Long-term IMPACT data find improved survival when targeted therapies matched to tumor-specific gene mutations

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Matching targeted therapies to tumor-specific gene mutations across tumor types improved progression-free survival (PFS) and overall

survival (OS) in patients with advanced disease relative to those receiving non-matched treatment (NMT), according to research from The University of Texas MD Anderson Cancer Center. The researchers also found that receiving matched targeted therapy (MTT) was an independent factor for predicting longer OS.

Long-term data from IMPACT show that the three-year OS was 15 percent in the MTT group compared to 7 percent in the NMT group. The 10-year OS was 6 percent in the MTT group, compared to 1 percent in the NMT group. Apostolia M. Tsimberidou, M.D., Ph.D., professor, Investigational Cancer Therapeutics, presented the findings on the press program at the 2018 American Society for Clinical Oncology Annual Meeting.

The study is the first and largest precision medicine trial to look at survival and has the longest follow-up of any such trial, explained Tsimberidou, IMPACT's principal investigator.

MD Anderson opened IMPACT in 2007 after her experience with the targeted therapy Gleevec showed how it changed both the treatment and survival rates for chronic myeloid leukemia (CML), once a deadly disease, she said.

"When we opened IMPACT, it was viewed as incredibly novel. Because of the variability, frequency and rarity of alterations in specific solid tumor types, it was thought it would be difficult to use molecular testing for clinical trial selection, without taking into consideration any specific characteristics," Tsimberidou said. "However, gleaning from our Gleevec-CML experience, we hypothesized that genetic and molecular analysis of solid tumors also could enable the selection of optimal therapy for patients with solid tumors."

The umbrella protocol enrolled 3,743 MD Anderson patients from 2007

to 2013. All were referred to MD Anderson's Phase I program with end-stage disease. The patients' median age was 57 years, with a range in age from 16 to 86. The ratio of women to men was 61 to 39 percent, respectively. The most common cancers treated were gastrointestinal, gynecologic, breast, melanoma and lung, with the rest being more rare types.

As expected in this population, patients were heavily pre-treated; the median number of prior therapies received was four, with some being treated with any many as 16 previous therapies, said Tsimberidou.

All 3,743 patients enrolled in IMPACT received molecular testing; 1,307 were found to have at least one molecular alteration, with 711 receiving MTT (with or without chemotherapy) and 596 receiving NMT. The majority of IMPACT participants who received MTT received an investigational drug then being tested in a clinical trial; others received an FDA-approved targeted therapy commercially approved for another indication.

In those who received MTT, the median PFS was 4 months and the median OS was 9.3 months, compared to 2.8 months and 7.3 months, respectively, in those who received NMT.

Given the quantity of patients enrolled and the length of follow-up, the MD Anderson researchers were able to analyze the different pathways that predicted response in the MTT groups.

Given the number of patients in the trial and the length of follow-up, the investigators were able to develop a prognostic score to predict OS. Taking into consideration all baseline characteristics in the 1,307 patients who received molecular testing, the absence of liver metastases, normal LDH levels, normal functional status, albumin levels and platelet counts were all found to be independent factors for longer OS. Most

interestingly, said Tsimberidou, receiving MTT was also found to be an independent factor associated with longer OS.

In contrast, shorter survival was associated with liver metastases, elevated LDH levels, poor functional status, low albumin levels, elevated platelet counts, and age 60 years or older. In addition, molecular alterations in the PI3K/AKT/mTOR pathway were an independent factor predicting shorter overall survival compared to other alterations.

When type of therapy was added to the model, NMT was found to be an independent factor predicting shorter survival, said Tsimberidou.

IMPACT's follow-up study, IMPACT2, is a randomized Phase II looking at PFS and is ongoing. Tsimberidou noted that the advances from IMPACT to IMPACT2, like next-generation sequencing technologies, and the use of immune features and new drugs, including immunotherapy, are staggering.

"When IMPACT first opened, we tested for no more than one-to-two genes," she said. "Now patients are being tested for hundreds of actionable genes, amplifications and mutations, as well as for immune markers. Ideally, in the future, patients' tumor testing and cell-free DNA analysis will become the standard of care at the time of diagnosis, in hopes of making a difference for patients upfront, especially in those with hard-to-treat cancers."

The study was supported by philanthropy funds from: Mr. Alberto Barretto, Jamie's Hope, Mr. and Mrs. Zane W. Arrott, and Mr. Steven McKenzie. Tsimberidou will present the study in full in a poster session on June 4, 2018. Tsimberidou serves as a consultant to Roche, Europe.

Provided by University of Texas M. D. Anderson Cancer Center