The Pathway of Belzutifan, from clinical trials to clinical practice: A conversation with Dr. Ramaprasad Srinivasan, MD, PhD

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KCJ: What is the significance of belzutifan approval for VHL patients? Can you give us your perspective about the incredible journey that led us to development of first-in-class belzutifan ?

Dr. Srinivasan: In order to fully understand what this approval means to VHL patients, I think we should begin by reviewing VHL and how it is currently treated. VHL is an inherited disorder characterized by a predisposition to developing tumors in kidneys, pancreas, adrenal glands, CNS, eyes and the inner ear. Typically, patients are treated with surgery (or laser ablation, retinal hemangioblastomas), with the goal of either minimizing the risk of metastatic disease or preventing local complications from a growing tumor. For instance, in patients with clear cell carcinoma of the kidney (patients generally develop multiple, bilateral tumors), it has been shown that tumors less than 3 cm have little to no risk of metastatic spread, while the risk increased with increasing tumor size beyond this size; the surgical paradigm, therefore, was to operate on tumors that are 3 cm or more to minimize the risk of spread. The approach typically used today is nephron-sparing surgery. Since patients develop tumors throughout their life, most patients need to undergo multiple surgical procedures during their lifetime. Over the last 40 years or so, the major advancements in the treatment of VHL have largely been in the form of improved surgical approaches. Our center is one of the biggest referral centers for the VHL patients and we follow over a thousand patients with the condition. One of my goals, therefore, when I started as an oncologist treating patients with kidney cancer in the early 2000s was to find alternative treatment options for patients with VHL-associated tumors that might minimize the need for surgery or delay surgery.

The development and evaluation of belzutifan can be traced back to several scientific discoveries over the last 30-40 years. By studying patients/families with VHL starting in the 1980s, Drs. Linehan, Berton Zbar and colleagues were able to identify germline inactivating mutations in the VHL gene in affected members and show that this gene functioned as a classical tumor suppressor gene. Somatic mutations in VHL have since been identified in sporadic forms of clear cell RCC. It was subsequently shown that the VHL protein plays a key role in the cellular response to changes ambient oxygen by regulating the cellular levels of the alpha subunits of a group of transcription factors known as hypoxia inducible factors; with loss of VHL, there is overexpression of hypoxia inducible factors. Hypoxia inducible factors, in turn, upregulate a variety of proteins (including VEGF) that are believed to play a key role in VHL-dependent oncogenesis. Several lines of evidence have subsequently implicated HIF2 as the key player in this process. As you know, the 2019 Nobel Prize in Medicine and Physiology was awarded to Drs. William Kaelin, Gregg Semenza and Peter Ratcliffe for their work in understanding how cells adapt to changes in oxygen levels.

Understanding the biochemical consequences of VHL inactivation and how these changes lead to clear cell kidney cancer were critical drivers of the next step-trying to design and test pharmacologic inhibitors of these pathways. While HIF2 was a logical target for pharmacologic intervention, it was initially believed that HIF itself was 'undruggable'; therefore early efforts targeted downstream consequences of HIF overexpression, particularly the VEGF pathway. While several VEGFR inhibitors were found to be effective in sporadic clear cell RCC, their role in the management of VHL patients was limited. Phase 2 studies showed that although these agents had some activity against VHL-associated renal tumors there was little activity against other VHL-associated tumors. Moreover, the side effects associated with these agents were too much for VHL patients, who often preferred surgical intervention rather than dealing with the changes in quality of life associated with these agents. Then a big breakthrough was made by a group of scientists at UT Southwestern (led by Drs. Richard Bruick and Kevin Gardner) when they identified a particular binding pocket in HIF2 alpha that led to the design of small molecules that could bind in this pocket and prevent the interaction of the alpha subunit with its obligate heterodimeric partner, ARNT.PT 2385 was the first of these agent studied in the clinic , but was soon replaced by belzutifan (formerly PT2977 and MK-6482), which was more potent and had better pharmacologic characteristics. PT2977 quickly went through phase 1 evaluation, was shown to be well tolerated, and then evaluated in a phase 2 study that led to its approval for patients with VHL-associated tumors. As a result of this approval, we have, for the first time, a viable non-surgical treatment option for helping patients with certain types of VHL-associated tumors. Incidentally, this is also the first HIF2a inhibitor to be approved for any indication.

KCJ: **That's a great summary. Before we delve into the results, can you please explain the trial design that studied the efficacy of the belzutifan in humans?**

Dr. Srinivasan: For this open-label phase 2 study, eligible patients had to have VHL disease with at least one measurable renal tumor that did not require immediate surgery, no evidence of metastatic disease and should not have received any prior systemic anticancer therapy for VHL. The primary end point was the objective response rate in VHL-associated RCC as evaluated by independent central radiology review. Secondary outcomes included duration of response (DOR), time to response, progression-free survival (PFS), safety and tolerability as well as response rate in non-renal VHL associated tumors evaluated individually in each affected organ system.

KCJ: **We are hearing a lot of clinical data from Study-004 trial. What are some key findings?**

Dr. Srinivasan: As presented at the 2021 ASCO Annual meeting, almost half of all patients achieved an objective response in their renal tumors and an overwhelming majority had some reduction in their tumor size. Additionally, we also saw responses in other affected organ systems, including the pancreas, CNS and eyes. Importantly, the side effect profile was quite favorable, and severe side effects that led to drug discontinuation were uncommon. Anemia, an expected side effect based on the mechanism of action of the drug, was one of the most common side effects but was mild and easily managed in most patients.

KCJ: **How would you compare study results from belzutifan Vs those agents that you may have used for treating patients with VHL-associated renal cell carcinoma?**

Dr. Srinivasan: There have been no head- to head comparisons of belzutifan with other agents such as VEGFR inhibitors. However, as mentioned before, VEGFR inhibitors such as sunitinib and vandetanib appear to have limited activity against non-renal tumors and are also associated with patient tolerability concerns that we hope will not be an issue with belzutifan. My impression is that we will be seeing more consistent and more widespread reduction in tumor size across all organs in patients taking belzutifan, as compared to previously evaluated agents.

KCJ: **Moving on from FDA approval based on phase 2 data involving 61 patients, you'll be seeing patients in a much broader context. How are you going to incorporate it into your real world scenario both in practice?**

Dr. Srinivasan: I believe that belzutifan will play an important role in the management of certain VHL patients and should be used judiciously along with surgery as part of a multidisciplinary strategy. My hope is that if properly used, belzutifan will help reduce the number of surgical procedures patients will need to undergo. A lot of questions remain to be answered such as what is the best time to start the drug, how will patients tolerate in the long term and will resistance to the agent emerge? These are important questions that we will be able to answer in time. What is clear, however, is that the approval of belzutifan represents a significant addition to the VHL therapeutic landscape and will fundamentally alter the approach to these patients.

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KCJ: **What are the key lessons from the Study 004 that you would like to see adopted and taken forward in phase 3 trials and further research stages?**

Dr. Srinivasan: Given the relative rarity of VHL, it would be difficult to conduct a large, randomized study. The choice of a comparator in a randomized study would also pose a challenge since there isn't another agent with established activity in VHL. What we have learned, however, is that a small but well-designed study can effectively address important clinical questions that can serve as the basis for FDA approval, a paradigm that could be used in other rare diseases.

KCJ: **Finally, can you sum up your expectations for the future in terms of how belzutifan in combination with TKIs/immunotherapies will continue to evolve?**

Dr. Srinivasan: Currently, an ongoing phase 3 multicenter international study is studying metastatic clear cell RCC patients who have failed standard therapy; patients are being randomized to get either belzutifan or everolimus. There are also studies looking at belzutifan in combination with IO and/or TKIs in patients with advanced ccRCC. However, these studies are being done in patients with sporadic ccRCC, not in VHL patients. Combinations in VHL should be explored cautiously. We have learned from prior studies that some VEGFR TKIs are not well tolerated by VHL patients, which will limit our ability to use these agents as combination partners. IO based combinations may be considered, but it is important to keep in mind that when designing these studies, toxicity considerations and not just efficacy, are going to be key.