Viewpoint
Paving the Way for Cancer Therapy a Nano Step at a Time

Cancer is a multicellular disease, and its treatment has evolved to account for the complex interplay of biologic pathways. Although angiogenesis inhibitors have been used to clinically treat tumors for over 20 years as monotherapies initially and subsequently in conjunction with other chemotherapies (Folkman 2006), it is only recently that they are being tested in combination with immune-based therapies (Ansari et al., 2022).

Tumor angiogenesis has several undesirable effects on the immune molecules within the tumor microenvironment. It often severely hampers the ability of immune effectors to control the growth and metastasis of tumor cells across various tumor types (Lee et al., 2020; Chen et al., 2021; Ren et al., 2021). A dysfunctional vasculature alters the tumor infiltration capacity of immune mediators such as the reduction in the ability of effector T cells to enter the tumor microenvironment. The dysregulated endothelial cells also express molecules such as programmed death–ligand 1 (PD-L1), which are known to play a role in hampering the function of effector T cells that manage to enter the tumor microenvironment. The cytokines and chemokines released due to the faulty angiogenesis processes also cause lowered rate of dendritic cell (DC) maturation and effective antigen presentation, as well as reprogramming the macrophages to acquire tumor-promoting characteristics. In turn, this immune milieu further upregulates the production of angiogenesis-promoting molecules such as the vascular endothelial growth factor (VEGF), thus creating a vicious circle (Lee et al., 2020). Therefore, combining agents that block angiogenesis with immune checkpoint blocking agents can target the tumor at two interrelated but mechanistically distinct vulnerabilities. The most prominent combination to be tested in clinical trials thus far is of the VEGF inhibitory antibody bevacizumab, with various immune checkpoint inhibitory molecules (Yi et al., 2019).

Although VEGF is a key driver of tumor angiogenesis and immunosuppression, VEGF inhibition can cause a negative feedback and lead to the upregulation of proteins that can restore tumor angiogenesis through nonredundant pathways (Bergers and Hanahan 2008). Angiopoietin-2 (Ang2) is one such molecule, and when targeted along with VEGF, it can promote durable antitumor responses (Rigamonti et al., 2014). In terms of designing a combination therapy clinically, using multiple drugs or antibodies can have toxic side effects even if they synergistically delay the tumor growth. A molecule that targets both VEGF and Ang2 has a big clinical edge in this regard and would be a good candidate to be used for combination studies, either with other chemotherapies or immunotherapies. Vanucizumab (or A2V), a bispecific antibody possessing such a dual targeting ability, has shown promise in preclinical models (Kienast et al., 2013) as well as early-stage clinical trials (Hidalgo et al., 2018; Heil et al., 2021).

The study by Hofmann et al. describes BI 836880, another molecule that can target both VEGF and Ang2. This molecule, as a smaller nanobody that only retains the variable domains of an antibody, has several advantages over a bispecific antibody (Sun et al., 2021). Its superiority lies in its ability to maximize targeting and bioavailability at the tumor sites when vasculature is leaky due to faulty angiogenesis. Often antiangiogenic therapies that are effective in preclinical models end up having limited translatability to humans (Eklund et al., 2013). Therefore, the validation of BI 836880’s ability using human samples/models as a molecule with high species specificity provides additional support toward its clinical potential. Indeed, the authors are able to also demonstrate the efficacy of BI 836880 over monotherapies targeting either Ang2 or VEGF.

Address correspondence to: Dr. Taha Merghoub, Weill Cornell Medicine, 1300 York Avenue, New York, NY 10065. E-mail: tmerghoub@med.cornell.edu

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ABBREVIATIONS: Ang2, angiopoietin-2; PD1, programmed death 1; PDX, patient-derived xenograft; VEGF, vascular endothelial growth factor.
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VEGF in several patient-derived xenograft (PDX) models spanning six different tumor types, strongly cementing its clinical relevance.

Hofmann et al. also attempted to evaluate the immunologic consequences of BI 836880 and whether it could be combined with anti–programmed death 1 (PD1) therapy in particular. However, given that PDXs are immune deficient, they had to adapt their therapy to an immune-competent murine model using murine cancer cells. Given the differences between human and mouse, BI 836880 targets Ang2 but does not target VEGF in mice. To overcome this difference, they came up with a clever alternative and used BI 836880 to block Ang2 in combination with a VEGF inhibitor to mimic the human effects of BI 836880 in mice. As the use of an antibody to specifically inhibit VEGF was too toxic when used with BI 836880 and anti-PD1 therapy, they had to use a US Food and Drug Administration (FDA)-approved inhibitor of the VEGF receptor, vatalanib, which also targets other kinases (Scholar, 2007). Although their results do indicate that a combination therapy of anti-PD1 with BI 836880 may have some potential, the drawbacks of the model used limit the ability to draw definitive conclusions. A particularly challenging limitation of the context is that the evaluation of the effects of BI 836880 versus those of vatalanib in combination with immune therapy is difficult to interpret. This limitation emphasizes an important need in the field of being able to test our drugs in more adequate models. Developing molecules that recognize both mouse and human proteins, using surrogate molecules that recognize the mouse protein and creating transgenic mice with the human genes, will bridge the gap between mouse and human studies for the entire angiogenesis field (Eklund et al., 2013). A few such existing alternate mouse models that would benefit further characterization of antiangiogenesis molecules including BI 836880 are: utilizing gene targeting strategies to convert key angiogenic drivers such as VEGF into their human homolog (Gerber et al., 2007) and a novel approach of engraftment of human blood vessels to monitor a human vasculature in mice using imaging techniques (Tsukada et al., 2021). In order to specifically evaluate the immunologic potential of angiogenesis inhibitors, approaches that can yield more translatable results to better design clinical trials are: the use of a humanized model where the immune system has been reconstituted using progenitors of human origin (Zumwalde and Gumperz 2018; Allen et al., 2019) and implanting the tumor and adoptively transferring the immune cells from the same patients in PDX models (Jespersen et al., 2017). Schmittnaegel et al. (2017), using the bispecific antibody vanucizumab, are able to demonstrate that the benefit of using an additional immune checkpoint blockade therapy varies significantly with change in the tumor models used for the study, thus highlighting the need to test multiple immunocompetent models to identify the best clinical context for novel drugs such as BI 836880.

Notwithstanding the limitations of the mouse models in this context, Hofmann et al. manage to perform some immunologic phenotyping analysis. They show that the percentage of effector T cells infiltrating into the tumor with the anti-PD1 therapy does not get enhanced by the addition of BI 836880, but there is need for further immune phenotyping to unearth the extent of immunologic changes that can promote an increased antitumor response. The extensive immune phenotyping from Schmittnaegel et al. (2017) for vanucizumab complements Hofmann et al.’s work and can shed some light on these results while also pointing toward the future analysis that can deepen our understanding of the immune response that can be elicited by BI 836880. The study by Schmittnaegel et al. (2017) demonstrates that although vanucizumab does not alter the percentage of infiltrating effector T cells, there is an increase in their number as well as their degree of activation, which could also be replicated by BI 836880. Vanucizumab is also able to reprogram myeloid cells such as dendritic cells (DCs) and tumor associated macrophages (TAMs); hence, further characterization of BI 836880 using techniques such as T cell receptor (TCR) sequencing and single cell analysis of immune populations would shed light on choosing the right immune modulator to combine with BI 836880 that may be a better partner as opposed to anti-PD1 (Fig. 1).

There is also some indication that BI 836880 on its own may be depleting the effector T cells in the tumor environment based on the data provided by Hofmann et al. Further in-depth characterization may indicate that BI 836880 may not promote an immune permissive tumor environment after all. Although it can definitely be beneficial to partner immunotherapy with antiangiogenic therapies, BI 836880 in particular may have more of a synergistic effect when combined with appropriate chemotherapies or other targeted agents.

Given the technical challenges involved in the extensive molecular characterization and model optimization required for effective future development of novel molecules such as BI 836880, partnered research programs between industry and leading academic centers can complement each other to accomplish this mammoth task in a timely manner. In conclusion, Hofmann et al. convey that BI 836880 has a lot of
potential to benefit cancer patients when the appropriate tumor context and the right partnering therapy is used to design clinical trials.

Divya Venkatesh and Taha Merghoub

Department of Pharmacology and Edward Meyer Cancer Center and Ludwig Collaborative and Swim Across America Laboratory, Weill Cornell Medicine, New York, New York

Authorship Contributions
Wrote or contributed to the writing of the manuscript: Venkatesh, Merghoub.

References


