BRAF, KIT–Mutation Targeters Offer Hope

BY PATRICE WENDLING

ORLANDO — The concept of targeted therapies in melanoma took a step closer to reality with two early trials reporting positive responses to agents that specifically target BRAF or KIT mutations.

In a phase I study of 55 patients with a variety of cancers, 21 metastatic melanoma patients were treated twice daily with at least 240 mg PLX4032, an investigational oral, small-molecule inhibitor that selectively targets the BRAF V600E kinase mutation occurring in most melanomas.

Partial responses by RECIST (Response Evaluation Criteria in Solid Tumors) were confirmed in 9 of 16 BRAF V600E mutation–positive patients. Five of the nine responders had M1c disease, the highest "M" stage, Dr. Keith Flaherty and his associates reported at the annual meeting of the American Society of Clinical Oncology.

Seven patients developed disease progression at 3-14 months while still on therapy. A preliminary analysis suggests a progression-free survival of about 6 months, but the data are very immature and that estimate is likely to change with longer follow-up, said Dr. Flaherty of the University of Pennsylvania, Philadelphia.

In contrast, no tumor regression was observed in the five melanoma patients lacking the BRAF mutation, and all developed progressive disease within the first 3 months.

Interim results from a second phase II study of imatinib in inoperable melanoma showed that a KIT mutation or amplification was present in 21% (31 of 146 tumors) screened. Thus far, 15 of the 31 patients, median age 71 years, have been treated with 400 mg imatinib twice daily on a continuous basis.

Of the 12 patients evaluable for response, the overall rate was 33% by RECIST and included two complete responses and two partial responses, said Dr. Richard Carvajal, an oncologist with Memorial Sloan-Kettering Cancer Center in New York. Stable disease was reported in six patients and disease progression in two. The responses have been durable, lasting 40 weeks in some patients.

Partial responses were confirmed in 9 of 16 BRAF V600E mutation–positive patients treated with PLX4032.

DR. FLAHERTY

Dr. Carvajal noted that only one response by RECIST was reported in three prior phase II studies of imatinib in a total of 62 nonselected patients with advanced melanoma.

The findings are proof of concept that targeted therapies work in melanoma, a heterogenous group of diseases, said Dr. Boris Bastian of the University of California, San Francisco, who was invited to discuss the studies. He acknowledged that it is obviously early and few patients were treated, but that "it's a decisive step toward personalized medicine for our melanoma patients."

In the dose-escalation PLX4032 trial, sponsored by Plexxikon Inc. and Hoffman-La Roche Inc., dose-limiting toxicities developed in four of six patients who received 1,120 mg twice daily, the highest dose evaluated. A 960-mg twice-daily dosage is being evaluated as the maximum tolerated dose in an expanded cohort of mutation-positive melanoma patients, Dr. Flaherty said.

Adverse events with PLX4032 were clearly dose related, but even at higher doses, they tended to be mild, he said. Of note, 11% (six patients) were diagnosed while on study with cutaneous squamous cell carcinoma. Grade 3 or higher rash, fatigue, and pruritus were each reported in 2% of patients.

The PLX4032 study investigators disclosed financial ties with Plexxikon and Hoffman-La Roche. Dr. Carvajal and associates disclosed no personal conflicts of interest, but the study was supported by a Food and Drug Administration grant, an ASCO Young Investigator Award, and the Live4Life Foundation. Dr. Bastian disclosed consulting for Novartis and Exelixis Inc. ■

Pages 20a—20b