

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-bleak 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 graveyard,” Dr. Eggermont of Erasmus University in Rotterdam, the Netherlands, said at a press briefing. “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.

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DR. EGGERMONT

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 Plexicon 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 cataclysmic; 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^{V600E} 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 BRAF^{V600E} 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 grade 3 events in the current trial were arthralgia (3%), rash (3%), photosensitivity (3%), and fatigue (7%).

A Disease of Subtypes

Dr. Chapman told reporters that genetic screening will have to become universal 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 example 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 armamentarium 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. Fisher said. Future strategies will likely include combination therapy and the use of agents prior to the development 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 monoclonal 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 congress.

DR. CHAPMAN

Dr. Chapman responded, “If you shrink the tumor too much with PLX4032, it may not be as sensitive to VEGF [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 BRAF^{V600E}-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 Plexicon’s Web site.

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

Dr. Chapman said he had no conflicts of interest. ■



Mycophenolate Mofetil May Reduce SCC Risk After Transplant

BY BRUCE JANCIN

BUDAPEST, HUNGARY — Switching renal transplant recipients from azathioprine to mycophenolate mofetil for long-term immunosuppression significantly reduced UVA photosensitivity in a crossover study.

This is likely to decrease the extraordinarily high rate of cutaneous squamous cell carcinoma (SCC) that renal transplant patients experience, Dr. Günther Hofbauer said at the annual congress of the European Society for Dermatological Research.

The medication switch did not affect glomerular filtration rate, urine protein-to-creatinine ratio, or other measures of allograft function, added Dr. Hofbauer of the University of Zurich.

SCC is the most common cancer in solid organ transplant recipients, with a 65- to 250-fold greater incidence than in the general population.

In response to the observation by other investigators that direct DNA damage occurs in response to azathioprine, Dr. Hofbauer and his coworkers measured photosensitivity to UVA and UVB in 16 kidney transplant recipients on long-term azathioprine and 17 on mycophenolate mofetil (CellCept).

They found that the mean minimal erythema dose for UVA in the azathioprine group was 21 J/cm², significantly less than the 34 J/cm² in patients on mycophenolate mofetil, according to Dr. Hofbauer. Thus, patients on azathioprine were markedly more photosensitive to UVA.

To follow up on this finding, the investigators conducted a switch from azathioprine to mycophenolate mofetil in 23 stable patients who had received a donor kidney a mean of 14.5 years earlier. Their minimal erythema dose for UVA on azathioprine was 16 J/m², but upon retesting after 3 months on mycophenolate mofetil, it increased to 25 J/m².

Azathioprine is a mainstay immunosuppressant given to prevent graft rejection in many types of transplant recipients. It is now known to cause selective UVA photosensitivity in the 320- to 400-nm wavelengths, with resultant incorporation of 6-thioguanine (6-TG)—the drug’s active metabolite—into the DNA of all cells in the body. The 6-TG absorbs UVA, with the resultant

production of reactive oxygen species capable of damaging DNA, Dr. Hofbauer explained.

The mean 6-TG level contained in the patients’ peripheral white blood cells dropped from 99 pmol/mg of total DNA while on azathioprine to 43 pmol/mg after 3 months on mycophenolate mofetil. A particularly striking finding, he said, was that the steeper the decline in DNA 6-TG, the greater the increase in the minimal erythema dose for UVA.

“The 6-TG levels didn’t drop to 0, so we have reason to believe that 6-TG stays in the system for much longer than our 3-month washout period,” he continued.

Study participants were typically on about 50 mg/day of azathioprine and were switched to 500 mg of mycophenolate mofetil twice daily.

“Our nephrologists say that dose of mycophenolate mofetil actually provides slightly greater immunosuppression, which should, if anything, decrease the rejection rate,” said Dr. Hofbauer, who had no conflicts of interest relevant to his presentation. ■



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DR. HOFBAUER