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NEWS

Tackling Mesothelioma With Immunotherapies

By Vicki Brower

The first large-scale genomic analysis of mesothelioma revealed a spectrum of actionable driver mutations that will enable some patients to be treated with certain existing drugs, according to lead investigator Raphael Bueno, M.D., chief of thoracic surgery at Brigham and Women's Hospital in Boston. Comparing 216 samples of malignant pleural mesothelioma (MPM) with normal tissue, Bueno and colleagues identified 2,500 gene alterations and 10 substantially mutated genes, including BRCA1, p53, and NF2 tumor suppressor, as well as the checkpoint target PD-L1 (ligand 1) (*Nat. Genet.* 2016;48,407–16; doi:10.1038/ng.3520). "These discoveries will change how some tumors are classified and treated, and help better define subsets of patients for clinical trials," Bueno said.

Raphael Bueno, M.D.

MPM, which affects the lung's pleura—the membranes lining the lung—is the most common mesothelioma. Eighty percent of cases develop years after exposure to asbestos. With only 3,200 new cases per year in the United States, approximately the same number die yearly from it, making it one of the deadliest and hard-to-treat malignancies. The disease has a mortality rate of 80%–90% within 5 years of diagnosis. Stage I disease and some stage II cases are operable, but MPM usually is not diagnosed early enough for surgery. First-line therapy, cisplatin and pematrexed, produces a median overall survival (OS) of 12–13 months. Genomic research and new immunotherapies in early-stage trials offer MPM patients new hope for extending life.

[The discovery of a spectrum of actionable driver mutations] "...will change how some tumors are classified and treated, and help better define subsets of patients for clinical trials."

Extending Survival

In March, researchers reported results of a pilot trial with a locally delivered immunotherapy–gene therapy vaccine in 40 patients with inoperable disease. They received two intrapleural doses of a replication-defective adenoviral vector containing the gene for human interferon-α2b with 14 days of the nonsteroidal anti-inflammatory drug celecoxib, followed by chemotherapy. Eighteen received pematrexedas first-line therapy, and 22 received second-line treatment with pematrexedor gemcitabine. The median OS for all with epithelial-based MPM was 21.5 months, compared with 7 months for those without epithelial histology. Patients in the first-line cohort had OS of 12.5 months, and for those receiving second-line treatment, 21.5 months. Thirty-two percent of patients are alive at 2 years.

"For the first time ever, we are now seeing 2–3 years' survival in some patients, which is remarkable," said Steven Albelda, M.D., William Maul Measey Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. "Interferon γ has been used with some success in early-stage disease, but it's limited by side effects when given systemically in sufficient doses," Albelda said. He indicated that interferon kills cells and stimulates the immune system to attack the cancer, and the adenoviral vector produces inflammation, which has similar effects. Celecoxib affects the immunosuppressive tumor environment and with chemotherapy causes immune stimulation and cell death. Of the 40 patients, 32 tolerated the treatment well, with adverse effects attributed to the vector and cytokine-release syndrome, Albelda explained.

In a phase I study with an oncolytic vaccinia virus, GL-ONC1, administered intrapleurally to 13 patients with advanced disease via malignant pleural effusion, results reported at the 2015 American Society of Clinical Oncology annual meeting showed infection of tumor samples in nine patients. The attenuated virus replicates only in tumor cells. The time to progression in five patients was 9 months, and in one patient, 18 months. The median survival of MPM patients with malignant pleural effusion is 4–6 months. A phase I/II study is ongoing.

Researchers are testing checkpoint inhibitors in MPM as well. In the phase Ib trial, KEYNOTE-028, pembrolizumab, a

programmed cell death 1 (PD-1) receptor inhibitor, produced controlled disease in 78% of 25 previously treated patients, all of whom were PD-1 positive. Seven, or 28%, had partial responses, and 48% had stable disease, which investigator Evan Alley, M.D., Ph.D., clinical associate of medicine and codirector of Penn Mesothelioma and Pleural Program at the University of University of Pennsylvania, called "unprecedented" when discussing the results at the 2015 American Association for Cancer Research annual meeting. Ten who remained in treatment were partial responders, with some responses lasting more than 24 weeks. Only 10% generally respond to second-line treatment. The ligand of PD-1 is overexpressed in mesothelioma and is associated with poor prognosis. A phase II study is ongoing.

Raffit Hassan, M.D., cochief of thoracic and gastrointestinal oncology and head of the thoracic and solid tumor immunotherapy section of the National Cancer Institute (NCI) reported results of a phase Ib study with the PD-L1 inhibitor avelumab in 20 patients in September 2015 at the European Cancer Congress in Vienna. Patients, who were not stratified by PD-L1 status, had an overall response rate of 15%, and median progression-free survival (PFS) was 16.3 weeks. Tremelimumab, a CTLA-4 (cytotoxic T-lymphocyte–associated protein 4) inhibitor, failed to hit its OS endpoint midstage as monotherapy in second- or third-line treatment in the phase IIb DETERMINE trial, as reported in March 2016 by its maker, AstraZeneca [no data released besides this].

Targeting Mesothelin

Mesothelin is a new target being exploited in many early-stage immunotherapy trials. A cell surface tumor antigen, mesothelin is the subject of two decades of research by Hassan. Mesothelin is highly expressed in mesothelioma and other epithelial malignancies, including pancreatic, ovarian, lung, bile duct, and triple-negative breast cancer, and in low levels in some normal tissues, making off-target effects a concern.

With Ira Pastan, M.D., cochief in the Laboratory of Molecular Biology and head of the molecular biology section at the National Cancer Institute, Hassan has developed several mesothelin-targeting treatments in the clinic. "Mesothelin overexpression is also associated with the expression of metalloproteinase-9, a protein linked to the degradation of extracellular matrix, which helps cancer cell migration and local invasion," said Prasad Adusumilli, M.D., deputy chief of the thoracic service at Memorial Sloan Kettering Cancer Center in New York.

SS1P, developed by Hassan and Pastan, is a recombinant antimesothelin immunotoxin that consists of a mouse antibody fragment linked to PE38, a truncated portion of the *Pseudomonas* exotoxin A. SS1P binds to and kills mesothelin-expressing cells by inducing apoptosis and inhibiting protein synthesis. As monotherapy in a phase I study in advanced, chemoresistant MPM, SS1P had limited efficacy, which researchers attributed to low tumor penetration due to tumor cell density and interstitial pressure. But SS1P showed synergy with chemotherapy, which disrupted clustering of cancer cells, enabling the immunotoxin to better reach the tumor. In a second phase I study, SS1P and pematrexed and cisplatin as frontline therapy showed better responses than with chemotherapy alone (41% for combined chemotherapy and 17% for cisplatin monotherapy), a response rate of 69%, and 77% in those receiving the maximum tolerated dose (*Cancer* 2014;120:3311–9; doi:10.1002/cncr.28875). They also showed that treating chemotherapy-resistant MPM with B- and T-lymphocyte–depleting pentostatin and cyclophosphamide prevents antibody formation in 10 patients, three of whom had major tumor regressions, with all alive at 15 months and two responding to chemotherapy after discontinuing immunotoxin therapy for a 30% partial response (*Sci. Transl. Med.* 2013; 5:208ra147; doi:10.1126/scitranslmed.3006941).

In April, Thierry Jahan, M.D., clinical professor in the department of medicine and Bonnie J. and Anthony Addario Endowed Chair in Thoracic Oncology at the University of California, San Francisco, reported results with CRS-207, a live, attenuated *Listeria monocytogenes* bacterium engineered to express mesothelin, with chemotherapy in 38 patients with advanced inoperable MPM. Speaking at the European Lung Cancer Conference in Geneva, Jahan said that in the phase Ib study, combination treatment yielded a disease control rate of 94% and a 59% response rate at median follow-up of 9.4 months. Median PFS was 8.5 months. Safety was good; side effects were temperature spike and chills, which both resolved within a day, according to Jahan. A randomized trial is being planned to open later this year.

Amatuximab, a chimeric antimesothelin antibody also developed by the NCI team, in its first phase II study, MORAb-009-003, had a 14.8-month median OS, which though comparing favorably to historical control of 13.3 months, did not improve OS at a statistically significant level. A new analysis, however, shows that in patients taking more frequent (weekly) doses, median OS was 375 days, and for the lower doses, 583 days, with similar effects on PFS. Amatuximab recently began a second phase II study, ARTEMIS, in 89 patients with chemotherapy, which is double-blind, randomized, and placebo controlled. All patients will receive chemotherapy with either amatuximab or placebo, followed by maintenance with either amatuximab or placebo.

At least three groups—NCI, Penn, and Memorial Sloan Kettering—are developing mesothelin-specific chimeric antibody receptor (CAR)-targeting T cells for MPM and other solid tumors. CAR T cells are engineered T cells, autologous or allogeneic, which have been modified to target specific tumor antigens.

Interim results from a phase I study with autologous CAR T cells transfected with antimesothelin mRNA without lymphodepletion were discussed at the April 2015 AACR meeting in Philadelphia by Janos Tanyi, M.D., Ph.D., principal investigator of immune therapy trials at Penn (abstract CT-105;). That endeavor found grade 3 and 4 side effects and evidence that the cells, modified to transiently express the antigen, reached the target tissue and did not cause off-target side effects. "We have now developed a fully human CAR T-cell construct, which will enter trials in the summer," Albelda said.

Adusumilli's group has treated two patients with metastatic MPM without side effects in a phase I study with its autologous CAR T cells delivered intrapleurally, plus cyclophosphamide. "In a previous study comparing intravenous to intrapleural administration, we found intrapleural is far more effective in delivering cells to the desired site and in their ability to expand," Adusumilli said (*Sci. Transl. Med.* 2014; 6:261ra15; doi:10.1126/scitranslmed.3010162). NCI also is recruiting patients with metastatic cancer for its CAR T-cell study with fludarabine.

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