The therapeutic options for patients with urothelial carcinoma, the most common form of bladder cancer, are limited. The standard first-line treatment, platinum-based chemotherapy, causes severe side effects, helps only about two thirds of the recipients, and has a median survival of only about 1.5 years. Options for the other 80 percent, in whom the cancer continues to progress or turns metastatic, are poor to nonexistent.

That bleak state of affairs could be altered by the results of a recent worldwide Phase III RANGE clinical trial. Its principal investigator was Daniel P. Petrylak, MD, Professor of Medicine and Urology, and Co-Director of the Signal Transduction Research Program. He and his co-investigators tested a new combination therapy on bladder cancer patients who had previously been unsuccessfully treated with platinum-based chemotherapy. About 10 percent of these patients also had failed to respond to checkpoint inhibitors. “This was a group that you would expect to do poorly,” said Dr. Petrylak.

The trial included 530 patients with advanced or metastatic bladder cancer from 124 sites in 23 countries. The patients were randomly split into two groups. About half of them received docetaxel, a non-platinum-based chemotherapy drug, plus a placebo. The other half received docetaxel in combination with ramucirumab, an anti-angiogenic drug. The results confirmed what Dr. Petrylak and his co-investigators had found in their Phase II study. “We showed about a doubling of the objective response rate, to 24 percent, and also significantly improved progression-free survival when ramucirumab was combined with docetaxel, compared to docetaxel alone,” said Dr. Petrylak. “This is the first Phase III trial in which a combination therapy has shown an advantage over chemotherapy alone,” said Dr. Petrylak.

He presented these results at the European Society for Medical Oncology (ESMO) Congress last September in Madrid. The investigators’ paper was published in The Lancet.

Ramucirumab inhibits VEGF-2 (human ‘vascular endothelial growth factor receptor 2’), a protein whose signals stimulate cells to form new blood vessels. Tumors are highly vascular. By blocking VEGF-2’s signals to nutrient-hungry cancer cells, ramucirumab cuts off the blood supply that cancer depends upon to survive and spread.

“Ramucirumab is already approved for other tumor types such as gastric cancer and lung cancer,” said Dr. Petrylak. “Adding anti-angiogenesis agents to chemotherapy has become a standard of care in those cancers, and it’s a way to move forward in the treatment of urothelial cancer.”

Dr. Petrylak hopes that the Phase III results will encourage the FDA to consider approving ramucirumab for bladder cancer, especially if the overall survival data for patients who took the combination therapy mirrors the progression-free survival data. “If we see a survival benefit, that trumps everything,” he said. He was pleasantly surprised to find that patients who received the combination therapy did not experience more side effects than patients who took docetaxel alone. “That’s important,” explained Dr. Petrylak. He was also pleasantly surprised to find that patients who received the combination therapy had less anemia. “With most chemotherapy agents,” he said, “you see a deterioration of performance status”—a measure of a patient’s general well-being—“but we didn’t see that here.”

The progression-free survival rate of patients on the combination therapy was 4.07 months versus 2.76 months for those on docetaxel alone, a small improvement that raised questions about its clinical relevance. “The counterargument is that the objective response rate doubled,” said Dr. Petrylak, “and in my mind that’s clinically significant.” In other words, the improved rate sounds notably relevant to patients who need a further option.

He also points out that that there is no FDA approved agent for patients who have failed as checkpoint inhibition therapy, as most do—75 percent don’t respond. Dr. Petrylak and his colleagues are currently running trials that combine immune checkpoint inhibition with anti-angiogenic agents—for instance, ramucirumab with the inhibitor pembrolizumab. They think such combinations may be synergistic.

“There are a lot of possible combinations, and they are opening a lot of doors,” said Dr. Petrylak. “It’s a very exciting time in bladder cancer. When I came to Smilow five years ago this was a disease that had no real options for treatment once patients progressed after primary chemotherapy, and now our patients will likely have multiple options in the next couple of years.”