Comparative Effectiveness of Ledipasvir/Sofosbuvir ± Ribavirin and Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir ± Ribavirin In 6,961 Genotype 1 Patients Treated in Routine Medical Practice

• Lisa Backus, MD, PhD, Department of Veterans Affairs, Palo Alto, California

In 2014, the Food and Drug Administration approved ledipasvir/sofosbuvir (LDV/SOF) with or without ribavirin (RBV) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (OPrD) with or without RBV for the treatment of hepatitis C virus (HCV) infection. Veterans Affairs, the largest integrated provider of HCV care, conducted an intent-to-treat cohort analysis of patients receiving a first course (eight to 12 weeks) of LDV/SOF with or without RBV or OPrD-based therapy in its 126 facilities.

While the sustained virological response (SVR) rates in clinical trials among genotype 1 HCV patients (the most prevalent group) were more than 90%, differences between outcomes in clinical trials versus those in routine medical practice have been observed often with prior HCV regimens. This study’s goal was to assess the effectiveness of these newer, more expensive pharmacotherapies in routine medical practice. The trial’s primary endpoint was SVR (HCV RNA below the limit of quantification after the end of treatment).

SVR rates (85.8% for OPrD with or without RBV; 95.1% with OPrD [1b]) with LDV/SOF with or without RBV or OPrD with or without RBV in routine medical practice nearly matched the high rates seen in clinical trials, Dr. Backus said. SVR rates were uniformly higher (except in human immunodeficiency virus patients) across subgroups in patients who received 12 weeks of treatment versus eight weeks of treatment. SVR rates were lower in patients 55 to 64 years of age; in African-Americans (odds ratio OR, 0.71 [0.59–0.86]; P < 0.01); in those with a body mass index of 30 kg/m² or higher (OR, 0.73 [0.60–0.89]; P < 0.01); in those with liver disease-severity marker Fibrosis–4 scores over 3.25 (OR, 0.60 [0.49–0.72]; P < 0.001); and in those receiving OPrD with RBV (OR, 0.60 [0.48–0.76]; P < 0.001).

Among 6,961 HCV patients, early discontinuations were lowest for LDV/SOF (5.35%) and highest for OPrD with RBV (15.2%), with rates somewhat higher among African-Americans. Dr. Backus noted also that LDV/SOF has a lower pill burden and frequency than the OPrD regimen.

Systematic Review and Meta-Analysis of Probiotics for Preventing Clostridium Difficile Infection in Hospitalized Adults Taking Antibiotics

• Nicole B. Shen, MD, NewYork–Presbyterian Weill Cornell, New York, New York

Clostridium difficile infection (CDI) is the leading healthcare-associated infection in hospitalized adults taking antibiotics in the U.S., according to Dr. Shen. Prior meta-analysis–based reviews suggest that CDI may be prevented by concurrent probiotic/antibiotic use. Probiotics are not recommended in the current American College of Gastroenterology and Society for Healthcare Epidemiology of America guidelines, although a 2015 Modified Delphi panel unanimously recommended CDI prophylactic use of Lactobacillus acidophilus and L. casei concurrently with antibiotics.

To determine if probiotics prevent CDI in hospitalized adults receiving antibiotics, Dr. Shen and colleagues conducted a meta-analysis including 6,942 patients (3,665 taking probiotics versus 3,277 controls) in 19 studies. Among individuals excluded from the analysis were those with diarrhea, compromised immunity, and acquired immune deficiency syndrome; those receiving chemotherapy or radiation; those with a history of CDI within three months; and those with gastrointestinal infection (CDI) prophylactic use of Lactobacillus acidophilus and L. casei concurrently with antibiotics.

Dr. Shen’s analysis found a CDI rate of 1.5% among those taking concurrent probiotics and a rate of 3.5% among controls. The number needed to treat was 50. Of the 19 trials, 17 showed a benefit for probiotics. The analysis also showed that the probiotic efficacy was higher in those studies showing higher CDI incidence. Adverse events were similar between groups (probiotic relative risk, 0.97 [0.86–1.09]).

Probiotic species, formulation, and dose did not affect efficacy. Dr. Shen pointed out that timing of probiotic use after the first antibiotic dose was the one consequential factor. The CDI relative risk was 0.32 among those taking the probiotic less than two days from the first antibiotic dose (P < 0.001), and it was 0.70 among those taking it more than two days from the first antibiotic dose (P = 0.02).
Overall, the quality of evidence was high, and Dr. Shen concluded that probiotics safely and effectively reduce CDI risk by more than 50% in hospitalized patients taking antibiotics. Further studies are needed to identify optimal species, dose, and duration.

“The findings suggest that as soon as you start taking antibiotics, you may be altering the gut flora in a way that creates vulnerability to CDI,” Dr. Shen said. The findings are strong enough, she said, to justify a guidelines change for those patients not among groups excluded from the analysis.

**Single-Day Low-Residue Diet Prior to Colonoscopy Shows Improved Tolerance and Bowel Preparation Quality Over Clear Liquid Diet: Interim Results From a U.S. Multicenter Randomized Controlled Trial**

- Jason B. Samarasena, MD, Associate Professor of Medicine, University of California at Irvine, Long Beach, California

Despite the fact that colonoscopy has been shown to reduce colon cancer deaths, screening participation remains low, Dr. Samarasena said. A factor often cited by patients as a strong deterrent is the dietary restriction associated with bowel preparation. “The clear-liquid diet [CLD] allowing only ‘Jell-O’ and drinks or broth you can see through leaves some people tired and hungry and is seen as uncomfortable and a hassle,” he said. Some practitioners have adopted a low-residue diet (LRD) allowing solid food that liquefies quickly in the small intestine. This low-fiber diet excludes vegetables, fruits, and seeds, but permits foods such as scrambled eggs, ice cream, macaroni and cheese, and even chicken breasts; it provides more calories and nourishment. Large studies comparing LRDs and CLDs are few, however.

The aim of this multicenter, randomized, single-blind prospective trial was to compare an LRD to a CLD in regard to bowel preparation quality, along with tolerance and satisfaction among a diverse patient population. It was conducted at a tertiary geriatric care center and a Veterans Administration hospital and included 83 patients undergoing colonoscopy. Investigators evaluated bowel preparation adequacy with the 10-point Boston Bowel Preparation Scale (BBPS) and hunger and fatigue pre- and postprocedure with a 10-point scale. They also assessed nausea, vomiting, bloating, abdominal cramping, and overall discomfort, as well as satisfaction with the diet, willingness to repeat the same preparation (diet and purgative), and the overall experience.

Interim analysis showed the BBPS for the LRD group to be better at 7.98 out of 10, compared with 7.54 out of 10 for the CLD group, with bowel preparation assessed as “adequate” in a higher number of patients in the LRD group ($P = 0.05$). BBPS scores of 7, 8, or 9 with no segment score of 0 or 1 were considered adequate.

As expected, evening hunger scores just prior to purgative intake were significantly lower in the LRD than the CLD group (3.5 versus 6.9, respectively; $P = 0.001$), and morning post-prep fatigue scores were also significantly lower in the LRD than the CLD group (3.5 versus 6, respectively; $P = 0.01$). Symptom scores were similar between groups, and diet satisfaction was higher in the LRD group (97% versus 46%; $P < 0.001$).

“This interim analysis demonstrates that patients using a low-residue diet before colonoscopy achieve a bowel preparation quality that may be superior to patients on a clear-liquid diet restriction. It shows also that a low-residue diet improves patient satisfaction and results in significantly better tolerability of bowel preparation. As a less restrictive dietary regimen, low-residue diet may help improve patient participation in colorectal cancer screening programs,” Dr. Samarasena said.

**Lack of Abuse Potential of Eluxadoline: Data From Phase 2 and 3 Studies**

- Reginald Fant, PhD, Director of Clinical Pharmacology and Abuse Potential Assessment, Pinney Associates, Inc., Bethesda, Maryland

Eluxadoline, an oral mixed mu-opioid receptor (OR), kappa-OR agonist, and delta-OR antagonist with low oral bioavailability (2–4 ng/mL), is approved by the Food and Drug Administration (FDA) for the treatment of adults with irritable bowel syndrome with diarrhea (IBS-D). With eluxadoline’s site of action occurring at the opioid receptors, its potential to be abused and to cause withdrawal symptoms is of interest and was evaluated at therapeutic doses (75 or 100 mg) in three phase 2 and phase 3 clinical trials (phase 3, IBS-3001 and IBS-3002; phase 2, IBS-3001). These trials have shown that eluxadoline (compared with placebo) improves abdominal pain and stool consistency in IBS-D patients and is well tolerated.

The trials included 2,776 patients (mean age, approximately 45 years; approximately 67% female; approximately 86% white). Analysis showed the overall incidence of adverse events potentially related to abuse to be similar across groups at 2.8% for placebo, 2.7% for eluxadoline 75 mg, and 4.3% for eluxadoline 100 mg. The assessment was based on the analysis of 210 terms proposed by the FDA in 2013 to capture abuse-related adverse events.

The most common adverse events potentially related to abuse were anxiety and somnolence, both of which occurred in less than 2% of patients in each treatment group. In the two-week post-treatment period (IBS-3001), incidence of any adverse event potentially associated with opioid withdrawal or rebound was similar across the groups: 1.9%, 1.9%, and 1.2% for placebo, eluxadoline 75 mg, and eluxadoline 100 mg, respectively. In the four-week single-blind withdrawal period of IBS-3002, incidence of any adverse event potentially associated with opioid withdrawal or rebound was similar across the groups: 5.8%, 5.8%, and 6.1% for placebo, eluxadoline 75 mg, and eluxadoline 100 mg, respectively. In the two phase 3 trials, median overall Subjective Opioid Withdrawal Scale scores (16 questions/0–4 scale) were low and similar across the groups: 3, 2, and 3 for placebo, eluxadoline 75 mg, and eluxadoline 100 mg, respectively.

“The message from these findings is that with IBS-D patients taking eluxadoline at therapeutic doses, you don’t have to worry about abuse potential or withdrawal symptoms,” Dr. Fant concluded.

Dr. Fant commented in an interview that, while buprenorphine is centrally active, eluxadoline is not, and very little passes through the blood–brain barrier. “You would need huge amounts to produce a effect,” he said. Also, exposure by alternative routes
of administration is expected to be severely limited by the low tamperability and low extractability of eluxadoline tablets. With oxycodone or hydrocodone, withdrawal effects might appear even after just two or three weeks of dosing, he added. However, patients have been on eluxadoline for nearly a year without the emergence of withdrawal symptoms upon discontinuation.

Efficacy and Safety of Induction Therapy with the Selective IL-23 Inhibitor BI 655066 in Patients With Moderate-to-Severe Crohn’s Disease: Results of a Randomized, Double-Blind, Placebo-Controlled Phase II Study

- Brian Feagan, MD, Robarts Clinical Trials, London, Ontario, Canada; and Wulf O. Böcher, MD, Boehringer Ingelheim Pharma GmbH and Co., Ingelheim, Germany

The interleukin-23 (IL-23) pathway has been implicated both genetically and biologically in the pathogenesis of Crohn’s disease. BI 655066, a humanized monoclonal antibody that selectively inhibits IL-23 through specific targeting of the IL-23 subunit, was the subject of a randomized phase 2 study conducted among patients with moderate-to-severe Crohn’s disease. The patients (n = 121) had clinically active Crohn’s disease (CD Activity Index [CDAI] score of 220 or higher) confirmed by endoscopy (CD Endoscopic Index of Severity score of 7 or higher [4 or higher for patients with isolated ileitis]) and had been treated previously with a tumor necrosis factor antagonist or conventional therapy. They were randomized double-blind to either 200 or 600 mg intravenous BI 655066 or placebo at weeks 0, 4, and 8. The primary endpoint was clinical remission (CDAI of less than 150) at week 12. The study included an induction period, a reinduction/washout period, and a subcutaneous maintenance period.

Clinical remission was achieved by 24.4% and 36.6% of patients with 200 mg and 600 mg of BI 655066, respectively, compared with 15.4% of patients with placebo (P = 0.308 and P = 0.025) in interim results after 12 weeks. Clinical response rates were 36.6% and 41.5% in the 200-mg and 600-mg BI 655066 arms, compared with 20.5% in the placebo group (P = 0.103 and P = 0.037). Endoscopic remission was achieved by 14.6% and 19.5% of patients with 200 mg and 600 mg of BI 655066, compared with 2.6% of patients with placebo (P = 0.056 and P = 0.017). Endoscopic response was achieved by 26.8% and 36.6% of patients with 200 mg and 600 mg of BI 655066, compared with 12.8% of patients with placebo (P = 0.117 and P = 0.014). Deep remission (clinical and endoscopic) was achieved by 2.4% and 12.2% of patients receiving 200 mg and 600 mg of BI 655066, respectively (P = 1.0 and P = 0.062), and for zero patients in the placebo group.

“This underscores how difficult to treat this population was,” Dr. Bocher commented in an interview.

While adverse events were similar among all treatment groups, discontinuations related to adverse events were more frequent in the placebo group and least frequent in the higher-dose BI 655066 group (15.4%, 12.2%, and 2.4%, respectively).

“In patients with active Crohn’s disease, selective blockade of IL-23 with BI 655066 was more effective than placebo for inducing clinical and endoscopic remission at 12 weeks and was well tolerated,” Dr. Feagan concluded.

A phase 3 trial is in the planning phase, according to Dr. Böcher.

American Society of Clinical Oncology (ASCO)

More than 35,000 cancer professionals attended this premier annual oncology meeting in Chicago, Illinois, June 3–7. We review key sessions across a wide range of disease states, including breast cancer, multiple myeloma, pancreatic cancer, glioblastoma, ovarian cancer, and melanoma.

A Randomized Trial of Extending Adjuvant Letrozole for Five Years After Completing an Initial Five Years of Aromatase Inhibitor Therapy Alone Or Preceded by Tamoxifen In Postmenopausal Women With Early-Stage Breast Cancer

- Paul Goss, MD, PhD, Harvard Medical School, Boston, Massachusetts

Prior research by Dr. Goss showed that five years of letrozole extended disease-free survival by 43% (P ≤ 0.001) and overall survival by 24% (P = 0.25) versus placebo in women with early-stage hormone receptor-positive breast cancer. This population, however, faces an indefinite risk of relapse. The phase 3 MA.17R trial was designed to elucidate the value of continued aromatase inhibitor therapy in preventing recurrences. In it, investigators extended adjuvant letrozole (2.5 mg orally once daily) or placebo for five years after an initial 4.5 to six years of aromatase inhibitor therapy alone or preceded by tamoxifen. The trial included 1,918 postmenopausal women with early-stage breast cancer.

After a median follow-up of 6.3 years, a 34% reduction in recurrence risk was found for letrozole compared with placebo (hazard ratio [HR], 0.66; P = 0.01). A 58% reduction in occurrence of contralateral breast cancer in women receiving extended letrozole was also significant (HR, 0.42; P = 0.007).

Overall survival was similar between groups, however (HR for letrozole, 0.97; P = n.s.).

Osteoporosis was doubled in the letrozole group, with more bone fractures (133 letrozole, 88 placebo). No emergent symptoms or toxicities were observed, however. While there was no worsening of quality of life in either group, physical function was better in the placebo group. The difference, Dr. Goss said, was less than clinically meaningful. He acknowledged, however, “Bone health remains as an important factor in risk–benefit considerations.”

“Ten years of any therapy is a long time,” commented ASCO breast cancer expert Harold J. Burstein, MD. “Fortunately, most women tolerate extended treatment reasonably well, with few side effects,” he added. “Now, women can talk with their clinical team and make informed decisions to extend adjuvant endocrine therapy or not.”

Dr. Goss concluded, “Unlike many anticancer therapies, aromatase inhibitors are readily accessible around the world,
and, therefore, our results will further improve the outcome for many women with breast cancer.”

The study was published online in the New England Journal of Medicine concurrently with presentation on June 5, 2016.1

Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival

• Philip L. McCarthy, MD, Roswell Park Cancer Institute, Buffalo, New York

Most autologous stem cell transplant (ASCT) patients with multiple myeloma will relapse or progress, Dr. McCarthy said—even those who have a complete response. While lenalidomide maintenance has been shown to reduce the risk of progression or death by about 50%, past studies have used progression-free survival (PFS) as their endpoint and have not examined overall survival (OS). To elucidate the OS of lenalidomide maintenance, Dr. McCarthy conducted a meta-analysis of three multiple myeloma trials (CALGB 100104, IFM 2005-02, and GIMEMA [RV-MM-PI-209]), which included 605 patients treated with lenalidomide and 604 with placebo or no treatment.

All patients had been randomized after ASCT to lenalidomide or control until progression. Lenalidomide maintenance in the IFM 2005-02 study was discontinued after a signal for increased rates of secondary primary malignancies (SPMs) was detected.

Seven-year OS in the pooled studies after a median follow-up of 80 months was 62% in the lenalidomide maintenance arm and 50% in controls (hazard ratio [HR], 0.74; 95% confidence interval, 0.62–0.89; \(P = 0.001\)). HRs favored lenalidomide for each of the trials considered separately (CALGB HR, 0.56; IFM HR, 0.91; and GIMEMA HR, 0.66). The findings show, Dr. McCarthy said, that lenalidomide maintenance is feasible for long-term disease control after ASCT.

Subgroup analysis showed an OS benefit for lenalidomide maintenance regardless of age, gender, or response after ASCT, but with greater benefit among those with stronger post-ASCT responses.

For both hematological (HR, 2.03; 95% confidence interval, 1.59–2.58) and solid tumors (HR, 1.71; 95% confidence interval, 1.27–2.31) cumulative incidence of SPMs was significantly higher in the lenalidomide maintenance groups. Putting that finding in a risk–benefit context, Dr. McCarthy commented, “There was a 26% reduction in the risk of death, representing an estimated 2.5-year increase in median survival. So the overall survival benefit of lenalidomide maintenance outweighs the risk of developing an SPM.”

Speaking further about SPM risk, Markus Renschler, MD, Global Head for Hematology and Oncology Medial Affairs at Celgene, the manufacturer of lenalidomide, said, “While the absolute risk for a secondary primary malignancy was nearly doubled, the actual risk is very low. The 26% improvement in overall survival includes that risk.” Dr. Renschler pointed out further in an interview that in the IFM study (the study in which lenalidomide maintenance was discontinued following the detection of SPM increase), the median survival duration was five months shorter than in the other trials that had continued lenalidomide treatment.

Dr. McCarthy concluded, “Lenalidomide maintenance after ASCT can be considered a standard of care.”

HERITAGE: A Phase 3 Safety and Efficacy Trial of the Proposed Trastuzumab Biosimilar MYL-1401O Versus Herceptin

• Hope Rugo, MD, University of California, San Francisco, Comprehensive Cancer Center, San Francisco, California

While biologics are complex proteins with high molecular weight, traditional small-molecule agents are usually simple chemicals with relatively low molecular weight. They are highly targeted. Trastuzumab, for example, has revolutionized the treatment of human epidermal growth factor receptor-2-positive (HER2+) breast cancer. Because these biologics are costly, however, access across the globe is limited, Dr. Rugo said. “Many biologics are losing patent protection soon; biosimilars have the potential to significantly improve access to expensive agents.” To achieve regulatory approval, however, they must demonstrate high structural and functional similarity to the reference drug. To date, no biosimilars for the treatment of cancer have been approved in the U.S. or Europe, although the Food and Drug Administration approved one biosimilar supportive drug last year.

Dr. Rugo conducted the HERITAGE study comparing a biosimilar, MYL-1401O, to its reference product, Herceptin (trastuzumab, Genentech), in 500 women with metastatic HER2+ breast cancer. The randomized, double-blind, phase 3 trial was conducted at 95 sites across Asia, Latin America, Africa, and Europe. All participants received taxane chemotherapy with either trastuzumab or MYL-1401O. The primary endpoint of objective response rate at 24 weeks was reported at 69.6% with MYL-1401O and at 64% with trastuzumab. The lack of difference was within a predetermined equivalence margin.

Trastuzumab’s published data show low immunogenic potential. Importantly, immunogenicity was similarly low for the biosimilar agent. Overall the drug antibody rates for MYL-1401O and for trastuzumab were 2.4% and 2.8%, respectively. Rates of serious side effects were also similar at 36% in the trastuzumab group and 38% in the MYL-1401O group.

“This was one of the first trials with biosimilars in oncology to demonstrate such equivalence,” Dr. Rugo said. “MYL-1401O has the potential to meet the need for an affordable treatment option for patients with HER2+ cancers.”

Findings From a Phase 3 Trial Comparing Adjuvant Gemcitabine and Capecitabine Chemotherapy to Gemcitabine Alone Following Pancreatic Cancer Surgery

• John P. Neoptolemos, MD, University of Liverpool, Liverpool, United Kingdom

Pancreatic cancer is the third most common cause of cancer death in the U.S. For the small proportion of pancreatic cancer patients who are candidates for surgery, adjuvant gemcitabine chemotherapy is the standard of care worldwide. “We thought that the combination of gemcitabine plus capecitabine might
MEETING HIGHLIGHTS: American Society of Clinical Oncology

be better than gemcitabine alone,” Dr. Neoptolemos said at an ASCO press conference.

In the ESPAC 4 trial, researchers at 92 European sites randomized patients with resected pancreatic ductal adenocarcinoma to gemcitabine (n = 361) or gemcitabine and capecitabine (n = 361) within 12 weeks of surgery. The primary endpoint was overall survival (OS). Dr. Neoptolemos said that a large proportion of the patients had unfavorable prognostic factors, such as locally advanced or aggressive disease, large tumor size, or incomplete tumor resection. The included population, he added, was representative of a real-world pancreatic cancer population.

Median OS of 28.0 months with the combination regimen compared favorably to 25.5 months for gemcitabine alone. Estimated five-year survival increased with the combination at 28.8%, compared with 16.3% for gemcitabine alone. “The difference in median survival may seem modest,” Dr. Neoptolemos said, “but the improvement in long-term survival is substantial for this cancer.” Five-year survival with surgery alone, he said, is about 8%.

Serious adverse event rates were similar between groups at 26% for gemcitabine alone and 24% for the combination. In general, toxicities were manageable and acceptable.

The combination, he said, is a new standard of care. “These findings are significant because they show that those patients who can undergo surgery have a fighting chance of surviving this cancer with the combination of two commonly used chemotherapies.”

ASCO pancreatic cancer expert Smitha Krishnamurthi, MD, commented, “Pancreatic cancer remains one of the most hard-to-treat cancers. It is a major win to find that adding a generic chemotherapy not only improves survival for these patients, but does so with little effect on patients’ quality of life.”

A Phase III Randomized Controlled Trial of Short-Course Radiotherapy With or Without Concomitant and Adjuvant Temozolomide in Elderly Patients With Glioblastoma

• James R. Perry, MD, Odette Cancer and Sunnybrook Health Sciences Centers in Toronto, Ontario, Canada

Glioblastoma affects older patients disproportionately. Prior research has shown that, in elderly patients with glioblastoma, the best practice is surgical resection with six weeks of radiation combined with chemotherapy (oral temozolomide), according to Dr. Perry. Inclusion criteria in this pivotal trial, however, allowed only patients younger than 70 years of age, and few patients older than 65 years of age were included. Trials in the elderly, Dr. Perry said in an ASCO press conference, have compared different radiation schedules or compared radiation to temozolomide, but have not tested combined therapy. Clear treatment guidelines are lacking and practices vary globally.

The Canadian Cancer Trials Group international phase 3 trial was the first study to test temozolomide chemotherapy during short-course radiation therapy followed by monthly maintenance temozolomide doses in elderly patients with glioblastoma. Investigators enrolled 562 newly diagnosed patients age 65 years and older and assigned them randomly 1:1 to short-course radiation therapy (40 Gy in 15 fractions over three weeks) with or without concurrent and adjuvant temozolomide (12 cycles). The primary endpoints were progression-free survival (PFS), overall survival (OS), and quality of life.

Dr. Perry reported that the temozolomide/radiation combination conferred longer median survival (9.3 months versus 7.6 months [hazard ratio, 0.67; 95% confidence interval, 0.56–0.80; P < 0.0001]). Median PFS was longer for the combination at 5.3 months versus 3.9 months for radiation alone. The one-year and two-year survival rates were 37.8% and 10.4% with radiation therapy plus temozolomide compared with 22.2% and 2.8% with radiation therapy alone. Dr. Perry emphasized that the improvements, while modest, are meaningful.

Median OS is generally longer among glioblastoma patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and that was the case among 165 patients in this trial with the MGMT genetic abnormality (13.5 months with temozolomide/radiation versus 7.7 months with radiation alone). Dr. Perry underscored that some patients with unmethylated tumors did derive clinical benefit from adding temozolomide to radiation therapy.

An expected slight increase in grade-3 and -4 hematological toxicity was reported in the combination group. Also, nausea, vomiting, and constipation were more common among those receiving temozolomide.

“Patients were, however, able to easily complete the treatment plan,” Dr. Perry said. Adherence to the three weeks of chemoradiation was more than 97%. Standardized quality-of-life measures (the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire–Core 30 and the EORTC Quality of Life Questionnaire–Brain Neoplasm) showed no differences in physical, cognitive, emotional, and social functioning between groups.

“Oncologists now have evidence to consider radiation therapy with temozolomide in all newly diagnosed elderly patients with glioblastoma,” Dr. Perry said.

OV21/PETROC: A Randomized Gynecologic Cancer Intergroup (GCIG) Phase II Study of Intraperitoneal Versus Intravenous Chemotherapy Following Neoadjuvant Chemotherapy and Optimal Debulking Surgery in Epithelial Ovarian Cancer

• Helen J. Mackay, MD, Head of Medical Oncology and Hematology, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada

Epithelial ovarian cancer, the fifth most common cancer in women, usually presents at advanced stages (stage III/IV) with high mortality rates. In the United States, about 40% of women with epithelial ovarian cancer receive neoadjuvant chemotherapy. While sparing other parts of the body from potentially toxic doses, intraperitoneal (IP) chemotherapy allows the delivery of higher doses of chemotherapy to the tumor, Dr. Mackay said at an ASCO press conference. The OV21/PETROC study evaluated whether patients receiving neoadjuvant chemotherapy followed by optimal cytoreductive
surgery benefit from IP chemotherapy with carboplatin and paclitaxel.

Dr. Mackay’s study included 200 women with epithelial ovarian cancer who were randomly assigned to intravenous (IV) chemotherapy with or without IP chemotherapy after they had undergone debulking surgery.

Nine months after treatment, the disease progression rate was 18.9 percentage points lower among women receiving IP chemotherapy (per protocol, 42.2%; 95% confidence interval [CI], 31.9–53.1; chemotherapy, 23.3%; 95% CI, 15.1–33.4; IP/chemotherapy, \( P = 0.01 \)). While median overall survival was longer in the IP/chemotherapy group (38.1 months versus 59.3 months; hazard ratio, 0.80; 95% CI, 0.47–1.35), the difference was not statistically significant (\( P = 0.40 \)). Dr. Mackay noted that the trial was not powered to detect an overall survival difference.

No differences between groups were detected in a quality-of-life analysis. “At this early time frame,” Dr. Mackay said, “we already see that women are doing better with IP/chemotherapy, without a significant difference in toxicity.”

Dr. Mackay noted that this was the first randomized study to explore the benefit of IP chemotherapy plus IV chemotherapy in women with epithelial ovarian cancer.

“This study provides reassurance for patients and providers,” said Don Dizon, MD, the press conference moderator, “that the carboplatin-based IP regimen is both effective and well tolerated with maintenance of quality of life. That said, we need to further define those who derive the greatest benefit from this approach and to identify better options for all women with ovarian cancer.”

Preliminary Results From Phase 2 Study of Combination Treatment With HF10, a Replication-Competent HSV-1 Oncolytic Virus, and Ipilimumab In Patients With Stage IIIb, IIIc, or IV Unresectable Or Metastatic Melanoma

• Robert H. I. Andtbacka, MD, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

HF10 is a spontaneously occurring mutant (not genetically modified) of the HF strain of herpes simplex virus type 1 (HSV-1). When combined as an intralesional therapy with systemic ipilimumab, it has both local and systemic activity in patients with metastatic malignant melanoma, according to Dr. Andtbacka’s phase 2 study.

The study enrolled 46 patients (median age, 67 years; 59% male) with stage IIIb, IIIc, or IV unresectable/unresected metastatic malignant melanoma who were given intratumoral injections of HF10 at 1x10^6 TCID50/mL in combination with intravenous infusions of 3 mg/kg ipilimumab. Sixty-five percent were HSV-1 antibody positive. For this analysis, the primary endpoint was best overall response at 24 weeks.

Maximal changes in tumor burden were as follows: complete response (CR) in 12%, partial response (PR) in 28%, stable disease (SD) in 25%, clinical benefit (CR+PR+SD) in 65%, and progressive disease in 30%. Overall response (CR+PR) was 40%.

“This is very encouraging,” Dr. Andtbacka said in an interview.

A post-24-week analysis revealed a trend toward increasing responses with a CR of 14% and PR of 35% (49% overall response). Responses were observed in 53% (eight) of the stage IV patients. The fact that about half of the patients had prior therapy made these findings especially impressive, Dr. Andtbacka said.

Grade 3 and higher toxicities were generally related to ipilimumab. While all patients experienced some treatment-emergent adverse events, grade 3 or higher events related to HF10 were reported in only four patients (9%), and none discontinued treatment because of them. Adverse events were consistent with those reported for other oncolytic viruses (grade 2 or lower chills, fatigue, headache, injection site reaction, malaise, nausea, and pruritus).

“Preliminary efficacy evaluation suggests HF10 plus ipilimumab has both local and systemic antitumor activity and substantially improves the response rate of ipilimumab alone and does not exacerbate ipilimumab toxicity,” Dr. Andtbacka concluded.

Dr. Andtbacka also commented on a further phase 2 trial of a different intralesional therapy, the chemo-ablative agent PV-10 combined with radiotherapy. Conducted among metastatic melanoma patients who failed to achieve a CR with PV-10, the study led by Matthew C. Foote, MD, of Princess Alexandra Hospital and University of Queensland in Brisbane, Australia, included 13 patients (mean age, 69 years). Commencing six to 10 weeks after injections of PV-10, they were treated with 30 Gy (six fractions of 5 Gy twice weekly over three weeks) 3-D conformal radiotherapy (photons or electrons).

The overall response rate after a median follow-up of 19.3 months was 87% (CR, 33%; PR, 53%), with a 12.2-month mean duration of CRs. CRs were more likely with metastases smaller than 10 mm. Treatment was well tolerated.

Dr. Andtbacka commented, “We see that adding radiation, in this small series, led to improved responses. The finding suggests larger studies combining PV-10 with radiation in patients who are not fully responding.”

Finally, Dr. Andtbacka commented on intralesional therapy with a second oncolytic virus, coxsackievirus A21 (CVA21). He noted that in patients for whom treatment with ipilimumab, pembrolizumab, or nivolumab had failed, biopsies showed very few tumor-infiltrating lymphocytes (TILs). In these patients, however, after only three injections of CVA21 there was a very robust increase in TILs including CD8+ T cells. “So that raises the question, ‘Can we now add back the checkpoint inhibitor and get a response?’ We’re now studying that,” he said.

REFERENCE