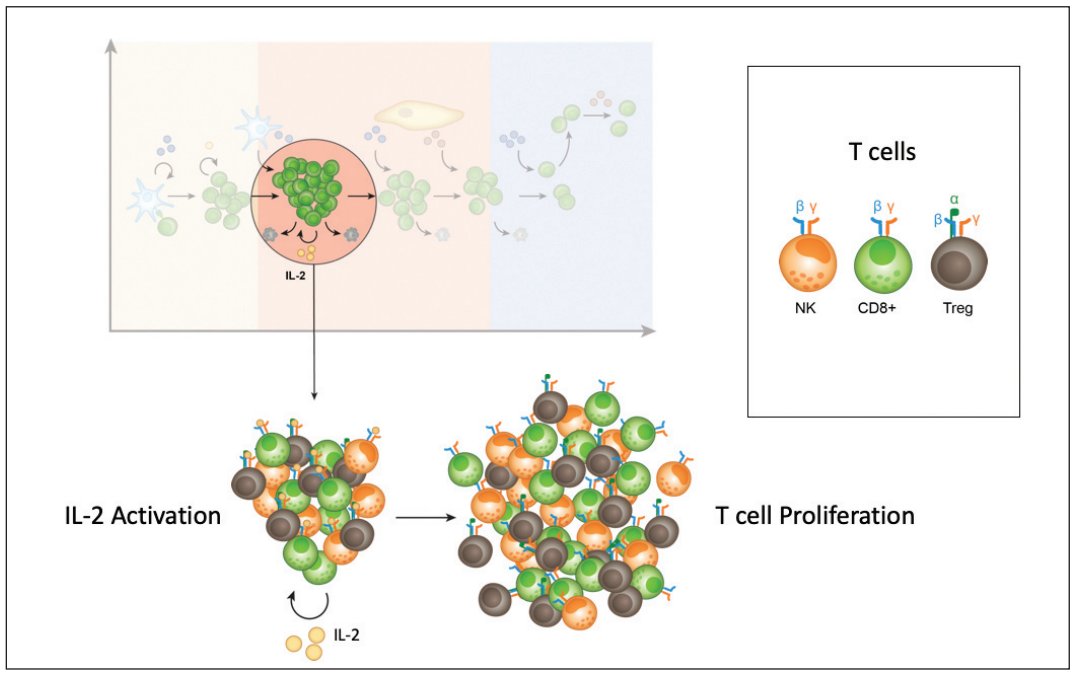

Figure 1. Tuning Receptor Selectivity
The IL-2 pathway regulates T-cell response and stimulates immune cell proliferation and activation of both tumor-killing CD8+ effector T cells and Natural Killer (NK) cells, and immuno-suppressive regulatory T cells (Treg).

two dose-limiting toxicities at 0.012 mg/kg: Grade 3 hypotension and Grade 3 syncope. Although the majority of patients had adverse events, Grade 3 TRAEs were observed in 6/28 (21.4%) patients, while none had Grade 4 AEs or capillary leak syndrome.[6] The most common TRAEs in order of decreasing frequency included fatigue, flu-like symptoms, pruritus, hypotension, rash, decreased appetite, and arthralgia, with the AEs generally occurring 3–4 days post dosing. Hypotension was the only Grade 3 TRAE that occurred in more than one patient, being Grade 3 in four patients. The hypotension can be managed in the outpatient setting with judicious use of IV fluids during the day of BEMPEG infusion and additional increased oral fluid intake by patients.[6]

Dr Figlin: HD IL-2 monotherapy produced durable responses in about 10% of patients with RCC. Is it your hope that BEMPEG can accomplish similar results as monotherapy?

Dr Tannir: Novel combination therapies comprising the immune CPIs that block different inhibitory receptors on the T-cell (cytotoxic T-cell-associated protein-4, programmed death protein 1 [PD-1]) and VEGFR–TKIs such as axitinib, cabozantinib, and lenvatinib have revolutionized the field of RCC therapeutics. It was clear for investigators involved in the development of BEMPEG that the focus of studies with this novel immunotherapy agent had to be on strategies combining BEMPEG with nivolumab, or with nivolumab plus ipilimumab, rather than developing it as a single agent.

Dr Hussain: Based on some of the pharmacokinetic and pharmacodynamic properties, BEMPEG provides strong rationale for evaluation in the clinical setting, particularly for RCC where there is an established role for IL-2-based therapy. In appropriately identified patients with good performance status, clear-cell RCC tumor histology, and no visceral/CNS/bone metastasis, HD IL-2 remains a viable treatment option despite the rapidly evolving RCC treatment landscape. It is certainly our hope that BEMPEG has at least a similar degree of activity to that observed with HD IL-2 in RCC, which would be an important step given its more favorable safety/ tolerability profile. This would contrast with low-dose IL-2 or subcutaneous IL-2, which generally have better tolerability profiles but are less active than HD IL-2. It should be noted that BEMPEG is only being evaluated in combination.

■ Rationale for Combining BEMPEG With a CPI

Dr Figlin: Please describe the preclinical rationale for combining BEMPEG with immunotherapy in RCC.

Dr Hussain: The role of immunotherapy in RCC is well established, and in fact the initial therapies for RCC were based on immunomodulation via cytokines such as interferons and IL-2. The therapeutic benefit of immunomodulation in RCC has been further reinforced with the demonstration of increased anti-tumor effects of immune CPIs in RCC as compared with targeted therapy. CPIs help reactivate the anti-tumor properties of exhausted $CD4^+$ and $CD8^+$ T cells within tumors. Enhanced expression of PD-1 by activated T cells leads to down modulation of T cell activity upon engagement of PD-1 by its ligands such as programmed death ligand 1 (PD-L1) present on tumor cells, creating a tumor-permissive environment. This forms the basis for targeting PD-1 or PD-L1 with specific antibodies that, as noted, reactivate the T cells against the tumor cells. Given these dynamics between the tumor and the immune system, this provides a strong rationale to develop treatment strategies for RCC that incorporate the T-cell-promoting activities of IL-2 and the immune CPIs. Furthermore, BEMPEG can increase PD-1 expression on T cells and PD-L1 expression on tumor cells, providing relevant targets for immune checkpoint blockade.(**Figures 1,2,3**)

Dr Tannir: BEMPEG has been shown to increase tumor-infiltrating lymphocytes (TILs), T-cell clonality (expansion of $CD4^+$, $CD8^+$, and NK cells with little effect on T_{regs}), and PD-1 expression as determined by immunohisto-

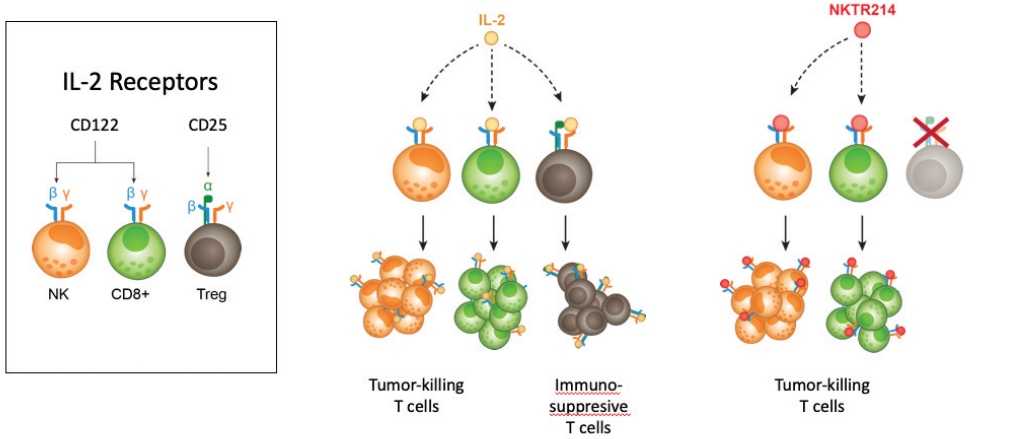

Figure 2. Tuning Receptor Selectivity
T cell proliferation is stimulated thorough the IL-2 receptor complexes CD122 (IL-2rβγ) on effector T cells and NK cells and CD25 (IL-2rαβγ) on Tregs. IL-2 binds to both CD122 and CD25 while NKTR-214 has a biased action on the CD122 receptor.

chemistry. Low levels of baseline TILs and T-cell inflammation are predictive of a poor response to CPIs. BEMPEG combined with nivolumab has been shown by immunohistochemistry to convert baseline tumors from PD-L1 negative (<1%) to PD-L1 positive (≥1%); hence, leveraging this conversion would increase the response to CPIs.

Dr Figlin: Please describe the phase 1 results of the combination of BEMPEG and nivolumab that served to inform the PIVOT-09 trial.

Dr Hussain: Based on large phase 3 trials, nivolumab as single-agent therapy has been approved in previously treated patients with clear-cell RCC, and more recently it is also approved in the first-line setting in combination with ipilimumab. Nivolumab plus IL-2-based therapy, such as with BEMPEG, would be a novel combination to evaluate for its relative clinical activity in RCC. In this regard, a phase 3 clinical trial (NCT03729245 A Study of NKTR-214 in Combination With Nivolumab Compared With the Investigator's Choice of a Tyrosine Kinase Inhibitor (TKI Therapy (Either Sunitinib or Cabozantinib Monotherapy) for Advanced Metastatic Renal Cell Carcinoma (RCC) is currently ongoing, and is evaluating BEMPEG plus nivolumab versus standard-of-care TKI in metastatic treatment-naïve clear-cell RCC across all IMDC patient risk groups (good, intermediate, poor), with co-primary endpoints being ORR and OS, and key secondary endpoint being PFS.[7] This trial has been informed by an initial dose-escalation and dose-expansion study with the combination in patients with various advanced solid tumors, including RCC, melanoma, non-small-cell lung cancer (NSCLC) and urothelial cancer (PIVOT-02, NCT02983045). In the expansion phase, the recommended phase 2 dose for these agents were BEMPEG 0.006 mg/kg IV every 3 weeks plus nivolumab 360 mg IV every 3 weeks. To date, no unexpected AEs have resulted from the combination treatment, with the most common TRAEs be-ing flu-like symptoms, rash, pruritus, nausea, and decreased appetite. Importantly, BEMPEG does not appear to increase the side-effect profile of nivolumab. Among the almost 300 patients treated with the combination across several solid tumors, 14% experienced Grade 3 or higher TRAEs. [8] Amongst the small number of patients with RCC treated with the combination to date, 12/26 (46%) have experienced a complete or partial response, which compares favorably with historical controls.

Dr Tannir: Yes, I agree with everything Arif has just said. In addition to what Arif notes, in the RCC expansion cohort of the PIVOT-02 trial, which combined BEMPEG at the dose of 0.006 mg/kg IV plus nivolumab 360 mg IV every 3 weeks, the ORR was in the range of 46% with low Grade 3/4 AE rates, and most AEs were Grade 1 and 2, with flu-like symptoms, fatigue, rash and pruritis starting 24 hours after the infusions and lasting 3–4 days. There was no increase in immune-related AEs compared with AEs observed with PD-1 antibodies alone.

■ Exploring the Phase 3 PIVOT-09 Trial and Its Endpoints

Dr Figlin: Let's consider some other aspects of the PIVOT-09 trial. Please describe the design of the pivotal trial, how you chose the comparator arm, the status of the trial, and your statistical endpoints to evaluate efficacy.

Dr Tannir: In most countries outside the US, Canada, and Western Europe, sunitinib or pazopanib remains the mainstay first-line therapy for patients with mRCC. Cabozantinib has been shown to produce a higher ORR and longer PFS compared with sunitinib in a randomized phase 2 trial of patients with advanced or metastatic clear-cell RCC with intermediate- or poor-risk disease. There are no data with cabozantinib as first-line therapy in patients with metastatic clear-cell RCC with favorable-risk disease, but it is anticipated that the clinical activity of cabozantinib would be at least comparable to sunitinib in patients with this risk group.

The phase 3 trial, PIVOT-09, is randomizing (1:1) treatment-naïve patients with advanced or metastatic clear-cell RCC to receive BEMPEG 0.006 mg/kg IV plus nivolumab 360 mg IV every 3 weeks (Arm A) or sunitinib 50 mg orally daily, 4 weeks on, 2 weeks off, or cabozantinib 60 mg orally daily (Arm B). Patients with any International mRCC Database Consortium IMDC prognostic risk group are eligible, and tumor tissue is required for PD-L1 testing. Stratification factors include the TKI choice (sunitinib vs cabozantinib) and IMDC prognostic

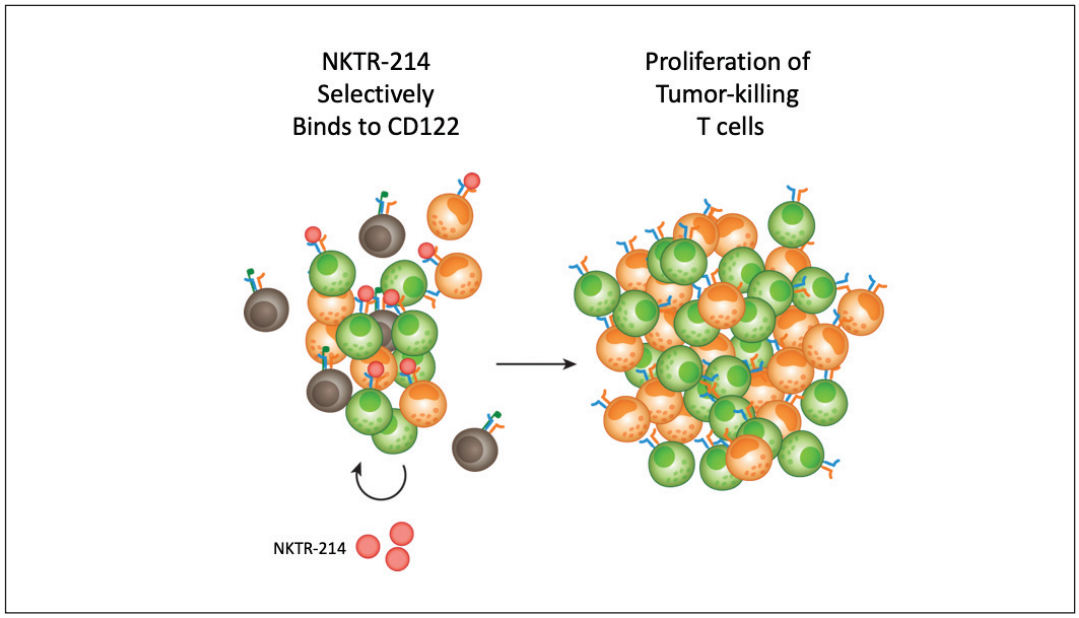

Figure 3. Tuning Receptor Selectivity
NKTR-214 preferentially stimulates proliferation of tumor-killing CD8+ effector T cells and Natural Killer cells without activating immunosuppressive regulatory T cells.

risk group. This trial aims to enroll a total of 600 patients at approximately 150 sites, although the vast majority of patients will be recruited from countries other than the US, Canada, and Western Europe. The co-primary endpoints are ORR by blinded independent central review (BICR) and OS. The key secondary endpoint is PFS by BICR. Other secondary endpoints include incidence of AEs, ORR using RECIST 1.1 by investigator and PD-L1 biomarker population, PFS by investigator and biomarker population, OS in biomarker population, and quality of life.

Dr Hussain: Recent phase 3 trials evaluating first-line therapies in RCC have used sunitinib as the standard comparator arm. The ongoing pivotal phase 3 trial with BEMPEG plus nivolumab is somewhat unique in this regard since the comparator arm is either sunitinib or cabozantinib, depending upon physician choice. This design takes into account the changing treatment patterns of RCC. Currently, there are three single-agent TKIs approved in the first-line setting, namely sunitinib, pazopanib, and cabozantinib. Among these, sunitinib and pazopanib are essentially similar in terms of treatment outcomes, with perhaps some differences in their respective side-effect profiles. Based on the CABOSUN trial, cabozantinib may have greater activity compared to sunitinib particularly among intermediate and poor risk RCC patients, and consequently is also being increasingly used as first-line monotherapy.[9] In this respect, the comparator arm 'bar' against which BEMPEG plus nivolumab is being compared is perhaps higher than if the comparator arm included only sunitinib.

A major challenge to the successful development of BEMPEG plus nivolumab for RCC is that first-line therapies, particularly some of the newer combination therapies (nivolumab + ipilimumab, axitinib + pembrolizumab, axitinib + avelumab), show significant and favorable activity compared with single-agent sunitinib. The ongoing pivotal phase 3 trial of BEMPEG plus nivolumab must show similar activity, and perhaps even better activity, compared with the above combinations and against a standard-of-care arm that not only includes sunitinib but also cabozantinib.

Dr Figlin: Do you believe there are any tissue or laboratory-based biomarkers that could identify the potential beneficiaries of this approach?

Dr Hussain: To date, no clear biomarkers have been identified that reliably predict treatment outcomes to HD IL-2 therapy. On the other hand, data across various malignancies support PD-L1 expression patterns as a potential predictor for response to immune checkpoint targeting, although there is increasing recognition that PD-L1 expression may not be adequately 'captured' during testing of tumor specimens as it is a dynamic marker. Further, although PD-L1 expression may identify subpopulations of responding RCC patients, those without significant PD-L1 expression can still respond to immune CPIs. Consequently, current RCC immune CPI treatment paradigms are essentially PD-L1 agnostic. It will be of interest to study and further define the role of PD-L1 testing in BEMPEG plus nivolumab RCC trials given that BEMPEG can in fact alter/enhance PD-1 and/or PD-L1 expression. Whether relative quantification of immune suppressor cells such as (myeloid-derived suppressor cells (MDSCs) and T_{regs} or/and TILs within tumors can serve as useful biomarkers to prognosticate or/and predict response to therapy remain important questions. Although exploratory, another open question would be whether there are certain cytokine signature patterns (for instance, within the circulation) at baseline and post therapy that can identify and potentially inform treatment outcomes for BEMPEG plus nivolumab or/and standard of care TKI therapy.

Dr Tannir: Immune profiling of blood and tissue and next-generation sequencing of tissue looking at prognostic and predictive markers for response to BEMPEG plus nivolumab and BEMPEG plus nivolumab and ipilimumab are ongoing.

■ Future development of BEMPEG

Dr Figlin: What other diseases or combinations will you be evaluating with respect to BEMPEG and its drug discovery platform?

Dr Hussain: The success of immune CPIs in many differ-

ent cancer types has established a paradigm for modulating the immune system for therapeutic benefit. Although IL-2-based treatments have, to date, focused primarily on melanoma and RCC, based on the immunomodulatory and potentially complementary effects of IL-2 with immune CPIs in reactivating and enhancing the immune system, this suggests that an approach integrating reformulated forms of IL-2 such as BEMPEG may have a broader role in treating malignancies beyond RCC. This may be a particularly viable approach if BEMPEG is integrated with immune CPIs or/and vaccine-based therapies in disease states where there is already a defined role for these latter treatments. It is of interest that pivotal phase 2/3 registrational trials are being carried out with BEMPEG and immune CPIs in other solid tumors, including melanoma, NSCLC, and urothelial cancers, which may provide a platform for further investigation into some of these other cancer types. It should be noted that metastatic prostate cancer is currently the only solid tumor for which a vaccine, sipuleucel-T, has been approved by the FDA. This autologous dendritic cell-based vaccine has been shown to improve OS, but not necessarily PFS, and significant room for improving upon this vaccine treatment remains. Whether BEMPEG or a CPI or both can be incorporated with sipuleucel-T to improve treatment outcomes in advanced prostate cancer is another potential area to consider.

As noted above, VEGF/VEGFR has been established as a pivotal axis in RCC angiogenesis and pathogenesis, targeting of which has led to significant improvements of RCC patients. Importantly, this axis not only enhances angiogenesis but also stimulates myeloid-derived suppressor cells (MSDCs) that contribute to an immunosuppressive and tumor-permissive environment. Thus, targeting VEGF/VEGFR can enhance anti-tumor immune responses by increasing T-cell trafficking into tumors, decreasing MDSC and T_{reg} activity, and producing immunosuppressive cytokines. The clinical relevance of targeting VEGF/VEGFR concurrently with immune modulation has now been well established in RCC based on several phase 3 trials that have shown positive outcomes with bevacizumab plus atezolizumab, axitinib plus pembrolizumab, and axitinib plus avelumab.[10,11] Thus, the VEGFR axis and the immune checkpoint axis provide a relevant framework in the context of BEMPEG, including exploratory co-targeting approaches that could evaluate BEMPEG plus VEGFR targeting, or even BEMPEG plus CPI plus VEGFR targeting in RCC and other solid tumors.

Recent work has identified a key role for PI3K -based signaling in immune cell function, particularly in immunosuppressive cells such as MDSCs. Targeting PI3K in combination with BEMPEG offers another potential opportunity to explore. In addition to the above, there have been significant efforts to modulate the metabolome, particularly glutamine metabolism, in RCC and other cancer types in combination strategies with TKIs and immune CPIs that could also inform further development of BEMPEG in the future.

Finally, although BEMPEG is being evaluated with nivolumab in the first-line setting in RCC via a pivotal ongoing phase 3 trial, another important and relevant aspect is to also explore and define a possible role for BEMPEG in the second-line or beyond settings in RCC patients progressing on initial immune CPI- or/and TKI-based therapies. For instance, is there any role or benefit to further immune modulation by BEMPEG among previously treated patients, either as single-agent therapy or more likely in combination with another targeting agent (e.g. PI3K inhibitor, glutaminase inhibitor, others)?

Dr Tannir: That is an accurate summary. I also would like to add that the two tumor types other than RCC where there is already promising preliminary data with the doublet of BEMPEG plus nivolumab are melanoma and urothelial carcinoma. In the melanoma expansion cohort of the PIVOT-02 trial, the ORR was 53% and CR 34%.

At the 2019 ASCO GU meeting, data were presented on the combination of BEMPEG and nivolumab from the PIVOT-02 cohort of first-line treatment of 41 patients with metastatic urothelial cancer who were cisplatin-ineligible or cisplatin-eligible and refused standard of care. The doublet of BEMPEG plus nivolumab was well tolerated. The most common TRAEs were Grade 1 and 2 flu-like symptoms, fatigue, rash, and pruritis. Six patients experienced a Grade 3 TRAE, which led to discontinuation of therapy in four patients (10%). There were no Grade 4 or 5 AEs. Among 27 evaluable patients for response, 13 patients had a complete or partial response for an ORR of 48%: 5 patients had CR and 8 patients had a partial response. Responses were noted in patients with PD-L1 <1% and in patients with PD-L1 ≥1%. In metastatic UC (mUC), responses were observed in patients with PD-L1-negative and CD8-TIL low tumors (4/8 or 50%) and CD3-TIL low tumors (3/7 or 43%).[14] The combination of BEMPEG plus NIVO is being evaluated in several other tumor types, including RCC, melanoma, UC, and NSCLC.

Conclusion

Results from pivotal clinical trials have demonstrated the immunomodulatory and potentially complementary effects of IL-2 with CPIs in reactivating and enhancing the immune system. A novel therapeutic approach, integrating reformulated forms of IL-2 such as BEMPEG with the checkpoint inhibitor nivolumab may have translational impact as first-line therapy in treating RCC. Although BEMPEG is being evaluated with nivolumab in the first-line setting in RCC via a pivotal ongoing phase 3 trial, another important and relevant aspect is to also explore and define a possible role for BEMPEG in the second-line or beyond settings in RCC patients progressing on initial immune CPI- or/and TKI-based therapies.

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