2012 American Society of Clinical Oncology and American Society of Hypertension 27th Annual Scientific Meeting and Exposition

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2012 American Society of Clinical Oncology

A total of 31,250 registrants—more than 25,000 professionals, 4,200 exhibitors, and 1,550 guests and reporters—attended the 48th annual ASCO meeting in Chicago from June 2 to 5, 2012. This report discusses two new approaches (a dendritic cell-based vaccine and a BRAF inhibitor) for the treatment of advanced melanoma, updated trials on second-generation tyrosine kinase inhibitors, and a multikinase inhibitor for GIST tumors. *Nab*-paclitaxel for non–small-cell lung cancer and a trial of the mTOR inhibitor everolimus for advanced breast cancer are also reviewed.

Adjuvant Dendritic Cell-Based Vaccine Therapy For Melanoma

- Natalia N. Petenko, MD, N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia
- Suresh S. Ramalingam, MD, Director, Lung Cancer Program, Emory University, Atlanta, Ga.

There is no standard, effective adjuvant therapy for patients with high-risk stage III and IV melanoma, Dr. Petenko said. In an exploratory clinical trial, 108 patients (mean age, 52.5 years) who had undergone successful surgical treatment were stratified in two well-balanced trial arms. One arm received a vaccine based on mature autologous monocyte-derived dendritic cells primed with autologous tumor lysate, and the other arm was assigned to observation only.

The vaccine arm included 56 patients (46 in stage III, 10 in stage IV); the control arm included 52 patients (47 in stage III, five in stage IV). The vaccine was administered every 2 to 6 weeks until disease progression. Investigators assessed disease-free survival and overall survival as efficacy endpoints.

At a median follow-up of 22 months, the hazard ratio (HR) for disease-free survival in a comparison of the vaccine arm with the observation arm was 0.45 (95% confidence interval [CI], 0.29–0.69; $P < 0.05$). For overall survival, the HR was 0.71 (95% CI, 0.40–1.25; $P = 0.23$). After 3 years, 63% of patients receiving the vaccine were still alive, compared with 50% in the observation arm ($P > 0.05$).

Strong delayed hypersensitivity reactions at the injection site were noted in 31 of 56 vaccinated patients (55%). Patients experiencing these reactions showed better overall survival than those who experienced mild or no reactions ($P = 0.0541$). Although the vaccine was generally safe and well tolerated, four cases of vitiligo were reported. These cases, however, were associated with more durable progression-free survival (PFS) and overall survival, with 75% of patients remaining disease-free. All other adverse reactions (erythema, itching, pain, induration, fever, myalgia, joint pain, fatigue, and weakness) were classified as grade 1 or 2.

Dr. Petenko noted that more highly powered, prospective, randomized trials of the dendritic cell vaccine would be conducted. Her poster received an ASCO Merit Award.

"The findings," commented Dr. Ramalingam in an interview, "are very promising and indicate the efficacy and uptake of the vaccine. They support the idea that dendritic cells are key players in 'policing' antitumor immunity and that they are important for antigen recognition. They show, as well, that stimulating dendritic cells can be an effective strategy to treat cancer."

Dr. Ramalingam, who is an investigator in a phase 3 trial of talactoferrin alfa in advanced lung cancer, noted that talactoferrin is an immunomodulatory protein that interacts with gut-associated lymphoid tissue (GALT), recruiting circulating immature dendritic cells and inducing their maturation.

Weekly *nab*-Paclitaxel Plus Carboplatin In Non–Small-Cell Lung Cancer

- Markus Frederic Renschler, MD, Adjunct Associate Professor, Stanford University, Stanford, Calif., and Celgene Chief Scientist for this study

Non–small-cell lung cancer (NSCLC) is a heterogeneous disease, with 1-year survival rates varying widely (from 14% to 29%) across histological subtypes. The poorest outcomes are observed in patients with squamous histological features. Several treatment options, such as erlotinib (Tarceva, OSI/Genentech) and bevacizumab (Avastin, Genentech) for adenocarcinoma, are effective for patients with nonsquamous NSCLC, but options are limited for those with squamous NSCLC.

The standard of care is platinum-based therapy. Solvent-based taxanes, which are recommended in combination with platinum-based therapy for NSCLC, induce peripheral neuropathy, pain, hearing loss, and edema. Compared with solvent-based paclitaxel (Taxol, Bristol-Myers Squibb), albumin-bound paclitaxel (*nab*-paclitaxel) delivers 33% higher drug concentrations to tumors in preclinical models and has demonstrated enhanced transport across endothelial cell monolayers. *Nab*-paclitaxel

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(Abraxane, Celgene) is approved for the second-line and third-line treatment of metastatic breast cancer.

Dr. Renschler compared findings with standard paclitaxel/carboplatin versus *nab*-paclitaxel/carboplatin according to specific disease histology in a multicenter, randomized phase 3 trial of first-line treatment of NSCLC. In that trial, overall response rates with *nab*-paclitaxel plus carboplatin were significantly higher (41% vs. 24%, respectively) for solvent-based paclitaxel plus carboplatin among patients with squamous cell carcinoma ($P < 0.001$). Also, median overall survival was extended by 1.2 months with the *nab*-paclitaxel/carboplatin regimen in those with squamous cell carcinoma (10.7 months vs. 9.5 months, respectively; HR = 0.89), as well as in patients with large-cell carcinoma (12.4 months vs. 10.6 months). Differences between overall response rates for patients with the differing histological features were not significant.

Myelosuppression was the most prevalent toxicity with *nab*-paclitaxel in association with carboplatin. In patients with squamous cell histology, grade 3 and 4 thrombocytopenia was reported in 22% of those receiving *nab*-paclitaxel and in 7% of those receiving solvent-based paclitaxel. In patients with nonsquamous cell histology, this event was also noted in 16% and 11%, respectively. Ten percent of patients needed transfusions, Dr. Renschler reported.

He concluded, "This provides an alternative for squamous cell patients, who desperately need new treatments. The *nab*-paclitaxel/carboplatin combination provides better tumor control with better response rates."

Weekly *nab*-Paclitaxel Plus Carboplatin as First-Line Therapy in Non–Small-Cell Lung Cancer

- Mark A. Socinski, MD, Professor of Medicine and Thoracic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pa., and Director, Lung Cancer Section, Division of Hematology/Oncology, University of Pittsburgh Cancer Institute

Although the median age of patients with advanced NSCLC in the U.S. is 71 years, elderly patients with this disease are generally undertreated, with only about 30% receiving systemic therapy because of poor performance status, comorbidities, or anticipated toxicities, Dr. Socinski said in an interview at his poster presentation. This is true even though previous research by Quoix et al.[1] showed that elderly patients with performance status (PS) 0 to 2 derived benefit from solvent-based paclitaxel (Taxol) plus carboplatin, compared with monotherapy (PS 0 = normal activity; PS 1 = some symptoms, but still nearly fully ambulatory). In preclinical models, *nab*-paclitaxel (Abraxane, which is albumin-bound), when compared with solvent-based paclitaxel, delivered higher concentrations to tumors in preclinical models.

Dr. Socinski et al. enrolled 1,050 patients with untreated stage IIIB/IV NSCLC and with a PS of 0 or 1. Patients were randomly assigned, in a 1:1 ratio, to receive carboplatin (an area-under-the-curve concentration of 6 on day 1) and either *nab*-paclitaxel (100 mg/m^2 on days 1, 8, and 15) or solvent-based paclitaxel (200 mg/m^2 on day 1 every 21 days). For this analysis, patients were stratified as younger than age 70 or as 70 years of age or older. Overall response rates and PFS were determined by a blinded centralized review.

In patients who were 70 years of age or older, overall response rates were nonsignificantly higher with *nab*-paclitaxel, compared with solvent-based paclitaxel (34% vs. 24%, respectively; $P = 0.196$). In patients younger than 70 years of age, the advantage in overall response rate for *nab*-paclitaxel was significant (32% vs. 25%, respectively; $P = 0.013$).

In patients younger than 70 years of age, there were no differences between treatments with respect to PFS or overall survival. In elderly patients, however, there was a nonsignificant trend favoring *nab*-paclitaxel for PFS (8.0 vs. 6.8 months, respectively; HR = 0.687; 95% CI, 0.420–1.123; $P = 0.134$). For median overall survival, a significant improvement was observed with *nab*-paclitaxel in patients 70 years of age or older (19.9 vs. 10.4 months, respectively; HR = 0.583; 95% CI, 0.388–0.875; $P = 0.009$).

Side-effect profiles distinctly favored *nab*-paclitaxel in elderly patients; these patients experienced less sensory neuropathy ($P = 0.001$), neutropenia ($P = 0.015$), and arthralgia ($P = 0.029$) of all grades, despite a higher weekly dose intensity with *nab*-paclitaxel versus solvent-based paclitaxel. However, they experienced more anemia ($P = 0.007$) than those receiving solvent-based paclitaxel.

Fewer elderly patients in the *nab*-paclitaxel arm experienced sensory neuropathy of grade 3 or higher (7% vs. 23%, respectively; $P = 0.002$). When neuropathy did occur, it developed later among patients in the *nab*-paclitaxel arm (median time to onset, 48.0 vs. 24.5 days, respectively; $P = 0.002$). Neuropathy, pain, hearing, and edema subscales were also improved with *nab*-paclitaxel in patient-reported scores on the FACT–Taxane questionnaire.

"The striking thing was that in patients 70 or older there was a really quite impressive survival advantage favoring *nab*-paclitaxel," Dr. Socinski said. "I think this could be quite a suitable regimen for the elderly patient—for whom you want to be aggressive from an efficacy point of view, but also where you don't want to overdo toxicity."

Theoretically, he said, the albumin-binding property of *nab*-paclitaxel may lead it into the tumor bed, causing it to be more exposed and therefore to have more activity.

"But that doesn't explain the greater benefit in the elderly unless there's something different about the albumin pathway in the receptors of older patients versus younger patients—which has not been studied," he added.

Regorafenib in Gastrointestinal Stromal Tumors: GRID, Phase 3

- George D. Demetri, MD, Associate Professor, Harvard Medical School, Boston; and Director, Ludwig Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston
- Sylvia Adams, MD, Assistant Professor, New York University, New York, N.Y., ASCO Press Conference Moderator

Imatinib mesylate (Gleevec, Novartis) and sunitinib malate (Sutent, Pfizer), Dr. Demetri said at an ASCO press briefing, inhibit the mutated, activated kinases proto-oncogene c-kit *(KIT)* or platelet-derived growth factor, alpha polypeptide *(PDGFRA)*,

which promote gastrointestinal stromal tumors (GISTs).

"While targeted therapy has revolutionized treatment for this rare cancer, we've been on the hunt for additional effective treatments for the 90% of patients whose cancer eventually develops resistance to the only two available therapies," said Dr. Demetri.

In earlier phase 2 studies among GIST patients experiencing treatment failure with imatinib and sunitinib, the oral multikinase inhibitor regorafenib (BAY 73-4506, Bayer) demonstrated substantial activity. GRID (GIST–Regorafenib In Progressive Disease), a phase 3, randomized, double-blind, placebo-controlled, multinational trial, evaluated the efficacy and safety of regorafenib in these patients with progressive GISTs.

Metastatic or unresectable GIST and objective failure of both prior imatinib and sunitinib treatment were inclusion criteria. GRID enrolled 199 patients, randomizing them in a 2:1 ratio to receive best supportive care plus either oral regorafenib (160 mg once daily, 3 weeks on/1 week off) or placebo. The primary endpoint was PFS.

Median PFS rates were 4.8 months for the regorafenib group (n = 133) and 0.9 months for the placebo group (n = 66) (HR = 0.27, 95% CI, 0.19–0.39; $P < 0.0001$). For the secondary endpoint of disease control (complete response + partial response + durable stable disease of 12 weeks or more), PFS rates were 52.6% with regorafenib and 9.1% with placebo.

For regorafenib and placebo, respectively, objective response rates were 4.5% and 1.5%. Stable disease at any time was reported among 71.4% of patients receiving regorafenib and in 33.3% receiving placebo, whereas rates of progressive disease were 21.1% for regorafenib and 63.6% for placebo. Neither group experienced complete responses.

Overall survival rates were better with regorafenib, but the advantage (HR = 0.77; 95% CI, 0.42–1.41) was not statistically significant ($P = 0.199$). That lack of statistical significance was expected, Dr. Demetri said, because placebo-treated patients could cross over to receive open-label regorafenib after a confirmation of disease progression.

The benefits of regorafenib were consistent for all GIST genotypes. An exploratory analysis of PFS, according to GIST genotypes, showed that for the most common mutation (*KIT* exon 11), and for a second mutation (*KIT* exon 9), PFS rates were 5.6 months and 5.4 months, respectively.

Side effects were as expected, with no significant grade 4 or 5 events reported. The three most important adverse events of grade 3 or higher were hypertension, diarrhea, and hand/foot skin reactions and rash with potential blisters. All of these effects were manageable with appropriate dose modifications.

"Among patients with resistance to the only two drugs available for prolonging disease control, this drug has unique activity." Dr. Demetri concluded.

"This research," commented Dr. Adams, "clearly shows that there are effective therapies for these patients with rare tumors."

Dasatinib (Sprycel) Versus Imatinib (Gleevec) In Chronic-Phase Chronic Myeloid Leukemia: DASISION, Phase 3 at 3 Years

- Andreas Hochhaus, MD, Professor of Internal Medicine, and Interim Head, Department of Hematology and Medical Oncology, Universitätsklinikum Jena, Jena, Germany
- Neil P. Shah, MD, PhD, Professor, University of California–San Francisco School of Medicine, ASCO Discussant

Three-year results of the phase 3 DASISION (Dasatinib Versus Imatinib Study I: Treatment-Naive CML) trial confirmed the persistence of benefits seen at 2 years among patients with newly diagnosed chronic-phase chronic myeloid leukemia (CP–CML) who were treated with dasatinib (Sprycel, Bristol-Myers Squibb). Earlier analyses had shown that deeper responses at 3 months were associated with fewer transformations to the accelerated or blast phase at 2 years. Patients receiving dasatinib were also more likely to achieve PFS than those receiving imatinib (Gleevec).

Deeper responses, defined as 10% or fewer chimeric oncogene *Bcr-Abl* transcripts, were achieved in 84% of patients receiving dasatinib and in 64% of patients receiving imatinib.

Speaking in an oral session, Dr. Hochhaus noted that in DASISION, 519 patients from 108 centers in 26 countries were randomly assigned to receive either dasatinib (100 mg daily) or imatinib (400 mg daily). To be eligible for the study, patients had to be enrolled within 2 months of diagnosis with Philadelphia chromosome–positive disease and had to have received no prior therapy for CML except hydroxyurea (e.g., Droxia, Bristol-Myers Squibb) or anagrelide (Agrylin, Shire) for platelet inhibition.

Three-year PFS rates were reported at 93.1% in dasatinib patients with deeper responses at 3 months and at 68.2% for those without deeper responses (i.e., with *Bcr-Abl* transcript levels above 10%; $P = 0.0003$). The pattern was similar with imatinib; PFS rates were 95.9% and 75.3%, respectively ($P < 0.0001$).

Transformation to the accelerated or blast phase at 3 years occurred in 4.7% of patients receiving dasatinib and in 6.7% of patients receiving imatinib. Rates tracked closely to 3-month *Bcr-Abl* transcript levels: 3.5% and 3.3% for dasatinib and imatinib, respectively, among patients with *Bcr-Abl* levels above 1% to 10%.

Three-year overall survival rates were also significantly higher for patients with deeper responses, when compared with those without these responses, at 95.9% vs. 85.9%, respectively ($P = 0.035$) in patients receiving dasatinib and at 96.0% and 88.0%, respectively, in those receiving imatinib.

The cumulative incidence of patients achieving a major molecular response (MMR), defined as *Bcr-Abl* levels of 0.1% or lower, at 3 years was 68% for dasatinib and 55% for imatinib (HR =1.62; $P < 0.0001$). At 2 years, rates had been 64% for dasatinib and 46% for imatinib.

Cumulative incidence rates for the deeper responses of 4-log and 4.5-log reductions in *Bcr-Abl* levels (MR^4 and $MR^{4.5}$) were 35% and 22% for dasatinib and 22% and 12% for imatinib ($P = 0.00635$ and 0.00069).

Dr. Hochhaus noted that dasatinib continued to be well tolerated, with minimal changes in adverse events at the 2- to 3-year follow-up. Overall survival data have remained immature.

"Three-year follow-up from DASISION continues to support dasatinib 100 mg daily as first-line treatment for patients with newly diagnosed CML in chronic phase," Dr. Hochhaus concluded.

"It seems reasonable, in the absence of data, to presume

that in general the deeper the response, the better the long-term outcome," said Dr. Shah in a poster discussion session on second-generation *Bcr-Abl* inhibitors. He said further that both dasatinib and nilotinib (Tasigna, Novartis) have produced MMRs in a higher proportion of patients than imatinib did.

Dr. Shah added, "There are notably fewer cases of disease transformation with dasatinib and nilotinib. This is the best evidence of clinical benefit that we have with these agents in the front-line setting to date."

Dasatinib (Sprycel) Versus Imatinib (Gleevec) in Chronic-Phase Chronic Myeloid Leukemia: CA180-034 Phase 3 at 6 Years

- Neil P. Shah, MD, PhD, Professor, University of California–San Francisco School of Medicine
- Michael J. Mauro, MD, Associate Professor, Knight Cancer Institute, Oregon Health & Science University, Portland, Ore.

Six-year follow-up findings from the randomized phase 3 CA180-034 study of dasatinib represent the longest-to-date follow-up of second-generation *Bcr-Abl* inhibition in chronic-phase chronic myeloid leukemia (CP–CML) patients, Dr. Shah said. They demonstrated that achieving *Bcr-Abl* levels of 10% or lower at 3 months predicted PFS at later follow-up evaluations.

In the dose-optimization study, the 670 CP–CML patients had been found to be either resistant or intolerant to imatinib or had suboptimal imatinib responses. Among these patients, 165 received dasatinib 100 mg once daily, which ultimately became the approved dose. Only findings for the 100-mg once-daily dose are reported here.

Ninety-two percent of patients achieved complete hematological responses; 63% achieved major cytogenetic responses (MCyRs), and 50% achieved complete cytogenetic response (CCyRs).

Transformation to the accelerated or blastic phase was reported in 6% of patients. The rate among patients who were imatinib-resistant was 7%, and the rate among those who were imatinib-intolerant was 2%.

The PFS rate was 49%, and the overall survival rate was 71%. Respective PFS and overall survival rates among imatinib-resistant patients were 46% and 69%, respectively; the rates among imatinib-intolerant patients were 58% and 78%, respectively.

In an exploratory landmark analysis, early responses predicted improved PFS and overall survival rates in the dasatinib patients. Those achieving *Bcr-Abl* levels of 10% or lower by 3 months had significantly higher PFS rates than those achieving that level in 12 months or more ($P < 0.002$). PFS rates were also higher in patients with *Bcr-Abl* levels of 10% or lower by 3 months regardless of baseline factors such as mutations or partial cytogenetic responses or complete hematological responses.

At the 6-year follow-up, 31% of patients remained on treatment; 21% discontinued because of disease progression, and 21% stopped because of toxicity from the study drug.

Dr. Shah concluded, "Collectively, these data support the use of dasatinib in patients with resistance, intolerance, or suboptimal response to imatinib."

"Progression-free survival and overall survival, even in the imatinib-resistant patients, were very good," commented Dr. Mauro. He noted that although the fraction of patients continuing with the study drug was small, rates of transformation to advanced CML were low.

Everolimus (Afinitor) for Postmenopausal Advanced Breast Cancer: Updated BOLERO-2 Results, Phase 3

- Jose Baselga, MD, Professor of Medicine, Harvard Medical School; and Chief, Division of Oncology, Massachusetts General Hospital, Boston

In the Breast Cancer Trials of Oral Everolimus (BOLERO-2), the oral mammalian target of rapamycin (mTOR) inhibitor everolimus (Afinitor, Novartis) (10 mg once daily) was added to the steroidal aromatase inhibitor exemestane (Aromasin, Pfizer) (25 mg once daily). The goal was to prolong progression-free survival (PFS) in postmenopausal women with advanced breast cancer whose estrogen receptor–positive disease had progressed or recurred after letrozole (Femara, Novartis) or anastrozole (Arimidex, AstraZeneca). Dr. Baselga presented updated 18-month data confirming the PFS benefits seen in earlier analyses and revealing also a widening survival benefit.

BOLERO-2 patients (N = 724; mean age, 62 years) were randomly assigned to receive, in a 2:1 fashion, everolimus plus exemestane (n = 485) or placebo plus exemestane (n = 239). Interim analyses at 12.5 months of follow-up had shown that everolimus plus exemestane improved PFS by 57% compared with placebo plus exemestane (HR = 0.43; 95% CI, 0.35–0.54; $P < 0.001$) based on local investigator assessment. Median rates of PFS were 6.9 and 2.8 months, respectively.

The estimated risk reduction was 55% (HR = 0.45; 95% CI, 0.38–0.54; $P < 0.001$) with everolimus plus exemestane, compared with placebo plus exemestane, by local assessment at the 18-month analysis. This corresponded to a clinically meaningful 4.6-month prolongation in median PFS, from 3.2 months with placebo plus exemestane to 7.8 months with everolimus plus exemestane.

By central assessment, the hazard ratio (HR) was stronger (0.38), as was the 6.9-month prolongation of PFS (11.0 vs. 4.1 months, respectively) with everolimus plus exemestane.

"The overall survival difference is widening," Dr. Baselga commented in an interview, noting that at the cutoff for this analysis when 200 deaths had occurred, the death rate was 25.4% in the everolimus/exemestane arm and 32.2% in the placebo/exemestane arm.

The most common grade 3 or 4 adverse events for everolimus plus exemestane—stomatitis (in 8%), hyperglycemia (in fewer than 6%), and fatigue (in fewer than 5%)—were consistent with those observed in prior studies with everolimus, Dr. Baselga noted.

He said, "At 18 months, we have a robust confirmed progression-free survival that is getting better and survival that is getting stronger."

Dr. Baselga added, "My impression is that at the end of the day, when the data are fully mature at 392 deaths, this study will be positive for survival."

Trametinib Versus Chemotherapy for Metastatic Melanoma: METRIC, Phase 3

- Caroline Robert, MD, PhD, Head of Dermatology, Institute Gustave Roussy, Paris, France
- Sylvia Adams, MD, New York University School of Medicine, New York, N.Y., ASCO Press Conference Moderator

In about 20% of all cancers, the mitogen-activated protein (MAP) kinase pathway leading to cell proliferation is activated. Specifically in melanoma and in pancreatic and colorectal cancers, Dr. Robert said at an ASCO press briefing, this pathway is turned on in about 60% of cases.

"That is what makes MEK [MAP kinase kinase] a very attractive target for treating these cancers," she said.

Trametinib is a highly selective and potent inhibitor of MEK_1 and MEK_2 and has shown efficacy in early phase trials in *BRAF*-mutated melanoma. The *BRAF* gene encodes a protein (B-Raf) that directs cell growth. About 50% of melanomas harbor activating *BRAF* mutations; the *BRAF V600E* mutation is most common, present in 90% of cases.

METRIC trial investigators enrolled 322 patients (mean age, 54 years) with advanced *BRAF*-mutated melanoma who had received up to one prior chemotherapy regimen. In a 2:1 ratio, they were randomly assigned to receive oral trametinib (GlaxoSmithKline) (2 mg daily) (n = 214) or chemotherapy with either dacarbazine (DTIC-Dome, Bayer) or paclitaxel (Taxol) (n = 108). The primary endpoint was progression-free survival.

The most common adverse events (occurring more frequently with trametinib and in 15% of patients or more) were diarrhea (57% vs. 10% for chemotherapy), peripheral edema (26% vs. 3%), acneiform dermatitis (19% vs. 1%), and hypertension (15% vs. 7%). Decreased ejection fraction with ventricular dysfunction, a known effect of trametinib, was noted in 7% of patients.

Higher-grade adverse events (grade 3 and 4) were reported for hypertension (12% grade 3) and rash (7% with grade 3; fewer than 1% with grade 4). There were no reported cases of cutaneous squamous cell carcinomas or hyperproliferative skin lesions. None of the patients required dose reductions.

Investigator-assessed median PFS was 4.8 months for trametinib and 1.5 months for chemotherapy, a 55% reduction in risk ($P < 0.0001$). In an analysis of best response, target lesion decreases of more than 30% were found in 39% of patients receiving trametinib and in 15% of patients receiving chemotherapy.

Chemotherapy patients whose disease progressed during treatment were allowed to cross over to treatment with trametinib. Despite the blunting effect this had on the overall survival analysis, Dr. Roberts said, there was a survival benefit: 6-month overall survival rates were 81% in the trametinib group and 67% in the chemotherapy group (a 46% reduction) ($P = 0.0136$).

Dr. Roberts concluded, "Trametinib provides an alternative treatment option for patients with *BRAF V600* metastatic melanoma."

She noted that trametinib is the first MEK inhibitor to show a statistically significant benefit in PFS, response rate, and overall survival compared with chemotherapy in patients with *BRAF V600* metastatic melanoma.

Dr. Adams said, "This is exciting for two reasons. First, it shows that in melanoma, inhibiting the MEK pathway is very effective, with both tumor shrinkage and a survival benefit. Second, it opens the landscape of treatments for *BRAF*-mutant melanomas and provides patients with additional options."

Reference

1. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 2011;378(9796):1079–1088.

American Society of Hypertension 27th Annual Scientific Meeting and Exposition

This year's meeting of the American Society of Hypertension (ASH) took place in New York City from May 19 to 22, 2012. This report describes the effect of sleep and awake administration times on ambulatory blood pressure in patients with type-2 diabetes, triple therapy in obese patients, cardiovascular outcomes suggesting the avoidance of thiazides in lean patients, and a novel GLP-1 agonist in type-2 diabetes. The meeting was attended by 1,905 hypertension specialists and other health care professionals.

Treatment Time-Dependent Effects On Ambulatory Blood Pressure in Type-2 Diabetes: The Hygia Project

- Juan J. Crespo, MD, Gerencia de Atencion Primaria de Vigo, Spain
- Samuel Mann, MD, Professor of Clinical Medicine, New York–Presbyterian Hospital, Weil–Cornell Medical Center, New York, N.Y.

In recent prior research, Dr. Crespo and colleagues documented that lowering blood pressure (BP) during sleep, a novel therapeutic target best achieved by taking antihypertensive medications at bedtime, is the most significant predictor of cardiovascular event-free survival in patients with diabetes. Their studies investigated the influence of hypertension treatment time on the circadian BP pattern and degree of BP control in patients with type-2 diabetes enrolled in the Hygia Project, which prospectively evaluated the risk of cardiovascular disease by 48-hour ambulatory BP monitoring in primary care centers in northwest Spain.

The project included 2,429 hypertensive patients with type-2 diabetes (1,465 men and 964 women) with a mean age of 65.9 ± 10.6 years. Among them, 1,176 were taking all of their BP-lowering medications on awakening, 336 were ingesting all of them at bedtime, and 917 patients were ingesting the full dose of some medications on awakening, and taking the other medications at bedtime.

Intake of one or more antihypertensive medications at bedtime was associated with lower mean systolic BP (129.7 mm Hg) during sleep compared with taking all medications on awakening (130.1 mm Hg). Also, mean systolic BP during sleep was significantly lower in patients taking all medications at bedtime (126.5 mm Hg) ($P < 0.001$). Patterns of mean diastolic

BP during sleep were similar.

The percentage of patients whose BP did not decline while asleep (the "non-dippers"), compared with when they were awake, was higher (68.6%) ($P < 0.001$) in patients who took all medications on awakening compared with those who took one or more medications at bedtime (55.8%; $P < 0.001$) and in those patients who ingested all medications at bedtime (49.7%; $P < 0.001$).

Similarly, the sleep-time decline in BP was significantly reduced in patients who took one or more antihypertensive medications at bedtime and in others upon awakening. The decline was reduced even further among those taking all medications on awakening.

An elevated BP pattern was also found more often (23.6%) among patients in the awakening-treatment group, compared with those ingesting some (20.0%) or all medications at bedtime (12.2%; $P < 0.001$). The latter group also showed a significantly higher prevalence of controlled ambulatory BP ($P < 0.001$) and required significantly fewer medications ($P < 0.001$).

"These findings indicate that bedtime hypertension treatment, in conjunction with proper patient evaluation by ambulatory monitoring to corroborate the diagnosis of hypertension and avoid treatment-induced nocturnal hypotension, should be the preferred therapeutic scheme for type-2 diabetes," Dr. Crespo concluded.

However, giving all medications at night, Dr. Mann cautioned, confers a risk of not helping to lower the daytime BP among the "dippers."

Patients with diabetes and kidney disease, he added, often have BP values that do not fall at night or that might even increase at that time.

"For them, it makes good sense," Dr. Mann added.

Olmesartan Plus Amlodipine Plus HCTZ in Obese Patients With Severe Hypertension: TRINITY

- Suzanne Oparil, MD, Professor of Medicine, University of Alabama, Birmingham

"A third of Americans are obese, and it is known that it is more difficult to bring blood pressure down by any given amount in obese subjects," said Dr. Oparil at her poster depicting the TRINITY (Triple Therapy with Olmesartan Medoxomil, Amlodipine, and HCTZ in Hypertensive Patients) trial.

TRINITY included 1,555 obese patients (mean age, 54 years) with a body mass index (BMI) of 30 kg/m^2 or higher and 937 non-obese patients (mean age, 57 years) with a BMI below 30 kg/m^2. Overall, approximately 62% of patients were obese and 25% of patients had severe hypertension; 27.1% of the obese patients had severe hypertension, and 21.7% of the non-obese patients had severe hypertension. Severe hypertension was defined as seated blood pressure (BP) of 180 mm Hg or higher or seated diastolic BP of 110 mm Hg or higher at baseline.

After 4 weeks of therapy with dual combinations of three agents—olmesartan medoxomil (Benicar, Daiichi Sankyo), amlodipine besylate (Norvasc, Pfizer), and hydrochlorothiazide (HCTZ)—a subset of subjects (n = 600) received triple therapy with all three drugs (olmesartan 40 mg, amlodipine 10 mg, and HCTZ 25 mg). The primary endpoint was a reduction in BP from baseline at week 12.

For patients receiving dual therapies, systolic BP reductions ranged from 27.4 mm Hg with olmesartan/amlodipine (Azor, Daiichi Sankyo) to 31.2 mm Hg with olmesartan/HCTZ (Benicar HCT) in obese subjects and from 30.5 mm Hg olmesartan/HCTZ to 34.0 mm Hg with olmesartan/amlodipine in non-obese subjects.

For patients receiving triple therapy, the reductions were 37.9 and 39.1 mm Hg in obese and non-obese patients, respectively.

Reductions in BP were more substantial among those with severe hypertension; systolic BP declined by 47.5 and 47.4 mm Hg in obese and non-obese subjects, respectively. Dual therapy reductions in this subset were about 11 mm Hg smaller (35.7–37.4 mm Hg) among obese patients and about 9 mm Hg smaller (38.6–39.3 mm Hg) among non-obese patients.

Treatment-related adverse events were mostly mild to moderate in severity with triple therapy, and rates were similar between groups.

Dr. Oparil concluded that reductions in systolic BP with the triple combination of olmesartan, amlodipine, and HCTZ were greater than reductions with any dual combinations of any of the same agents. With this triple-therapy combination, she added, more severe hypertension, and not the presence of obesity, was associated with larger BP reductions, the TRINITY analysis showed.

Body Mass and Cardiovascular Outcomes: ACCOMPLISH, Phase 3

- Michael Weber, MD, Professor of Medicine, State University of New York (SUNY) Downstate Medical Center, Brooklyn, N.Y.

That obese individuals have had lower rates of cardiovascular (CV) adverse events in major clinical trials (SHEP, LIFE, INVEST) has been considered to be an "obesity paradox." Given that the higher rates of CV events in lean patients occurred mostly or entirely among those receiving thiazide therapy, Dr. Weber conducted an investigation to determine whether the excess CV risk in lean patients would be prevented with a non-diuretic strategy.

Dr. Weber and colleagues stratified the findings of the ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) trial. Subjects included obese patients (BMI, 30 kg/m^2 or above; n = 5,709); overweight patients (BMI, between 25 and 30 kg/m^2; n = 4,157); and lean patients (BMI, below 25 kg/m^2; n = 1,616).

The investigators compared CV outcomes among those receiving HCTZ-based therapy plus the angiotensin-converting enzyme (ACE) inhibitor benazepril (Lotensin HCT, Novartis) with amlodipine (Norvasc)-based therapy plus benazepril (Lotrel, Novartis). The primary outcome for this analysis was the composite of CV death or nonfatal myocardial infarction (MI) or stroke.

Overall primary endpoint CV adverse event rates per 1,000 patient-years were 24.6 in the lean population, 19.5 in the overweight patients, and 17.2 in the obese patients ($P = 0.025$). Also, CV death rates were lowest in the obese population ($P = 0.0005$).

For patients treated with benazepril and HCTZ separately, primary endpoint rates of CV events were 30.7% for lean patients, 21.9% for overweight patients, and 18.2% for obese patients ($P = 0.0034$). Event rates for CV death, again, were lowest in obese patients, as follows: 13.8% for lean patients, 8.4% for overweight patients, and 5.7% for obese patients ($P = 0.0004$).

When investigators looked at results for patients receiving benazepril/amlodipine, however, primary endpoint rates did not differ among the three weight classes, as follows: 18.2% for lean patients, 16.9% for overweight patients, and 16.5% for obese patients ($P = 0.9721$).

Primary endpoint CV adverse event rates with both combinations were similar among obese patients but were significantly lower with benazepril/amlodipine (Lotrel) than with benazepril/HCTZ (Lotensin HCT) in overweight patients (HR = 0.76; 95% CI, 0.59–0.94; $P = 0.0369$) and in the lean patients (HR = 0.57; 95% CI, 0.39–0.84; $P = 0.0037$).

There was a 69% increased CV risk in lean patients, compared with obese patients in the group receiving thiazides, Dr. Weber concluded. By contrast, in patients receiving amlodipine, compared with HCTZ, CV event rates were 11%, 24%, and 43% lower in obese, overweight, and lean patients, respectively.

Either therapy, Dr. Weber stated, is appropriate in obese patients; in the obese patients, hypertension is associated with excess volume. In non-obese patients, however, thiazides may stimulate adverse mechanisms that worsen CV outcomes.

"Calcium-channel blocker therapy should be preferred in non-obese, high-risk hypertensive patients," Dr. Weber said.

Dulaglutide and Ambulatory Blood Pressure and Heart Rate in Type-2 Diabetes: Phase 2

• Keith C. Ferdinand, MD, Professor of Clinical Medicine, Section of Cardiology, Tulane University School of Medicine; and Chief Science Officer, Tulane Heart and Vascular Institute, New Orleans, La.

Glucagon-like peptide-1 (GLP-1) agonists, such as liraglutide (Victoza, Novo Nordisk) and exenatide (Byetta, Amylin/Eli Lilly), are approved in the U.S. for the treatment of type-2 diabetes. Although these medications are associated with reductions in systolic blood pressure (BP) and small increases in heart rate, these evaluations have been conducted through clinical measurements. To more fully assess the pharmacodynamic profile of Eli Lilly's dulaglutide (an investigational long-acting GLP-1 agonist) and its potential effects on cardiovascular (CV) risk, Dr. Ferdinand and colleagues prospectively studied dulaglutide through ambulatory BP monitoring.

Speaking at a late-breaking clinical trial session, Dr. Ferdinand said that all subjects (mean age, 56.5 years) enrolled in the 755-patient trial had type-2 diabetes with clinical BP values between 90/60 mm Hg and 140/90 mm Hg while receiving three or fewer antihypertensive agents. Glycosylated hemoglobin (HbA_{1c}) levels were between 7.0% and 9.5% with one or more oral antihyperglycemic agents. On top of their oral antihyperglycemic agents, patients received either placebo (n = 250) or dulaglutide at subcutaneous (SQ) doses of 0.75 mg (n = 254) or 1.5 mg (n = 251) once weekly for 26 weeks.

Mean ambulatory BP at baseline was 131/76 mm Hg, and mean ambulatory heart rate was approximately 80 beats per minute (bpm).

Both doses of dulaglutide met the primary non-inferiority BP measurement (a margin of 3 mm Hg). Mean 24-hour systolic BP reductions at 26 weeks were 2.66 mm Hg and 1.71 mm Hg for dulaglutide 1.5 mg and 0.75 mg, respectively ($P = 0.002$ for dulaglutide 1.5 mg, compared with placebo).

Mean 24-hour diastolic BP changes were nonsignificant between the groups. Mean 24-hour heart rates increased by 3.5 bpm and 1.26 bpm for dulaglutide 1.5 mg and 0.75 mg, respectively.

"The heart rate changes were small and statistically nonsignificant. At this point, we don't think they are clinically significant," Dr. Ferdinand said.

For both dulaglutide doses at 16 and 26 weeks, HbA_{1c} levels were reduced from baseline significantly ($P < 0.001$) compared with placebo.

Small increases in diarrhea (12.4% with dulaglutide1.5 mg; 7.6% with placebo) and nausea (13.5% with dulaglutide 1.5 mg and 6.0% with placebo) were reported for the higher dulaglutide dose. Dulaglutide was generally well tolerated.

Dr. Ferdinand commented, "Future studies may confirm whether these blood pressure effects correlate with long-term clinical outcomes." ■