Durvalumab immunotherapy with standard chemotherapy improved survival in malignant pleural mesothelioma

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The PrE0505 phase 2 clinical trial results are published in the November 8 issue of *Nature Medicine*. The study evaluated the addition of

durvalumab immunotherapy to standard chemotherapy in patients with previously untreated, inoperable malignant pleural mesothelioma (MPM), a cancer of the tissues that line the lungs. The trial met its primary endpoint with a median overall survival of 20.4 months—significantly longer than the 12 months with historical control (Vogelzang NJ. *J Clin Oncol* 2003). For patients with epithelioid tumors, the most common subtype of MPM, the median overall survival was 24.3 months.

"Concurrent durvalumab immunotherapy with platinum-based chemotherapy has promising clinical activity in patients with malignant pleural mesothelioma (MPM), and responses appear to be driven by the genomic background of the disease," said Peter J. O'Dwyer, MD, CEO and chair of PrECOG, LLC. "In the PrE0505 phase 2 trial, survival for patients with epithelioid MPM exceeded two years, and some of these patients continue to be free from tumor progression today."

The multi-center study PrE0505 (NCT02899195) was conducted at 20 university cancer centers and community hospitals across the US with Patrick Forde, MD (Johns Hopkins University) as the lead investigator. The study involved 55 patients with previously untreated MPM who received a fixed dose of durvalumab immunotherapy intravenously once every three weeks, in combination with chemotherapy (pemetrexed and cisplatin or carboplatin) for up to six cycles.

"There has been limited progress in the treatment of mesothelioma in the past two decades; the PrE0505 results provide a novel strategy to extend survival," said senior author Suresh S. Ramalingam, MD, executive director of the Winship Cancer Institute at Emory University in Atlanta. "Also, the in-depth translational studies conducted in conjunction with the clinical trial by the PrECOG team provide additional insights into patient selection methods for this novel regimen."

The median follow-up for the study was 24.2 months. The primary endpoint was overall survival. The estimated percentages of patients alive were 87% at six months, 70% at 12 months, and 44% at 24 months.

The objective response rate (ORR), a secondary endpoint, was 56.4%. ORR is defined as the percentage of patients for whom a therapy causes significant tumor shrinkage.

The most commonly reported adverse events were predominantly low-grade and included fatigue, nausea, and anemia. All patients in the study received at least one cycle of durvalumab with chemotherapy; 48 patients (87%) completed six cycles.

Differences were noted by the histological subtype of the MPM tumors. Patients with tumors of the epithelioid subtype had a higher ORR than those with non-epithelioid tumors (66% versus 29%). Similarly, patients with epithelioid MPM had longer overall survival than those with non-epithelioid MPM (24.3 months versus 9.2 months), as well as significantly longer progression-free survival (8.2 months versus 4.9 months).

The *Nature Medicine* publication also features in-depth analyses of the genomic and immunologic features of responding tumors.

The genomic analysis of the PrE0505 data was led by Valsamo (Elsa) Anagnostou, MD, Ph.D. and colleagues at the Johns Hopkins Kimmel Cancer Center and Bloomberg~Kimmel Institute for Cancer Immunotherapy in Baltimore, MD. Among the authors' observations:

- MPM tumors with a high immunogenic mutation load responded favorably to chemo-immunotherapy, especially in the epithelioid group
- In addition to changes in the sequence of the genetic material of

cancer cells, genome-wide structural changes and a signature of homologous recombination deficiency (indicating defects in repair mechanisms of damaged DNA in cancer cells) were more pronounced in responding tumors
- Patients with deleterious germline mutations in cancer-predisposing genes, including but not limited to genes involved in DNA damage repair, had significantly longer progression-free and overall survival with chemo-immunotherapy
- In looking at the tumor microenvironment (which comprises normal cells and blood vessels that surround the tumor, contains immune cells, and can affect how cancer cells grow and spread), tumors that responded to therapy were surrounded by a greater variety of a specific population of immune cells, called T cells

Pleural mesothelioma is a rare and aggressive form of cancer with a poor prognosis and limited treatment options. Historically, the five-year survival rate is less than 10%. The majority of these cancers are caused by exposure to asbestos and consequent chronic inflammation in the pleura—a thin layer of tissue that covers the lungs and lines the interior wall of the chest cavity.

PrECOG and lead US investigator Dr. Forde are collaborating with the University of Sydney through its NHMRC Clinical Trials Centre and TOGA (Thoracic Oncology Group of Australasia) on an international phase 3 trial called DREAM3R (PrE0506, NCT04334759). The DREAM3R study opened to patient enrollment in early 2021 and is currently enrolling patients with inoperable MPM at multiple study sites in the US, Australia, and New Zealand to further investigate the durvalumab-chemotherapy combination versus chemotherapy alone. This study also includes additional exploration of genomic characteristics of response.

More information: Patrick Forde, Durvalumab with platinum-

pemetrexed for unresectable pleural mesothelioma: survival, genomic and immunologic analyses from the phase 2 PrE0505 trial, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01541-0. www.nature.com/articles/s41591-021-01541-0

Nicholas J. Vogelzang et al, Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma, *Journal of Clinical Oncology* (2003). DOI: 10.1200/JCO.2003.11.136

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