# Immunotherapy Improves Outcomes for People With Locally Advanced Lung Cancer

Imfinzi tripled progression-free survival in previously treated patients with inoperable lung cancer.

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A treatment that helps the immune system fight cancer significantly increased progression-free survival for people with Stage III non-small-cell lung cancer, according to results from the PACIFIC trial presented this week at the European Society for Medical Oncology meeting in Madrid.

More than half of patients treated with Imfinzi (durvalumab) following radiation and chemotherapy were still alive with no worsening of disease after one year, compared with just over a third of those who received a placebo. The median progression-free survival duration was 16.8 months in the Imfinzi group and 5.6 months in the placebo group.

Non-small-cell lung cancer, which accounts for more than 80 percent of all lung cancers, is often detected late and has a high mortality rate. It is the leading cause of cancer-related death for both men and women in the United States, according to the Centers for Disease Control and Prevention.

Stage III lung cancer, also known as locally advanced, means that the cancer has metastasized, or spread, to lymph nodes around the lungs and possibly to other organs and structures in the chest, but it has not yet spread to the other lung or to distant organs. Lung cancer at this stage often cannot be completely removed by surgery, and it is usually treated with radiation and chemotherapy. About a third of people with non-small-cell lung cancer have Stage III disease at the time of diagnosis.

Imfinzi, from AstraZeneca, is a monoclonal antibody that interferes with the PD-1 receptor, an immune checkpoint on T cells. Some cancers can hijack PD-1 to disable immune responses against them. Unlike PD-1 checkpoint blockers such as Keytruda (pembrolizumab) and Opdivo (nivolumab), which attach to the PD-1 receptor itself, Imfinzi attaches to its binding partner or ligand (called PD-L1) on cancer cells.

Blocking the interaction between PD-1 and PD-L1 can restore the activity of T cells, enabling them to locate and destroy tumors. This type of immune-based treatment is often better tolerated than

traditional chemotherapy, which kills not only cancer cells but also rapidly dividing healthy cells throughout the body.

Luis Paz-Ares, MD, of Hospital Universitario Doce de Octubre in Madrid, presented findings from the Phase III PACIFIC trial, which enrolled more than 700 patients in 26 countries.

The participant had inoperable non-small-cell lung cancer and had received standard therapy consisting of radiation and chemotherapy using platinum-based drugs. Seventy percent were men, a majority of them were white and the median age was 64. More than 20 percent had PD-L1 expressed on at least a quarter of their tumor cells, while just over 40 percent had less than 25 percent PD-L1 expression and the rest had not been tested.

Study participants were randomly assigned to receive IV infusions of Imfinzi or a placebo every two weeks for up to a year. They stopped treatment if they experienced disease progression or unacceptable side effects. This so-called consolidation therapy was started one day to six weeks after radiation and chemotherapy.

Paz-Ares reported that the median duration of progression-free survival was significantly longer with Imfinzi compared with the placebo in an interim analysis: 16.8 months versus 5.6 months. Imfinzi is the first medication to show improved progression-free survival in this patient population, according to an AstraZeneca press release.

After 12 months, 55.9 percent of Imfinzi recipients were still alive without worsening of disease, compared with 35.5 percent of placebo recipients. After 18 months, progression-free survival rates were 44.2 percent and 27.0 percent, respectively. The combined risk of disease progression or death decreased by nearly half in the Imfinzi group.

The objective response rate, meaning complete or partial tumor shrinkage, was 28.4 percent in the Imfinzi group and 16.0 percent in the placebo group. People taking Imfinzi were less likely to develop new tumors during treatment, including cancer spread to the lymph nodes or the brain.

The median duration of response was 13.8 months in the placebo group, but it could not be determined in the Imfinzi group because most patients were still responding. Study participants have not yet been observed long enough to determine overall survival, and follow-up is continuing.

Imfinzi “offers hope to increase the cure rate in this setting, but more mature follow-up is needed to assess its impact on survival,” Paz-Ares said.

Imfinzi worked better than the placebo in people with both higher and lower PD-L1 expression levels. This has also been seen in trials of other PD-1 checkpoint blockers for various kinds of cancer, making it difficult to predict which patients will respond well.

Treatment with Imfinzi was generally safe and well tolerated. Thirty percent of patients in the Imfinzi group experienced severe adverse events, but so did 26 percent of those in the placebo group. About 15 percent of Imfinzi recipients and 10 percent of placebo recipients stopped

treatment due to adverse events.

The most common treatment-related side effects were cough (35 percent in the Imfinzi group versus 25 percent in the placebo group), lung inflammation possibly caused by radiation (34 percent versus 25 percent), fatigue (24 percent versus 21 percent) and shortness of breath (22 percent versus 24 percent). The most frequent severe adverse event was pneumonia, observed in about 4 percent of patients in both groups.

The major concern with PD-1 checkpoint blockers is immune-related adverse events. These drugs are designed to work by restoring immune responses against cancer cells, but they can also take the brakes off the immune system more broadly, leading to excessive inflammation of healthy tissue. Immune-related adverse events were more common overall in the Imfinzi group than in the placebo group, but severe events were similar in both groups (about 3 percent).

Imfinzi "demonstrated significant and clinically meaningful improvement in progression-free survival, which was supported by secondary endpoints, and was well tolerated," the researchers concluded. "[Imfinzi] is a promising therapeutic option in this setting."

A limitation of this study is that it excluded people with the most severe Stage IV lung cancer as well as people with Stage III cancer who experienced disease progression after radiation and chemotherapy.

This summer AstraZeneca reported preliminary results from the Phase III MYSTIC trial, which showed that Imfinzi used alone or in combination with another type of immunotherapy (tremelimumab) did not improve progression-free survival compared with chemotherapy in Stage III or IV lung cancer patients being treated for the first time. Follow-up is continuing to see whether there is a benefit in terms of overall survival.

Imfinzi has received Food and Drug Administration "breakthrough therapy" status as a potential treatment for patients with locally advanced, inoperable non-small-cell lung cancer that has not progressed after radiation and chemotherapy. It is currently approved for bladder cancer and is under study, alone and in combination regimens, for a variety of other cancer types.

To read the study abstract, click here.

To read an AstraZeneca press release about the study, click here.

Results from the PACIFIC trial were published online in the New England Journal of Medicine

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