Agent Targeting BRAF Mutations Shows Promise

BY PATRICE WENDLING

BERLIN — An investigational agent that targets the BRAF mutation and is present in at least half of melanoma patients has shown impressive results in a second phase I trial. Response rates with the oral agent PLX4032 reached an unprecedented 70% in metastatic melanoma, signaling a fundamental shift in the way this deadly disease will be treated.

“What’s very encouraging is actually that the response rate in nonmutated melanoma is 0%; so we know exactly what we’re doing,” European Cancer Organization (ECCO) president Dr. Alexander Eggermont told reporters at the joint congress of ECCO and the European Society for Medical Oncology, where the latest data were presented. The ability to target therapy based on genetic mutation status is expected to transform the once-blighted field of melanoma, which has seen no improvement in overall survival in the last 30 randomized trials using various chemotherapeutic agents and vaccines. The 5-year survival rate for stage IV melanoma remains at just 18%.

“If I have a young, talented medical oncologist at a cancer center, now I would have no reservations to recommend him to become a melanoma specialist because it’s going to become a very exciting field instead of a grave- clysmic; this is hugely important,” Dr. David E. Fisher, chief of the dermatology service and director of the cutaneous biology research center at Massachusetts General Hospital, Boston, said in an interview. “One of the fellows here said, ‘Wow, this is fantastic; now I will get time to get to know my metastatic melanoma patients.’ That’s how bad the field was. So this is simply fantastic.”

The phase I extension trial included 31 metastatic melanoma patients who had a BRAF mutation known as V600E and who were treated twice daily with 960 mg of PLX4032. Among 27 evaluable patients, the response rate was 70% by RECIST, including 18 partial responses and 1 complete response. One partial responder subsequently became a complete responder after the data analysis cutoff date.

Progression-free survival is about 8.5 months, although the median has not yet been reached, lead author Dr. Paul Chapman said. Overall survival was not measured. Tumor shrinkage on MRI showed that, after just 15 days of treatment, FDG (18fluorodeoxyglucose) uptake was essentially shut down.

Enthusiasm for the study, which was supported by Plexxicon Inc., was not diminished by the preliminary nature of the data or a string of disappointing late-phase results from other promising melanoma agents.

“My take—and I think it’s pretty representative of many in the melanoma academic world—is that this is catalytic; this is hugely important,” Dr. David E. Fisher, chief of the dermatology service and director of the cutaneous biology research center at Massachusetts General Hospital, Boston, said in an interview. “Clinicians can predict which patients will respond and which won’t, based on the presence of the BRAF mutation. In addition, there is a very compelling mechanistic connection between precisely how this drug works and the nature of the clinical response, he said.

In a previous phase I dose-escalation trial in 55 patients with a variety of cancers, partial responses were reported in 9 of 16 metastatic melanoma patients with the BRAFV600E mutation who received sufficiently high doses of PLX4032. Patients who were lacking the BRAF mutation did not respond, according to data presented at this year’s annual meeting of the American Society of Clinical Oncology.

Because of the selectivity of the molecule, adverse events have tended to be mild, said Dr. Chapman, an attending physician on the melanoma/sarcoma service at Memorial Sloan-Kettering Cancer Center in New York. Common dermatologic events in the current trial were arthralgia (3%), rash (3%), photosensitivity (3%), and fatigue (7%).

A Disease of Subtypes

Dr. Chapman told reporters that genet- ic screening will have to become univer- sal in melanoma, just as KRAS testing is essential in treating colorectal cancer. Screening can be completed in 1-2 weeks at active, participating centers.

The BRAF mutation is not the first ex- ample of a genetic subtype targeted in metastatic melanoma; Dr. Fisher and his colleagues reported dramatic results last year after targeting the c-KIT mutation with imatinib (Gleevec). Although the ar- mamentarium is not deep for drugs that block BRAF, there are several available agents that target c-KIT, including nilotinib (Tasigna) and sunitinib (Sutent).

Although the signal from the PLX4032 trials is strong, the early data suggest that the single agent is not going to be enough, Dr. Chapman said. Future strategies will likely include combination therapy and the use of agents prior to the develop- ment of metastatic disease.

“We need complete remission. We need these tumors to melt away,” he said.

Reporters questioned whether PLX4032 could be used with the mono- clonal antibody bevacizumab (Avastin), which increased overall survival by more than 40% when combined with the chemotherapeutic agents carboplatin and paclitaxel in a phase II metastatic melanoma trial that was also presented at the con- gress.

Dr. Chapman responded, “If you shrink the tumor too much with PLX4032, it may not be as sensitive to antiangiogenic vascular endothelial growth factor] inhibition, but from a toxicity point of view, I don’t think there’s any reason why we couldn’t combine them.”

Further Trials

A phase II single arm trial (BRIM2) is evaluating 960 mg twice daily of PLX4032 in about 100 BRAFV600E-positive patients who have progressed after at least one prior melanoma treatment. Enrollment is expected to be complete by the end of 2009, according to Plexi- cons Web site.

The randomized, phase III BRIM3 tri- al is expected to start by the end of 2009 in first-line patients. Plexicon is code- veloping PLX4032 with Roche.

Dr. Chapman said he had no conflicts of interest.