American Society of Clinical Oncology, 2010 Annual Meeting

and

Rose Bengal: From a Wool Dye to a Cancer Therapy

Walter Alexander

More than 5,000 abstracts were presented at this year's American Society of Clinical Oncology (ASCO) annual meeting, which took place from June 4 to 8 in Chicago. Slightly more than half of the nearly 33,000 attendees (26,000 professionals) traveled to the U.S. This article covers clinical trials of longer-term and alternative use of established drugs as well as promising investigational agents, including two agents for metastatic melanoma.

ASCO Highlights Tyrosine Kinase Inhibitors and Promising Melanoma Agents

Dasatinib (Sprycel) and Imatinib (Gleevec) In Chronic-Phase Chronic Myelogenous Leukemia: The Phase 3 DASISION Study

- Hagop Kantarjian, MD, MD Anderson Cancer Center, Houston, Tex.

Prior research has shown that once-daily dasatinib (Sprycel, Bristol-Myers Squibb), a tyrosine kinase inhibitor (TKI), can induce high rates of complete cytogenetic responses (CCyRs) and progression-free survival (PFS) in patents with chronic-phase chronic myeloid leukemia (CP–CML) after failed treatment with imatinib (Gleevec, Novartis). Investigators have also found that patients receiving imatinib who achieve CCyRs and major molecular responses (MMRs) by 12 months have longer PFS and reduced risks of disease progression or death. In a phase 2 study of first-line therapy with dasatinib, CCyR and MMR rates were high.

Results of the phase 3 DASISION study (Dasatinib versus Imatinib Study in Patients with Newly Diagnosed Chronic-Phase CML) (CA180-056) suggest that dasatinib 100 mg once daily should be considered as first-line therapy for newly diagnosed CP–CML, according to Dr. Kantarjian.

DASISION included 519 patients (mean age, 47 years) with CML who were randomly assigned to receive either dasatinib 100 mg/day (n = 259) or imatinib 400 mg/day (n = 260). Dose escalations to dasatinib 140 mg once daily and to imatinib 600 to 800 mg once daily were permitted when responses were suboptimal. The mean duration of therapy was 14 months. The primary endpoint was confirmed CCyR by 12 months (defined as a CCyR detected in two consecutive assessments). MMR was defined by the presence of 0.1% or fewer *bcr–abl* mutations.

At 12 months, CCyRs were noted in 83% of the dasatinib arms and in 72% of the imatinib arms ($P = 0.0011$); confirmed CCyRs were reported in 77% and 66% of patients in the two groups, respectively ($P = 0.0067$). An analysis of CCyR rates at 3, 6, 9, and 12 months revealed that the likelihood of achieving CCyRs at all points remained approximately 50% higher with dasatinib than with imatinib throughout the study ($P < 0.001$; hazard ratio [HR], –1.53).

MMR rates followed a similar pattern, with 12-month rates at 46% for dasatinib 100 mg once daily and 28% for imatinib 400 mg once daily ($P < 0.0001$). Patients were twice as likely to achieve MMRs at any time with dasatinib than with imatinib. The median time to achieve MMRs was 6.3 months for dasatinib and 9.2 months for imatinib. Progression to the accelerated or blast phase was less frequent with dasatinib (1.9%) than with imatinib (3.5%). None of the patients who achieved MMRs progressed to the accelerated or blast phase. Twelve-month overall survival was similar for both groups (97.2% for dasatinib and 98.8% for imatinib). Adverse event-related discontinuations were low (1.2% with dasatinib and 0.4% with imatinib).

Dr. Kantarjian concluded that dasatinib 100 mg once daily should become first-line therapy in patients with newly diagnosed CP–CML.

He added, "Based on the predictive value of complete cytogenetic responses, longer follow-up of first-line dasatinib may demonstrate better long-term outcomes than imatinib."

Dasatinib (Sprycel) in CP–CML at Four Years

- Neil P. Shah, MD, Assistant Professor of Medicine, University of California, San Francisco, Calif.

Among patients with CP–CML that has been resistant, suboptimally responsive to, or intolerant to prior therapy with imatinib (Gleevec), a four-year follow-up evaluation showed that dasatinib 100 mg once daily offered the most favorable

The author is a freelance medical writer living in New York City.

risk–benefit profile. As a potent TKI, dasatinib is indicated for imatinib-resistant or imatinib-intolerant CML (all phases) or Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL).

The study's objective was to evaluate the four-year efficacy and safety of dasatinib 100 mg/day in this population and to assess the predictive value of cytogenetic responses (CyRs) at six and 12 months with a dose of 100 mg/day on long-term progression-free survival (PFS).

Using a 2 × 2 factorial design, investigators randomized 662 subjects to one of four treatment arms: 100 mg once daily (n = 167), 50 mg twice daily (n = 168), 140 mg once daily (n = 167), and 70 mg twice daily (n = 168). Dr. Shah reported that at a four-year follow-up, PFS was 66% and overall survival was 82% with dasatinib 100 mg/day. The rate of transformation to the accelerated phase/blast crisis at 48 months was 4%.

He commented: "I think the less than 4% rate of transformation to accelerated or blast phase in a second-line setting, along with the 82% overall survival, is rather encouraging."

Similar percentages of patients achieved the highest standard of response, major molecular responses (MMRs)—44% receiving dasatinib 100 mg once daily; 43%, 70 mg twice daily; 42%, 140 mg once daily; and 41%, 50 mg twice daily. Fifty percent of patients receiving 100 mg once daily achieved CCyRs, and 49% to 53% achieved CCyRs with the other doses.

A landmark analysis of PFS, according to responses at 12 months with dasatinib 100 mg once daily, showed that 93% of patients who achieved a MMR (plus a CCyR) had PFS at 48 months, compared with a PFS rate of 77% among patients who achieved CCyRs but not MMRs at 12 months. The rate of PFS for patients without a CCyR at 12 months was 45%.

The lowest rate of patient withdrawals owing to drug toxicity was reported at 16% with dasatinib 100 mg/day, compared with 22% for 140 mg/day, 19% for 50 mg twice daily, and 26% for 70 mg twice daily.

"These findings argue, in general for this population of patients, that a trial of dasatinib for a year to see if they can achieve a complete cytogenetic response is reasonable. With a complete cytogenetic response, you can expect a 4% to 5% chance of their disease transforming to accelerated or blast phase," Dr. Shah said.

Nilotinib (Tasigna) and Imatinib (Gleevec) For CP–CML: ENESTnd Beyond One Year

- Richard Larson, Director, University of Chicago Medical Center, Chicago, Ill.

Longer-term follow-up beyond one year of ENESTnd (*E*valuating *N*ilotinib *E*fficacy and *S*afety in Clinical *T*rials in *N*ewly *D*iagnosed Patients) continues to show nilotinib (Tasigna, Novartis) to be superior to the current standard, imatinib (Gleevec), in patients with CP–CML. The finding suggests that nilotinib should be "a new standard of care" in this population, according to Dr. Larson.

In ENESTnd, 846 subjects were randomly assigned to receive nilotinib 300 mg twice daily (n = 282), nilotinib 400 mg twice daily (n = 281), and imatinib 400 mg once daily (n = 283), with planned five-year follow-up and a primary endpoint of major molecular response (MMR). MMR was defined as 0.1% or fewer *bcr–abl* mutations at 12 months and 24 months. All subjects had received a diagnosis of Ph+ CP–CML within the previous six months.

In previously reported 12-month findings, 44% of subjects receiving nilotinib 300 mg twice daily, 43% receiving nilotinib 400 mg twice daily, and 22% receiving imatinib 400 mg once daily achieved the MMR primary endpoint ($P < 0.0001$ for both nilotinib groups vs. imatinib).

At the time of this report, which included 525 of the total 846 patients in the trial with a median follow-up of 18.5 months, MMR rates were 63% for nilotinib 400 mg twice daily (n = 175) and 36% for imatinib 400 mg once daily (n = 172). MMR rates at 24 months (n = 145/846) were 86% for nilotinib 300 mg twice daily (n = 49), 88% for nilotinib 400 mg twice daily (n = 48), and 48% for imatinib 400 mg once daily (n = 48).

Progression to accelerated-phase CML or blast crisis was reported in fewer than 1% of the nilotinib patients (0.7% receiving nilotinib 300 mg twice daily; 0.4% receiving nilotinib 400 mg twice daily) and in 4.2% of imatinib patients receiving 400 mg once daily ($P = 0.006$ and 0.003, respectively, for nilotinib 300/400 mg twice daily vs. imatinib 400 mg once daily). Also, CML-related deaths were significantly less common for nilotinib 400 mg twice daily, compared with imatinib (one death vs. eight deaths, $P = 0.03$), with a trend favoring nilotinib 300 mg twice daily (two deaths, $P = 0.28$).

Edema was more common with imatinib. Grade 3 and 4 adverse events (AEs) were rare (less than 1%) for all treatments. No clinically relevant prolongation of the QT interval or left ventricular ejection fraction was reported.

Dr. Larson concluded, "With longer follow-up, rates of major molecular responses and complete cytogenetic response remain superior for nilotinib versus imatinib. Molecular responses are continuing to deepen over time."

Ipilimumab Alone or with Glycoprotein Peptide 100 Vaccine for Melanoma: A Phase 3 Study

- Stephen O'Day, MD, Chief of Research and Director, Melanoma Program, The Angeles Clinic and Research Institute, Santa Monica, Calif.
- Lynn Schuchter, MD, Professor of Medicine, University of Pennsylvania, Philadelphia, Pa., and moderator of the ASCO press briefing

Patients receiving the human monoclonal antibody ipilimumab experienced prolonged overall survival in a phase 3 clinical trial (MDX010-20), the first to show a survival advantage in metastatic melanoma, according to Dr. O'Day. Ipilimumab is an investigational human monoclonal antibody directed against cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) on the T-cell surface. The trial analysis also found no additional survival benefit from adding glycoprotein peptide vaccine (gp100) to ipilimumab.

Previously treated adults with unresectable stage III or IV melanoma were randomly assigned to receive ipilimumab plus placebo 3 mg/kg three times per week for four doses (n = 137), ipilimumab plus gp100 vaccine 1 mg three times per week for four doses, or gp100 plus placebo (n = 136). The primary endpoint was overall survival.

The hazard ratio (HR) for survival, compared with gp100

Table 1 Survival at One and Two Years with Ipilimumab and Glycoprotein Peptide 100 (gp100) Vaccine

	Ipilimumab plus gp 100 (N = 403)	Ipilimumab plus Placebo (N = 137)	gp100 plus Placebo (N = 136)
At one year	44%	46%	25%
At two years	22%	24%	14%

alone, revealed a 32% reduction for ipilimumab/gp100 (HR = 0.68; $P = 0.0004$) and a 34% reduction for ipilimumab/placebo (HR = 0.66; $P = 0.0026$). Median overall survival rates were 10 months for ipilimumab/gp100, 6.4 months for gp100/placebo, and 10.1 months for ipilimumab/placebo. One-year and two-year survival rates also favored the ipilimumab/placebo group (Table 1). Dr. O'Day commented that the prognosis is poor in metastatic melanoma patients, with one-year survival typically at about 25% and two-year survival at approximately 10%.

Immune-related adverse events (AEs) were reported in approximately 60% of ipilimumab patients and in about 30% in those receiving only gp100. Overall, ipilimumab was well tolerated. Most AEs were grade 1 and 2 and were managed rapidly; 10% to 14% of events were more severe and necessitated that the drug be stopped and high-dose steroids initiated.

Dr. Schuchter said, "These are very significant findings. There has been no treatment that prolonged survival in patients with stage IV melanoma. So to show in this randomized, large clinical trial this kind of benefit is really a step forward."

Future research into combinations, including ipilimumab, may reveal further benefit, she added.

Metastatic Melanoma and PV-10 (Rose Bengal)

- Sanjiv Agarwala, MD, Section Chief, Hematology/Oncology, St. Luke's Hospital and Health Network, Bethlehem, Pa.

In a phase 2 study, most patients with metastatic melanoma receiving chemoablation with PV-10, a 10% solution of rose bengal (Provectus), had robust responses. Developed originally in the 1870s as a coal tar–derived wool dye, rose bengal has been used medically since then, most commonly as a stain for detecting ocular conditions. A detailed history of rose bengal is presented on page 474.

In this study, 80 patients with measurable stage III or IV melanoma received PV-10 injections as initial treatment to one to 20 cutaneous, subcutaneous, or nodal lesions per patient. New or incompletely responsive lesions were treated again at weeks 8, 12, or 16, with follow-up extending to 52 weeks. The investigators were allowed to leave one or two lesions untreated. Target lesions were 0.2 cm or larger in diameter, with a biopsy confirmation of at least one target lesion. The recently completed study's primary endpoint was the response rate of injected lesions.

Among the first 40 patients evaluable (median age, 75 years), 486 lesions were treated. Thirty-three percent of patients achieved complete remission, 28% achieved partial remission, and 18% achieved stable disease in their target lesions. Further, 33% of 21 patients with evaluable bystander lesions achieved complete remission in these lesions, along with 10% of patients achieving partial remission and 14% achieving stable disease.

Mean progression-free survival (PFS) for all patients was 8.5 months. Patients with an overall response achieved significantly longer PFS (11.1 months) than those with stable disease or progressive disease (2.8 and 2.7 months, respectively). No grade 4 or 5 AEs were reported. In general, AEs were predominantly mild to moderate.

"PV-10/rose bengal 10% solution offers potential locoregional control of metastatic disease," Dr. Agarwala concluded. He also said that responses of injected lesions appeared to be unrelated to disease stage or prior treatment.

Dr. Agarwala commented, "What's really interesting is that we are seeing responses not only in the injected lesions but in lesions that we are not injecting. So we think this systemic effect is based on an immune response."

Aldesleukin (Proleukin) in Renal Cell Carcinoma

- David McDermott, MD, lecturer, Department of Cell Biology, Harvard Medical School, Boston, Mass.

Aldesleukin (Proleukin for Injection, Prometheus) received FDA approval for metastatic renal cell carcinoma (mRCC) in 1992 based on a 14% major response (complete response plus partial response rate [CR + PR]) and durable remissions in phase 2 trials. This synthetic protein has the same actions as native human interleukin-2 (IL-2).

"Because of significant toxicity, cost, and limited efficacy, its application is narrowed to selected patients treated at a few centers," Dr. McDermott noted.

The Cytokine Working Group conducted the present trial to answer this question: "Can we pick likely responders before we begin high-dose aldesleukin (HD IL-2)?"

Investigators sought to prospectively determine how response rates with HD IL-2 in mRCC patients with specific pathological predictive features or matching other prognostic models differed significantly from those in a historical, unselected population. In a multicenter, prospective study, 128 patients with histologically confirmed measurable metastatic or unresectable RCC received HD IL-2 (600,000 U/kg per dose intravenously) every eight hours on days 1 through 5 and on days 15 to 19, for a maximum of 28 doses every 12 weeks. The primary endpoint of the study was to determine the major response rate of patients with "favorable" predictive features. The overall group's response rate was 29% (35/120) with seven CRs and 28 PRs. This figure was significantly greater than the historical response rate of 14% (95% CI, 21%–38%; $P = 0.0009$).

Median progression-free survival (PFS) was 4.4 months, with 20 responses ongoing (range, 4 to 35 or more months). Notably, the response rate for patients with clear-cell RCC (96% of the cohort) was 30% (35/115) (95% CI, 22%–40%; $P = 0.0004$), compared with that of historical controls.

Responses to HD IL-2 were not associated with any pretreatment clinical factors. There were no responses in patients

with non–clear-cell histological features or in those with high survival rates after nephrectomy and immunotherapy (UCLA SANI) scores.

"The major response rate for HD IL-2 in this trial was significantly better than historical experience, likely as a result of patient selection," Dr. McDermott concluded. "Clear-cell histology may select patients who will respond to IL-2," he added.

In an interview, Dr. McDermott also said that those who are candidates for HD IL-2 should be urged to receive it first:

"We have seen reduced efficacy and some significant toxicity in those folks who receive targeted therapy up front and then come to us for IL-2."

Zoledronic Acid (Zometa) and Clodronate In Multiple Myeloma: MRC Myeloma IX

• Gareth J. Morgan, PhD, Institute of Cancer Research, The Royal Marsden National Health Service Foundation Trust, London, U.K.

Results of a large trial of multiple myeloma (MM) treatment have shown that zoledronic acid (Zometa, Novartis) is superior to an experimental agent, clodronate disodium (clodronic acid), for preventing skeletal-related events and, independently of the reduction of these events, for prolonging overall survival. Clodronate is approved in Canada, the U.K., and Italy as Bonefos, Loron, and Clodron. It is prescribed as a bone-resorption inhibitor and as an antihypercalcemic agent.

The Medical Research Council (MRC) Myeloma IX study was a large trial comparing a second-generation bisphosphonate (clodronate) against a third-generation bisphosphonate (zoledronic acid), induction chemotherapy regimens, and thalidomide maintenance versus no maintenance therapy. Dr. Morgan's presentation offered findings on the severity of bone disease and overall survival with an amino-bisphosphonate (zoledronic acid) and standard clodronate.

Dr. Morgan had noted that several bisphosphonates showed anticancer activity in preclinical models. Zoledronic acid has shown the highest level of activity among approved bisphosphonates and has demonstrated antitumor activity in preclinical and clinical studies in various cancer types, including MM.

To determine whether bone-targeted therapy would improve survival in MM, the team randomly assigned patients with newly diagnosed MM (n = 1,960) at 121 centers to receive intravenous (IV) zoledronic acid 4 mg every 21 to 28 days or oral clodronate 1,600 mg daily plus anti-myeloma therapy. Treatment continued at least until disease progression.

After a median follow-up of 3.7 years, overall survival rates improved significantly with zoledronic acid, yielding an increase of 5.5 months ($P = 0.04$), compared with clodronate. The relative risk of death (overall survival) was reduced by 16% (HR = 0.842; $P = 0.012$). Progression-free survival (PFS) was increased by 12% (HR = 0.883; $P = 0.018$).

At the same time, skeletal-related events were significantly reduced with zoledronic acid (27%), compared with clodronate (35.3%), for a 24% relative risk reduction ($P = 0.0004$). To ascertain whether improved overall survival was attributable to the prevention of skeletal-related events, the researchers conducted a further analysis, adjusted for skeletal-related events, and found a 15% reduction in risk of death with zoledronic acid (HR = 0.850; $P = 0.018$).

"We used a Cox model with skeletal-related events as a time-dependent covariate and showed that the survival benefit was not related to the prevention of skeletal-related events. So it's an anti-myeloma effect," Dr. Morgan said.

Both bisphosphonates were generally well tolerated. The incidence of confirmed jaw osteonecrosis was also low, but it was higher with zoledronic acid (3.5%) than with clodronate (0.3%).

"Osteonecrosis of the jaw cases were generally mild, grade 1, and self-resolving without the need for surgical intervention," said Dr. Morgan.

He concluded, "Zoledronic acid should be considered for early integration into treatment regimens in patients with newly diagnosed multiple myeloma."

Ovarian Suppression with Tamoxifen (Nolvadex) or Anastrozole (Arimidex) Alone or with Zoledronic Acid in Breast Cancer: ABCSG-12 (Mature Results)

• Michael Gnant, Professor of Surgery, Medical University of Vienna, Austrian Breast and Colorectal Study Group

A mature analysis of ABCSG-12 (the Austrian Breast and Colorectal Cancer Study Group, Trial 12) offered further evidence that beyond preventing treatment-induced bone loss, zoledronic acid (Zometa) has anti-cancer effects. Adding zoledronic acid to endocrine therapy in premenopausal patients with endocrine-responsive breast cancer significantly prolonged disease-free survival. In revealing a death rate of 4% after more than five years of follow-up, the analysis also confirmed that breast cancer could be successfully treated without adjuvant chemotherapy in this population. Earlier research, including prior ABCSG-12 analyses, has provided evidence of anticancer activity for bisphosphonates in early breast cancer and in other tumor types.

ABCSG-12 examined the efficacy of adjuvant therapy in premenopausal women with hormone-responsive early breast cancer who were receiving AstraZeneca's goserelin acetate implant (Zoladex) plus anastrozole (Arimidex) or tamoxifen citrate (Nolvadex) with or without zoledronic acid. Patients (n = 1,803) had received tamoxifen 20 mg/day or anastrozole 1 mg/day with or without zoledronic acid 4 mg every six months. Women in all arms of the study received goserelin 3.6 mg for 28 days.

The ABCSG-12 results, announced in 2008, showed that adding zoledronic acid reduced contralateral breast cancer, locoregional recurrence, and distant non-bone recurrence. In addition, ZO-FAST (*Zo*meta–*F*emara *A*djuvant *S*ynergy *T*rial) findings in postmenopausal women with breast cancer (N = 1,065) showed a significantly reduced risk of disease-free survival with zoledronic acid.

With a median follow-up currently at 62 months, the hazard ratio (HR) for the primary endpoint of disease-free survival with zoledronic acid was 0.68, compared with no zoledronic acid ($P = 0.008$), in a univariate analysis. Benefits of zoledronic acid were seen in both the node-negative and node-positive cohorts and in women receiving anastrozole and tamoxifen.

In a univariate analysis, the HR for overall survival was 0.67 for zoledronic acid, compared with no zoledronic acid ($P = 0.09$). There was a trend toward reductions in bone metastases with zoledronic acid as well (HR = 0.65; $P = 0.12$).

Rates for the primary endpoint of disease-free survival were similar for patients receiving tamoxifen and anastrozole (HR = 1.08; $P = 0.61$). In a univariate analysis, however, overall survival was significantly higher for tamoxifen (HR = 1.75; $P = 0.016$). Survival after a first event and after a distant first event both favored tamoxifen (HR = 1.99, $P = 0.006$) over anastrozole (HR = 1.16; $P = 0.039$). Dr. Gnant suggested, however, that the lower overall survival with anastrozole was probably due to the fact that patients in that group received palliative aromatase inhibitors less frequently than those in the tamoxifen group.

There were no reports of osteonecrosis of the jaw. Arthralgia, bone pain, and pyrexia were significantly more common in the anastrozole arms; endometrial hyperplasia and uterine polyps were significantly more common in the tamoxifen arms.

Dr. Gnant concluded, "Adding zoledronic acid to endocrine therapy significantly prolonged disease-free survival with a trend toward improved overall survival."

The anastrozole results, he added, support the use of aromatase inhibitors as a first-line treatment.

Oral Panobinostat plus Bortezomib (Velcade) In Multiple Myeloma: A Phase 1b Study

- Jesus F. San-Miguel, MD, Hospital Universitano de Salamanca, Salamanca, Spain, presented by Kenneth C. Anderson, MD, Dana Farber Cancer Institute, Boston

In patients with relapsed or relapsed and refractory multiple myeloma (MM), combining panobinostat (LBH589, Novartis) with intravenous (IV) bortezomib (Velcade, Millennium) has shown promising activity, even among those with disease that is refractory to prior bortezomib-containing treatment. Panobinostat is an oral pandeacetylase inhibitor that increases acetylation of proteins involved in multiple oncogenic pathways. It promotes cytotoxic misfolded protein and the death of MM cells.

In preclinical studies, panobinostat showed single-agent activity as well as activity when it was combined with the proteasome inhibitor bortezomib and dexamethasone, inhibiting tumor growth and reducing bone density loss. A single-agent study of panobinostat in MM suggested going forward with a panobinostat/bortezomib combination, said Dr. Anderson.

Forty-seven patients (32 men and 15 women; median age, 62 years) with relapsed MM (N = 24) or relapsed and refractory MM (N = 22) received oral panobinostat three times per week and IV bortezomib on days 1, 4, 8, and 11 in a 21-day cycle. The patients had a median of two prior IV lines of therapy (range, from one to 10 IV lines). A dose-escalation phase established panobinostat at 20 mg plus bortezomib 1.3 mg/m^2 as the maximum tolerated dose.

Grade 3 and 4 thrombocytopenia was reported in 81% of the patients, with grade 3 or 4 neutropenia experienced by 57%, anemia by 21%, and leukopenia by 17%, respectively. Dr. Anderson emphasized that thrombocytopenia was readily managed with dose modifications, platelet transfusions, or both.

Asthenia, the most common non-hematological adverse event, was reported in 25% of patients. Grade 1 and 2 diarrhea, nausea, and pyrexia occurred in 64%, 55%, and 51% of patients, respectively. Electrocardiograms did not show any dose-related increases in the corrected QT interval for the heart rate using Fredericia's formula (QTcF).

The response rates (CRs + very good PRs + PRs + minimal responses) were 70% for all patients and 60% for patients with bortezomib-refractory disease. Dr. Anderson said that "the main reason this is so exciting" was that 76% of patients receiving panobinostat 20 mg/bortezomib 1.3 mg/m^2 had greater than a minimal response, including three CRs.

He concluded that oral panobinostat three times weekly could be safely combined with bortezomib at dose levels up to 20 mg and 1.3 mg/m^2, respectively. The combination showed promising activity, including in patients with refractory disease.

BIBW 2992 (Tovok) for Lung Cancer: LUX-Lung 2 (Phase 2)

- Chih-Hsin Yang, MD, Taiwan University Hospital, Taipei

A phase 2 study of BIBW 2992 (Tovok, Boehringer Ingelheim), a novel, investigational, oral potent irreversible TKI of the endothelial growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2), revealed high objective response rates (ORRs) and progression-free survival (PFS) rates in patients with EGFR mutations and non–small-cell lung cancer (NSCLC).

The subpopulation of patients with NSCLC whose tumors show EGFR mutations display a unique responsiveness to EGFR–TKIs, Dr. Yang said. After testing for EGFR mutations, 129 patients (median age, 61.5 years) received BIBW 2992. First-line therapy was administered to 61 patients, and second-line therapy was given to 68 patients.

Del 19 mutations were discovered in 52 patients; *L858R* mutations, in 54 patients; and other mutations, in 23 patients. In all, 38 first-line patients and 20 second-line patients remained on treatment at the time of the analysis, with the longest duration of treatment at 28 months. The original intent had been to give BIBW 2992 at 50 mg/day until disease progression, but the starting dose was lowered to 40 mg/day to optimize a balance between tolerability and efficacy. Responses were assessed at 4, 8, and 12 weeks and subsequently at eight-week intervals. The primary endpoint was the ORR, and the secondary endpoint was the PFS.

Efficacy was high in both first-line and second-line settings and for all subgroups, Dr. Yang said, with an ORR of 60% and a disease control rate of 86%. The median overall survival rate was 24 months, and the median PFS was 14 months. Dr. Yang noted that tumors with *del 19* or *L858R* mutations responded comparably to those in the overall group (64%, ORR; 88%, disease control rate).

Adverse events (AEs), reported in all 128 patients, were manageable with supplementary care and dose adjustments. The most common AEs were diarrhea and rash or acne, similar to those associated with other EGFR–TKIs. Ten discontinuations (8%) were attributable to drug-related AEs.

"This study of this new drug confirms that this EGFR–TKI is very effective in patients with activated mutations," Dr. Yang concluded.

The FDA has granted a fast-track designation to BIBW 2992 for NSCLC in patients previously treated with another EGFR–TKI. Phase 3 trials comparing BIBW 2992 40 mg with chemotherapy in NSCLC are ongoing.

Rose Bengal: From a Wool Dye to a Cancer Therapy

- Sanjiv Agarwala, MD, Section Chief, Hematology/Oncology, St. Luke's Hospital and Health Network, Bethlehem, Pa.
- Eric Wachter, PhD, Senior Vice President, Provectus Pharmaceuticals, Inc., Knoxville, Tenn.

When a 79% response rate with PV-10 (rose bengal 10% solution, Provectus) in patients with metastatic melanoma (MM) emerged from a presentation at the 2010 ASCO meeting (see page 471). Considerable interest was aroused—primarily for the impressive results in a formidably difficult-to-treat cancer. But further interest was piqued by the common name of the investigational drug—rose bengal—a chemical originating neither from a plant nor a South Asian region.

An additional "spice" to the clinical findings arose out of the fact that lesions that were not directly subjected to chemoablation with PV-10 injections also responded, according to Dr. Agarwala, lead investigator. Systemic responses in these "bystander" lesions, he said, suggest an immune response. A full one-third of patients with bystander lesions had complete responses (CRs).

The phase 2 trial enrolled 80 patients with measurable stage III and IV MM, all of whom received initial treatment with PV-10 in up to 20 cutaneous, subcutaneous, or nodal lesions. New or incompletely responsive lesions were treated again at week 8, 12, or 16, with follow-up to 52 weeks. Target lesions were 0.2 cm or more in diameter, with at least one lesion confirmed by biopsy. Investigators were allowed to leave one or two lesions untreated, including some visceral lesions. The study's primary endpoint was the response rate of injected lesions.

Among the first 40 patients completing the study (median age, 74.5 years; range, 37–92 years), 26 were men. The median time from diagnosis with MM and enrollment was 34 months. Thirty-three percent of patients achieved CRs, 28% had partial remissions, and 18% had stable disease in their target lesions. In addition, 33% of 21 patients with evaluable bystander lesions achieved complete remission of these lesions, 10% achieved partial remission, and 14% achieved stable disease. Mean progression-free survival (PFS) for all subjects was 8.5 months.

Patients with CRs achieved significantly longer PFS (11.1 months) than those with stable disease (2.8 months) or progressive disease (2.7 months); further, the responses of the injected lesions appeared to be unrelated to disease stage or prior treatment. No grade 4 or 5 adverse events (AEs) were attributed to PV-10. Overall, AEs were predominantly mild to moderate. Dr. Agarwala concluded that the safety and efficacy profile of PV-10 compared favorably with available and emerging options for these patients.

Rose bengal has been in use for about 140 years but not principally as a therapeutic agent, stated Dr. Wachter in an interview. It can be traced back to Basel, Switzerland, where in 1882, German patent No. 32584 was granted to Ghnem for a new family of wool dyes. Ghnem took different halogens and added them to fluorescein to produce molecules with different colors. Presumably, the deep rosy-red color, similar to that of the middle-of-the-forehead dot indicating marriage in women of the Bengali region of India, led to the name. One late-19th century encyclopedia noted the color "bengal red" as being similar to eosin, but bluer, and stated that the name rose bengal was also in use.

Rudolf Nietzki, PhD, a professor at the University of Basel in Switzerland,[1] identified the principal constituents of rose bengal as iodine derivatives of di- and tetra-chlorfluorescein, with those prepared from tetrachlorphthalic acid being the bluest. The original rose bengal version combined two iodines, and subsequent modifications through the 1920s, adding two more iodines, led to the form currently called rose bengal.

The first known clinical application of rose bengal was Römer's addition of it to safranin victoria yellow to combat ocular pneumococcal infection in 1914. Corneal applications remained the primary medical use for nearly a century, according to Dr. Wachter's review of the rose bengal history.

Kleefeld's discovery that rose bengal was an effective stain for visualizing corneal ulcers in 1919 was the watershed event for its adoption as an ocular biological staining agent. Modern clinical trials in the 1960s and 1970s, conducted by Norn and then Marsh, leveraged pioneering work by Sjögren in 1939 and led to the commercial introduction of rose bengal as the ophthalmic diagnostic modality (Rosettes and Minims) that continues to be in use today.

On a parallel track, Delprat in 1923 found that rose bengal could be used as a marker for impaired liver function and developed an intravenous (IV) assay in humans by 1925. The test remained in use until the 1950s, when Taplin devised more sensitive radioisotope labeling with iodine-131 (^{131}I) rose bengal sodium (Robengatope, RB Diagnostics). By the late 1980s, radiolabeling, in turn, had been eclipsed and replaced as the preferred diagnostic strategy when magnetic resonance imaging (MRI) and computed tomography (CT) allowed direct visualization of the liver.

But what accounts for rose bengal's grand entrance onto the stage of oncological therapeutics? Was there a "penicillin moment," an astonishing laboratory observation in a Petri dish of expiring cancer cells in the presence of triumphant rose bengal?

No—but yes, according to Dr. Wachter. In a manner reflective of the ascendancy of published medical research as a resource for discovery, it was a data-mining finding that strengthened the commitment of investigational attention that Provectus was already turning toward rose bengal. And rather than a serendipitous laboratory mishap (Fleming had mistakenly left the Petri dish in his basement laboratory uncovered), it required modern computer literature search capacities and the insight to pause over an apparently disappointing study by investigators bent on finding that rose bengal *caused* cancer.

In the 1980s, when the FDA and the Japanese Ministry of Health and Welfare were increasing their scrutiny of artificial food colorings, Akihiro Ito and colleagues at the University of Hiroshima decided to evaluate the tumorigenicity of red food dye No. 105 (rose bengal) in 300 mice of a strain known for its tendency to develop spontaneous tumors.[2] Mice in three groups were fed pure water or water with either 0.125% or 0.5% of rose bengal for two years. The expectation, Dr. Wachter said, presumably was that there would be "severe toxicity to the thyroid" and tumor development. Thyroid goiters caused by excessive intake of iodine through seaweed consumption are

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common in parts of Japan. After 82 weeks of exposure, an analysis did show increases in thyroid goiters but no tumorigenicity. Rather glaringly, the authors documented in a three-line sentence, but failed to comment on, dose-dependent survival increases in the mice receiving rose bengal. Only 52% of male mice and 64% of female mice receiving rose bengal 0% solution were alive, whereas in the 0.125% and 0.5% rose bengal groups, survival rates were 74%/92% and 90%/94%, respectively, at the end of the study.[2]

How did Dr. Wachter's team stumble onto Dr. Ito's three-line sentence on improved survival in his 1986 journal article?[2] The Provectus co-founders, including Dr. Wachter, a laser specialist; Craig Dees, PhD, a molecular virologist; and Tim Scott, PhD, a chemical engineer, had met while working at the Oak Ridge National Laboratory. They became interested in photodynamic therapy, and in the late 1990s they were looking for a candidate agent with antineoplastic activity. Known agents posed some problems: they were either uncontrollably toxic throughout the body, or they failed to penetrate the disease site sufficiently. A commercial data search service identified several hundred potential agents. Then, through their own internal screening process, which quickly narrowed the candidates to only those agents with powerful effects, the Provectus researchers turned to rose bengal. Preclinical tests with bacterial and cancer cell lines quickly showed rose bengal to have impressive cytotoxic activity and to be worthy of deeper study. Intensive review of the literature uncovered Ito's work with the nearly hidden three-line report of a striking survival advantage.

The next hurdle lay in the fact that Dr. Wachter, a true laser aficionado, was absolutely certain that rose bengal had to be activated by laser energy.

"I was a laser expert, and I was very psyched about finding this perfect molecule to go with our exciting laser techniques," he said.

Drs. Scott and Dees, however, were worried that the technology was too sophisticated for routine use in the clinic and that the severe phototoxicity reported in prior experience with photodynamic therapy, which required patients to stay not only out of direct sunlight but also away from intense indoor lighting for up to several weeks, would hamper wide acceptance despite the agent's efficacy. They reformulated rose bengal for use without laser activation and came back to Dr. Wachter with results from tests of injected (and laser-less) rose bengal showing the same antineoplastic efficacy as had been achieved with laser activation. Their subsequent animal, and then human, studies confirmed that when rose bengal was delivered within lesions, it was a potent and selective agent for ablating cancers. Thus, PV-10 was born.

Beyond melanoma, PV-10 is being evaluated for primary and metastatic liver tumors. Ultimately, systemic administration of PV-10 may be explored for other indications, Dr. Wachter said.

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