The Clinical Cancer Letter

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Leukemia

Adding Imbruvica to Bendamustine/Rituximab Combination Increases PFS in Phase III Trial

Patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma that received Imbruvica (ibrutinib) in combination with bendamustine and rituximab experienced an 80 percent reduction in the risk of progression or death when compared to patients receiving bendamustine, rituximab and placebo in a phase III trial.

Imbruvica patients also experienced a higher overall response rate, including achieving a higher rate of complete responses, after a median follow-up of 17 months.

On March 16, an independent data monitoring committee recommended that the trial, named HELIOS, be unblinded based on clinically meaningful and statistically significant treatment benefit observed in the Imbruvica arm compared to placebo and BR.

(Continued to page 2)

Melanoma

Trial: Tafinlar/Mekinist Combination Benefits BRAF V600E/K Mutation-Positive Patients

Data from the phase III COMBI-d study showed a significant survival benefit for patients with BRAF V600E/K mutation-positive metastatic melanoma when treated with the combination of Tafinlar and Mekinist compared to Tafinlar alone.

The final analysis included the 423 patients enrolled in COMBI-d and showed that the combination of Tafinlar (dabrafenib) and Mekinist (trametinib) achieved a statistically significant overall survival benefit compared to Tafinlar monotherapy, with median of 25.1 months compared to 18.7 months, respectively (HR=0.71 [95% CI, 0.55-0.92], p=0.011).

(Continued to page 2)

Lung Cancer

Gilotrif Reduces Risk of Death by 19 Percent In Phase III Squamous Cell Carcinoma Trial

Overall survival results from the LUX-Lung 8 trial comparing two EGFR-directed treatments, Gilotrif (afatinib) and Tarceva (erlotinib), in patients with advanced squamous cell carcinoma of the lung progressing after treatment with first-line chemotherapy, demonstrated that treatment with Gilotrif significantly reduced the risk of death by 19 percent, extending the survival of patients to a median of 7.9 months compared to 6.8 months on Tarceva.

Significantly more patients treated with Gilotrif were still alive at one year compared to those treated with Tarceva (36.4 vs. 28.2 percent).

(Continued to page 3)

Imbruvica plus BR Increased PFS Compared to BR plus Placebo

(Continued from page 1)

The trial data was presented at the annual meeting of the American Society of Clinical Oncology in Chicago. Imbruvica is jointly developed by Pharmacyclics LLC and Janssen Biotech Inc.

HELIOS is a randomized, double-blind phase III study conducted in 21 countries, which evaluated 578 patients with relapsed/refractory CLL/SLL who had received at least one prior therapy. Patients were randomized to receive either the combination of oral, once-daily ibrutinib 420 mg and six cycles of BR, or a matching regimen of oral, once-daily placebo and six cycles of BR. Treatment with ibrutinib or placebo continued until disease progression or unacceptable toxicity.

Progression-free survival was the primary endpoint of the study. At 18 months, PFS rates were 79 percent for patients in the ibrutinib+BR arm compared with 24 percent for patients in the placebo+BR arm.

At a median follow-up of 17 months, PFS was significantly longer with Imbruvica compared to placebo (median not reached vs. 13.3 months; HR: 0.203, 95% CI: 0.150-0.276, P<0.0001). Patients with the genetic mutation del 17p CLL were excluded from the study, but PFS rates were consistent across all other high-risk subgroups.

Secondary endpoints included ORR and overall survival. Patients in the Imbruvica arm experienced higher rates of ORR and CR/CRi (CR with incomplete hematopoietic recovery), 82.7 and 10.4 percent, respectively, compared to patients in the placebo arm, 67.8 and 2.8 percent, respectively. The median OS has not yet been reached after a median follow up of 17 months.

Six cycles of BR were completed in the majority of patients in the Imbruvica and placebo arms (83 and 78 percent, respectively).

The safety profile of Imbruvica was consistent with the known individual safety profiles for the therapies. The addition of Imbruvica had no impact on the ability of BR to be administered in patients, with a similar number of BR cycles administered in both arms of the study.

Ninety patients (31 percent) in the placebo arm with confirmed progressive disease crossed over to receive ibrutinib, as permitted in the protocol. AEs were the primary reason for discontinuation in patients taking Imbruvica (14.2 vs. 11.8 percent in patients taking placebo).

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Prostate Cancer

Retrospective Analysis Shows Benefit with Custirsen in mCRPC Patients with Poor Prognosis

Results from a retrospective analysis of the phase III SYNERGY trial showed a benefit with custirsen therapy in men with metastatic castrate-resistant prostate cancer who had a poor prognosis.

The analysis, exploring the effect of clusterin inhibition in men at risk for poor outcomes, showed that over 40 percent of men in the trial had at least two of five common risk factors for poor prognosis. In these men, the analysis found a 27 percent lower risk of death when custirsen was used in combination with first-line docetaxel compared to docetaxel alone.

The results were presented at the annual meeting of the American Society of Clinical Oncology in Chicago.

Custirsen is designed to block the production of the protein clusterin, which is overexpressed in a number of cancers and has been linked to faster rates of cancer progression, treatment resistance and shorter survival duration in patients, according to the drug's sponsor, OncoGenex Pharmaceuticals Inc.

Clusterin is upregulated in tumor cells in response to treatment interventions such as chemotherapy, hormone ablation and radiation therapy and has been found to be overexpressed in a number of cancers, including prostate, lung, breast and bladder. Custirsen has been granted Fast Track designation by the FDA for

NSCLC and metastatic CRPC.

Researchers defined a simple five-criteria characterization for poor prognosis in prostate cancer based on the SYNERGY trial, which include: poor performance status, elevated prostate specific antigen, elevated lactate dehyrdogenase, decreased hemoglobin, and the presence of liver metastasis.

SYNERGY evaluated custirsen plus docetaxel/prednisone compared with docetaxel/prednisone alone in 1,022 men with metastatic CRPC. Following 509 deaths, median overall survival was 23.4 months in the custirsen arm compared to 22.2 months in the control arm (HR=0.93; P=0.42).

In retrospective analyses, a prognostic scoring system was developed in the control arm using multiple variable modeling and was used to dichotomize patients into good and poor prognosis. The analysis included 984 patients with complete data. Median survival for the poor and good prognosis groups in the control arm was 14.0 months and 30.4 months, respectively (HR = 3.66).

The custirsen HR effect differed between poor and good prognosis groups (interaction P=0.069). The HR estimate for custirsen survival benefit for those in the poor prognosis group was 0.73 (95% CI: 0.59 to 0.90) and 1.02 (95% CI: 0.76 to 1.37) for those in the good prognosis.

When analyzed separately (n=492), the median OS in the poor prognostic group was 17.0 months in the custirsen arm vs. 14.0 months in the control arm (HR=0.73, 95%CI: 0.59 to 0.90, P = 0.004).

A more simplified prognostic index score showed that over 40 percent of men in the trial had at least two of five common risk factors for poor prognosis. In these men, the analysis also showed a 27 percent lower risk of death when custirsen was used in combination with first-line docetaxel compared to docetaxel alone.

"With these additional analyses from the SYNERGY trial, we believe we now have criteria for better assessing the patient population that is most likely to respond to custirsen," said Scott Cormack, president and CEO of OncoGenex.

"These findings are particularly important because our ongoing AFFINITY and ENSPIRIT phase III custirsen trials already include a higher percentage of patients who are at increased risk for poor outcomes. Evaluating survival specifically in these high-risk populations will be critical as we move forward with the custirsen development program."

OncoGenex plans to meet with FDA officials in June to discuss a proposed amendment to the phase III AFFINITY trial protocol and statistical analysis plan that would include a co-primary endpoint evaulating survival in men who are at increased risk for poor outcomes. In the AFFINITY trial, custirsen is being evaluated with second-line chemotherapy in men with metastatic CRPC. Results from this trial are expected later this year or in early 2016, according to OncoGenex.

Custirsen is also being evaluated in the international phase III ENSPIRIT trial of patients with non-small cell lung cancer who have progressed following initial treatments.

Melanoma

Tafinlar/Mekinist Combination Increases PFS vs. Tafinlar Alone

(Continued from page 1)

A 33 percent reduction in the risk of progression or death was demonstrated with the combination therapy compared to monotherapy (median PFS of 11.0 months in the 211 patients receiving combination therapy vs 8.8 months in the 212 patients receiving monotherapy; HR 0.67 [95% CI, 0.53-0.84], p<0.001).

The combination achieved an ORR of 69 percent compared to 53 percent for monotherapy (95% CI, 6.0%-24.5%; p=0.001).

The median DoR for the 144 responders receiving combination therapy was 12.9 months (95% CI, 9.4-19.5) compared to 10.6 months in the 113 responders receiving monotherapy (95% CI, 9.1-13.8).

The safety results were consistent with the profile observed to date for the combination and consistent with the profile observed for Tafinlar monotherapy; no new safety concerns were observed. The most common adverse events in the combination arm were pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, joint pain, hypertension, vomiting, cough and peripheral edema.

Tafinlar and Mekinist target two different serine/threonine kinases—BRAF and MEK, respectively—in the RAS/RAF/MEK/ERK pathway, which is implicated in NSCLC and melanoma, among other cancers. This is the first combination of BRAF/MEK inhibitors to demonstrate a statistically significant overall survival benefit for this patient population in two phase III studies, according to sponsor Novartis.

Results were presented at the annual meeting of the American Society of Clinical Oncology in Chicago, and were also published in The Lancet.

The study randomized 423 patients from investigative sites in Australia, Europe and North and South America. There was no crossover between

treatment arms.

Completion of COMBI-d is a post-marketing requirement for the FDA's accelerated approval for the combination in the U.S. Combination use of Tafinlar and Mekinist in patients with unresectable or metastatic melanoma who have BRAF V600E/K mutation is approved in the U.S., Australia, Chile and Canada.

In addition to results from the COMBI-d study, long-term data from a phase I/II study showed a three-year overall survival rate of 38 percent (95% CI, 25%, 51%) after treatment with the combination of Tafinlar and Mekinist in all patients with BRAF V600E/K mutation-positive metastatic melanoma. Safety results from this study were consistent with those observed in other trials evaluating the combination.

Lung Cancer

Trial: Gilotrif Increases PFS in Squamous Cell Carcinoma

(Continued from page 1)

The OS analysis was presented at the annual meeting of the American Society of Clinical Oncology in Chicago. LUX-Lung 8 (NCT01523587) was conducted across 23 countries and is the first prospective trial to compare two different tyrosine kinase inhibitors in patients with advanced SCC of the lung (n=795).

According to Gilotrif's sponsor Boehringer Ingelheim, the complete results from this study will be the basis for global regulatory submissions later this year. Gilotrif is not approved for use in patients with SCC of the lung.

OS was the key secondary endpoint of the randomized phase III head-to-head trial, and was analyzed following positive results for the primary endpoint of progression-free survival presented in 2014.

The updated analysis of PFS confirmed a significant reduction in the risk of cancer progression by 19 percent in patients treated with Gilotrif compared with Tarceva.

The delay in cancer progression seen with Gilotrif treatment was accompanied by improved control of cancer-related symptoms: a higher proportion of patients treated with Gilotrif reported improvement in cough (43.4 vs. 35.2 percent), shortness of breath (51.3 vs. 44.1 percent) and overall well-being/quality of life (35.7 vs. 28.3 percent) compared with Tarceva.

The rate of severe adverse events was similar between Gilotrif and Tarceva treatment arms (57.1 vs. 57.5%). A higher incidence of severe diarrhea and stomatitis (mouth sores) was observed with Gilotrif compared to Tarceva (grade 3/4 diarrhea: 9.9/0.5 vs. 2.3/0.3%, grade 3 stomatitis: 4.1 vs. 0.0%), while a higher incidence of severe rash/acne was reported with Tarceva compared to Gilotrif (grade 3 rash/acne: 10.4 vs. 5.9%).

Gilotrif is approved in more than 50 countries for the first-line treatment of distinct types of EGFR mutation-positive NSCLC. Approval of Gilotrif in this indication was based on the primary endpoint of PFS from the LUX-Lung 3 clinical trial where Gilotrif significantly delayed tumor growth when compared to standard chemotherapy.

Gilotrif is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 substitution mutations.

Myelofibrosis

Pacritinib Demonstrates Control Of Symptoms in Phase III Trial

Data from PERSIST-1, a phase III trial examining pacritinib for the treatment of myelofibrosis, showed that compared to best available therapy (exclusive of a JAK inhibitor), pacritinib therapy resulted in a significantly higher proportion of patients with spleen volume reduction and control of disease-related symptoms.

Spleen enlargement is a common and debilitating symptom of myelofibrosis. Within one year of diagnosis, the incidence of disease-related low platelet counts, severe anemia, and red blood cell transfusion requirements increase significantly.

The trial compared pacritinib to best available therapy, which included a range of currently utilized off-label treatments, in 327 patients with myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis), regardless of the patients' platelet counts. Pacritinib is an investigational oral multikinase inhibitor with specificity for JAK2 and FLT3.

The trial was presented at the annual meeting of the American Society of Clinical Oncology in Chicago.

At study entry, 46 percent of patients were thrombocytopenic; 32 percent of patients had platelet counts less than 100,000 per microliter; and 16 percent of patients had platelet counts less than 50,000 per microliter; normal platelet counts range from 150,000 to 450,000 per microliter.

The trial met its primary endpoint of spleen volume reduction (35 percent or greater from baseline to week

24 by MRI/CT scan) in the intent-to-treat population. These results included patients with severe or life-threatening thrombocytopenia.

Trial data show that when measuring the volume of spleen reduction, the greatest difference in treatment arms was observed in evaluable patients with the lowest platelet counts, <50,000 per microliter: 33.3 percent with pacritinib compared to 0 percent with BAT (p=0.037).

The median duration of treatment was 16.2 months in patients treated with pacritinib, compared to 5.9 months in patients undergoing best available treatment. The majority (79 percent) of patients in the BAT arm eventually crossed over to receive pacritinib therapy.

Patients treated with pacritinib also experienced a sustained improvement in myelofibrosis-associated symptoms or Total Symptom Score as measured by the Myeloproliferative Neoplasm Symptom Assessment Form electronic diary.

When measuring the secondary endpoint—the proportion of patients with a 50 percent or greater reduction in TSS from baseline to Week 24—patients treated with pacritinib experienced greater improvement in their symptoms when compared to BAT, regardless of their baseline platelet counts.

In the ITT patient population, 24.5 percent of pacritinib-treated patients showed improvement vs. 6.5 percent of BAT-treated patients (p<0.0001); in the evaluable patient population, 40.9 percent of pacritinib-treated patients showed improvement, compared to 9.9 percent of BAT-treated patients (p<0.0001).

Twenty-five percent of patients treated with pacritinib who were severely anemic and transfusion dependent—requiring at least six units of blood in the 90 days prior to study entry—became transfusion independent, compared to zero patients treated with BAT (p<0.05).

Among patients with the lowest baseline platelets (<50,000/uL) who received treatment with pacritinib, a significant increase in platelet counts was observed over time compared to BAT (p=0.003), with a 35 percent increase in platelet counts from baseline to Week 24.

The most common adverse events, occurring in 10 percent or more of patients treated with pacritinib within 24 weeks, of any grade, were: mild to moderate diarrhea (53.2 percent vs 12.3 percent with BAT), nausea (26.8 percent vs 6.6 percent with BAT), anemia (22.3 percent vs 19.8 percent with BAT), thrombocytopenia (16.8 percent vs 13.2 percent with BAT), and vomiting (15.9 percent vs 5.7 percent with BAT).

Of the patients treated with pacritinib, three discontinued therapy and 13 patients required dose interruption (average one week) for diarrhea. Patients received a daily full dose of pacritinib over the duration of treatment. Gastrointestinal symptoms typically lasted for approximately one week and few patients discontinued treatment due to side effects. There were no Grade 4 gastrointestinal events reported.

CTI BioPharma and Baxter BioScience entered into a worldwide license agreement in November 2013 to develop and commercialize pacritinib. CTI BioPharma and Baxter will jointly commercialize pacritinib in the U.S. while Baxter has exclusive commercialization rights for all indications outside the U.S.

In August 2014, pacritinib was granted Fast Track designation by the FDA for the treatment of intermediate and high risk myelofibrosis, including but not limited to patients with disease-related thrombocytopenia, patients experiencing treatment-emergent thrombocytopenia on other JAK2 inhibitor therapy, or patients who are intolerant of, or whose symptoms are sub-optimally managed on other JAK2 inhibitor therapy.

Kidney Cancer

Phase II Study Compares Afinitor As Second-Line Treatment Following Various VEGFR Inhibitors and Cytokine Therapy

Progression-free survival data from a phase II study evaluating Afinitor (everolimus) as a second-line therapy in advanced renal cell carcinoma were presented at the annual meeting of the American Society of Clinical Oncology in Chicago.

Results from the RECORD-4 study—which evaluated Afinitor in 134 patients who had progressed following a first-line treatment including cytokine therapy and various different vascular endothelial growth factor receptor inhibitors—demonstrated an overall median progression-free survival of 7.8 months (95% CI: 5.7-11.0).

In the trial, patients were divided into three cohorts based on their prior first-line therapy: sunitinib (n=58); other anti-VEGFR therapies (n=62, including sorafenib, bevacizumab, pazopanib, tivozanib and axitinib); or cytokines (n=14).

PFS was 5.7 months (3.7-11.3) after sunitinib in the first line, 7.8 months (5.7-11.0) after other anti-VEGF therapies in the first line, and 12.9 months (2.6-not evaluable) after first-line cytokine therapy.

Patients received everolimus 10 mg each day until progression of disease, as determined by Response

Evaluation Criteria in Solid Tumors criteria 1.0. The primary endpoint was PFS. Secondary endpoints include OS and safety; OS data are not yet mature.

The most commonly reported Grade 3 or 4 adverse events associated with everolimus were anemia, stomatitis/mouth ulceration, hyperglycemia and hypertriglyceridemia.

Data from the phase II RECORD-3 trial were also presented at the ASCO meeting, including the final overall survival results. The trial's primary endpoint—median PFS non-inferiority of first-line treatment with Afinitor versus first-line treatment with sunitinib—was not met.

RECORD-3 compared first-line Afinitor treatment followed by sunitinib versus first-line sunitinib treatment followed by Afinitor in 471 treatment-naïve patients with metastatic RCC.

Patients in the sunitinib-Afinitor arm had a median OS of 29.5 months and patients in the Afinitor-sunitinib arm had a median OS of 22.4 months (HR=1.09; 95% CI: 0.87-1.37); the seven-month OS difference was not statistically significant.

In addition, the median combined first- and second-line PFS was 21.7 months for patients in the Afinitor-sunitinib arm and 22.2 months in the sunitinib-Afinitor arm (HR, 1.2; 95% CI, 0.91-1.59). The safety profiles of Afinitor and sunitinib were consistent with those previously reported.

Pancreatic Cancer

PEGPH20 Shows Doubling of PFS Among Patients with High Levels Of Hyaluronan in Phase II Trial

Interim findings from an ongoing phase II clinical study of PEGPH20 showed a doubling of progression-free survival and an improvement trend in overall survival in metastatic pancreatic cancer patients with high levels of hyaluronan.

The trial included 135 treated patients in stage 1, of whom a total of 44 patients—23 receiving PEGPH20 in combination with Abraxane (paclitaxel) and gemcitabine and 21 receiving Abraxane and gemcitabine alone—had available biopsies that were determined in a retrospective analysis to have high levels of hyaluronan.

Hyaluronan is a chain of natural sugars throughout the body that can accumulate around cancer cells inhibiting other therapies. PEGPH20 is designed to degrade HA to improve the access to tumor cells for chemotherapy, monoclonal antibodies and other immuno-therapy agents, according to the drug's sponsor, Halozyme Therapeutics Inc.

The data were presented at the annual meeting American Society of Clinical Oncology in Chicago.

Median progression-free survival was 9.2 months in the PEGPH20 arm compared to 4.3 months in the control arm in high HA patients (HR=0.39; p=0.05).

The overall response rate was 52 percent in patients receiving PEGPH20 versus 24 percent in the control arm (p=0.038). Duration of response was 8.1 months compared to 3.7 months, respectively.

In the 30 high HA patients who were evaluated for response prior to the April 2014 clinical hold and subsequent PEGPH20 treatment discontinuation, the overall response rate was 73 percent versus 27 percent (p=0.01), respectively, consistent with findings presented in January.

The data also showed a trend toward improvement in median overall survival of 12 months compared to 9 months in high HA patients treated with PAG versus AG (HR=0.62) despite discontinuation of PEGPH20 in more than half of the PAG-treated patients at the time of the clinical hold in April 2014, according to Halozyme.

Data was also presented on the rate of thromboembolic events in 55 patients treated in stage 2 of the trial. Stage 2 began after a protocol amendment in July 2014, excluding patients at high risk of TE events and adding prophylaxis with low molecular weight heparin (enoxaparin) to all patients in both treatment arms.

Reported results included: a TE event rate of 13 percent in 38 patients treated with PAG versus 18 percent in 17 patients receiving AG; and in the 20 PAG patients receiving 1 mg/kg/day of enoxaparin, no TE events have been reported to date.

FDA granted orphan drug designation to PEGPH20 for treatment of pancreatic cancer and fast track for PEGPH20 in combination with gemcitabine and nab-paclitaxel for the treatment of metastatic pancreatic cancer. Additionally, the European Commission, acting on the recommendation from the Committee for Orphan Medicinal Products of the European Medicines Agency, designated investigational drug PEGPH20 an orphan medicinal product for the treatment of pancreatic cancer.

Breast Cancer

Phase III Prolia Trial Meets Endpoint in Clinical Fractures

A phase III trial of adjuvant Prolia (denosumab) therapy in postmenopausal women with early hormone receptor positive breast cancer receiving aromatase inhibitor therapy met its primary endpoint of time from randomization to first clinical fracture (HR=0.5, 95 percent CI 0.39-0.65, p<0.0001).

The observed 50 percent reduction in fractures between the Prolia and placebo arms, 92 versus 176, respectively, was similar in patients with normal bone health at baseline (n=1,872, HR=0.44, p<0.0001) and in patients who started the trial with early signs of bone loss (n=1,548, HR=0.57, p=0.0021).

This is the first Prolia trial to enroll patients independent of baseline bone mineral density and with the majority in the normal BMD range, according to Prolia's sponsor, Amgen. The randomized, double-blind study, which enrolled a total of 3,425 patients, was conducted by the Austrian Breast and Colorectal Cancer Study Group.

The data were presented at the annual meeting of the American Society of Clinical Oncology in Chicago, and were also was published by The Lancet.

Evaluation of secondary endpoints showed that Prolia reduced the incidence of new vertebral and new or worsening of pre-existing vertebral fractures at 36 months (p<0.01). Statistically significant increases in BMD of the lumbar spine, total hip and femoral neck were observed in the Prolia-treated group at 36 months. The other secondary endpoints of disease-free survival, bone metastasis-free survival and overall survival have not been completed.

The safety profile of Prolia therapy was similar to placebo, and no major safety events were reported. The most frequently reported adverse events in this study included arthralgia, hot flush, back pain, osteoarthritis and bone pain.

Prolia is the first approved therapy that specifically targets RANK Ligand, an essential regulator of bone-removing cells.

Prolia is approved in the U.S. for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Prolia is also approved for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Chemotherapy

Electric Nerve Stimulation Shown to Be as Effective as Pilocarpine in Treating Radiation-Induced Dry Mouth

Results from the phase III stage of a clinical trial demonstrated that acupuncture-like, transcutaneous electrical nerve stimulation may be equally effective as pilocarpine, the current prescription medication in a pill, to treat radiation-induced dry mouth.

The study was published in the International Journal of Radiation Oncology • Biology • Physics, the official scientific journal of the American Society for Radiation Oncology.

The trial, RTOG 0537, is a phase II/III, multi-center, randomized trial comparing the procedure, ALTENS, with pilocarpine, the current standard of treatment for radiation-induced xerostomia.

Electrodes are placed on the skin at the locations of pre-selected acupuncture points and deliver low-frequency, high-intensity pulses to relieve the radiation-induced dry-mouth. Phase II results of RTOG 0537, published in 2012, proved a positive response in patients who received ALTENS for radiation-induced xerostomia and demonstrated it was feasible to deliver ALTENS treatment in a multi-center trial.

Patients eligible for the phase III portion of the trial had completed radiation therapy with or without chemotherapy three months to two years prior to enrolling in the study with no evidence of recurrence; reported grade 1 or higher xerostomia based on the Common Terminology Criteria for Adverse Events version 3.0; and had a Zubrod performance status of zero to two.

Of the 146 patients included in the study, 73 patients were randomized to receive pilocarpine, and 73 patients underwent the procedure, which included two, 20-minute ALTENS sessions each week for 12 weeks, for a total of 24 sessions.

Patients were allowed two weeks of no treatment, and any missed sessions were rescheduled during the 12-week period; patients did not exceed three sessions per week. Patients in the pilocarpine arm received 5 mg of pilocarpine orally three times a day for 12 weeks.

Patients' xerostomia symptoms were assessed

before treatment and at four, six, nine and 15 months after the patient's randomization date using the University of Michigan's Xerostomia-Related Quality of Life Scale—a patient-reported, 15-item scale that measures four domains: physical functioning, pain/discomfort, personal/psychologic functioning and social functioning. Patient responses to all four domains were averaged, and the total scores ranged from zero to four; an increased xerostomia burden is indicated by a higher score.

In the 96 patients eligible for analysis, the mean baseline XeQOLS score of the ALTENS arm was slightly lower than the pilocarpine arm (1.5 compared to 1.7), which indicates a slightly higher quality of life.

Baseline XeQOLS scores were subtracted from follow-up XeQOLS scores. At the nine-month follow-up, the median change in XeQOLS score was -0.53 for patients in the ALTENS arm and was -0.27 for patients in the pilocarpine arm.

At follow-up 15 months from randomization, the median change in XeQOLS score was -0.60 for patients in the ALTENS arm and was -0.47 for patients in the pilocarpine arm. The median change in XeQOLS scores consistently improved for patients in the ALTENS arm, however, none of the differences were statistically significant. The proportions of patients who had 20 percent or more improvement from their baseline XeQOLS scores were consistently higher in the ALTENS arm and the difference was significant at 15 months from randomization.

Overall results yielded one grade three adverse event (headache) in the ALTENS arm, and two grade three adverse events (dry mouth and blurred vision) in the pilocarpine arm. In the ALTENS arm, 20.9 percent (15) of patients reported nonhematologic adverse events of grade three or less. In the pilocarpine arm, 61.6 percent (45) of patients reported nonhematologic adverse events of grade three or less. At follow-up nine months from randomization, there was no significant difference in the highest grade of adverse events related to treatment between the two arms of patients.

"Radiation-induced xerostomia is a challenging side-effect to treat because it makes it difficult and sometime painful for patients to swallow food, thereby affecting their nutrition and physical well-being. Oral pilocarpine and similar medications are not well tolerated by patients due to various side effects including sweating, diarrhea, frequent urination and dizziness. Multiple previous studies using needle acupuncture supported the potential for acupuncture approaches in treating xerostomia symptoms, so RTOG 0537 was developed to specifically explore those findings," said Raimond Wong, the study's lead author and a radiation oncologist and associate professor in the Department of Oncology at McMaster University in Hamilton, Ontario.

"These phase III results of RTOG 0537 indicate that ALTENS, a needleless acupuncture approach, could provide an alternative treatment option that has fewer side effects and, in turn, helps improve quality of life for patients with radiation-induced xerostomia. Some patients in the ALTENS group demonstrated lasting response and indicated the possibility to induce salivary gland tissue regeneration. Randomized, controlled, placebo trials are necessary to confirm ALTENS' treatment efficacy for painful, radiation-induced dry mouth, a debilitating condition for many patients."

NCI CTEP-Approved Trials For the Month of June

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Phase I

PBTC-043: A Phase I Trial of Pomalidomide for Children with Recurrent, Progressive or Refractory CNS Tumors. Pediatric Brain Tumor Consortium; Fangusaro, Jason R. (312) 227-4846

Phase II

9706: Randomized Phase II Study to Assess the Role of Nivolumab as Single Agent to Eliminate Minimal Residual Disease and Maintain Remission in Acute Myelogenous Leukemia (AML) Patients After Chemotherapy. University of Chicago Comprehensive Cancer Center P2C; Liu, Hongtao (773) 834-0589

AMC-096: A Phase II Study of sEphB4-HSA in Kaposi Sarcoma. AIDS-Associated Malignancies Clinical Trials Consortium; Wong-Sefidan, Ida C. (858) 822-6276

EAI142: [18F] Fluoroestradiol (FES) PET as a Predictive Measure for Endocrine Therapy in Women with Newly Diagnosed Metastatic Breast Cancer. ECOG-ACRIN Cancer Research Group; Dehdashti, Farrokh (314) 362-1474

EAY131: Molecular Analysis for Therapy Choice (MATCH). ECOG-ACRIN Cancer Research Group; Flaherty, Keith Thomas (617) 726-8566

URCC-14079: Effectiveness of Prophylactic Topical Agents for Radiation Dermatitis. University of Rochester NCORP Research Base; Ryan, Julie Lynn (585) 276-3862

Phase III

AAML1331: A Phase III Study for Patients with Newly Diagnosed Acute Promyelocytic Leukemia (APL) Using Arsenic Trioxide and All-Trans Retinoic Acid. Children's Oncology Group; Kutny, Matthew A. (205) 638-9285

NRG-BR003: A Randomized Phase III Trial of Adjuvant Therapy Comparing Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel with or Without Carboplatin for Node-Positive or High-Risk Node-Negative Triple-Negative Invasive Breast Cancer. NRG Oncology; Valero, Vicente (713) 792-2817

Other Phases

9846: Patient-Derived Models Tissue Procurement Protocol for the National Cancer Institute. NCI LAO; Doroshow, James H. (301) 496-4291

9902: Phosphorylated (Tyrosine 705) STAT3 Status as a Predictor of Benefit from Anti-HER2 Therapy in Breast Cancer. Mayo Clinic; Perez, Edith A. (904) 953-7283

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Drugs and Targets

Lenvatinib Launched in U.K. For Advanced Thyroid Cancer

Lenvima (lenvatinib) launched in the U.K. as a treatment option for adult patients with progressive locally advanced or metastatic, differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

Lenvatinib demonstrated significantly prolonged progression-free survival in RAI refractory DTC versus placebo. Lenvatinib showed a median 18.3 months progression free survival PFS versus 3.6 months for placebo (HR=0.21; 99% CI, 0.14-0.31; $p<0.0001$).

In addition, the study underlines the rapid response of lenvatinib, with a median time to first objective response of two months.

The SELECT study, published in the New England Journal of Medicine, is a randomized, double-blind, multicenter trial for people with progressive radioactive iodine refractory differentiated thyroid

cancer (n=392). Lenvatinib significantly improved objective response rate versus placebo (64.8 vs. 1.5 percent; p<0.0001).

For lenvatinib, the most common treatment related adverse events were hypertension, diarrhea, fatigue, decreased appetite, decreased weight, and nausea.

"The launch of Lenvima represents great news for both Eisai and for patients who will now have access to this significant new treatment. Lenvima is a drug that was developed in the UK, will be manufactured in the UK and has now been launched first in the UK, something we at Eisai are very proud of," said Gary Hendler, president and CEO of Eisai EMEA and president of the Eisai Oncology Global Business Unit.

Lenvatinib is an oral molecular tri-specific targeted therapy that possesses a potent selectivity and a binding mode different to other tyrosine kinase inhibitors. Lenvatinib simultaneously inhibits the activities of several different molecules including vascular endothelial growth factor receptors, fibroblast growth factor receptors, RET, KIT and platelet-derived growth factor receptors.

Lenvatinib has been approved for the treatment of refractory thyroid cancer in the United States, Europe and Japan, and has been submitted for regulatory approval in Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil. Lenvima was granted Orphan Drug Designation in Japan for thyroid cancer, in the United States for treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer and in Europe for follicular and papillary thyroid cancer.

The European Commission approved Aloxi (palonosetron HCl) injection for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, in pediatric patients one month of age and older.

This is the first European approval of a product for the prevention of acute chemotherapy-induced nausea and vomiting in children aged one to six months.

The approval of the pediatric indication is based on a randomized, double-blind, non-inferiority pivotal trial comparing single-dose intravenous Aloxi 20 mcg/kg given 30 minutes prior to chemotherapy to a standard of care IV ondansetron regimen of 0.15 mg/kg given 30 minutes prior to chemotherapy followed by ondansetron infusions four and eight hours after the first dose. Within the first 24 hours after chemotherapy, complete response, defined as no vomiting, no retching and no antiemetic rescue medication, was achieved in 59.4 percent of patients who received Aloxi and in 58.6 percent of those who received ondansetron.

Treatment-emergent adverse events were comparable across both treatments, with headache being the most frequent event in the palonosetron group. Although pediatric patients were administered a higher dose per kg than adults to prevent CINV, palonosetron safety profile was consistent with its established profile in adults.

The approval follows a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use. Aloxi is sponsored by the Helsinn Group.

Merck Canada Inc. announced that Keytruda (pembrolizumab) was authorized for sale with conditions by Health Canada.

Keytruda is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

The product has been approved in Canada under the Notice of Compliance with Conditions policy on the basis of promising evidence of clinical effectiveness and pending the results of trials to verify its anticipated benefit. Keytruda is the first of anti-PD-1s approved in Canada.

FDA granted an orphan drug designation for APTO-253 for the treatment of acute myeloid leukemia.

APTO-253, a first-in-class inducer of the KLF4 gene, is in a phase Ib clinical trial in patients with AML, high-risk myelodysplastic syndrome and other hematologic malignancies in which KLF4 silencing is reported as operative, according to the drug's sponsor, Aptose Biosciences Inc.

Epigenetic suppression of the Krüppel-like factor 4 gene has been reported in the scientific literature as a transforming event in AML. APTO-253 has demonstrated a favorable safety profile with no evidence of suppression of the normal bone marrow. Preclinical studies have shown potent single-agent activity to kill AML cells and strong synergy as part of a combination strategy with various marketed and investigational agents.

If APTO-253 is approved to treat AML, the orphan drug designation provides Aptose with seven years of marketing exclusivity.

The Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion recommending a change to the terms of the marketing authorization for Imbruvica (ibrutinib) in the European Union to indicate the treatment of adult patients with Waldenström's macroglobulinemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Imbruvica is also the first and only FDA-approved treatment for WM in the US. Imbruvica is jointly developed and commercialized in the United States by Pharmacyclics Inc. and Janssen Biotech Inc. In Europe, Janssen-Cilag International NV holds the marketing authorization and its affiliates market Imbruvica in Europe, Middle East and Africa, as well as the rest of the world.

Imbruvica is already approved in Europe to treat adult patients with relapsed or refractory mantle cell lymphoma and adult patients with chronic lymphocytic leukemia who have received at least one prior therapy or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

The CHMP recommendation was based on a multi-center, phase II study that evaluated the efficacy and tolerability of Imbruvica in 63 patients with previously treated WM. Initial data from the study submitted for review in the EU showed an overall response rate of 87.3 percent after a median duration of treatment of 11.7 months.

Updated results from the study were published on in the April 9, 2015 edition of The New England Journal of Medicine, indicating an ORR of 90.5 percent after a median duration of treatment of 19.1 months using criteria adopted from the International Workshop on WM. At 24 months, the estimated rate of progression-free survival was 69.1 percent (95% CI, 53.2 to 80.5), and the estimated rate of overall survival was 95.2 percent (95% CI, 86.0 to 98.4).

No new safety issues were observed in the clinical trial. The most commonly occurring adverse reactions in WM patients treated with Imbruvica were neutropenia and thrombocytopenia.

Janssen Research & Development initiated the rolling submission of its Biologic License Application for daratumumab to FDA for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double refractory to a PI and an IMiD.

Daratumumab, an investigational human anti-CD38 monoclonal antibody, received Breakthrough Therapy Designation by the FDA for this set of patients in May 2013. A rolling submission allows the company to submit portions of the regulatory application to the FDA as they are completed.

In August 2012, Janssen and Genmab A/S entered into an agreement which granted Janssen a worldwide exclusive license to develop, manufacture and commercialize daratumumab. With the exception of one study sponsored globally by the French multiple myeloma cooperative group, Intergroupe Francophone du Myelome, Janssen is the global sponsor of all current and future clinical studies for daratumumab.

The regulatory submission for daratumumab will be primarily supported by data from the phase II MMY2002 (SIRIUS) monotherapy study announced in May 2015 at the annual meeting of the American Society of Clinical Oncology, along with additional data from four other studies, including the phase I/II GEN501 monotherapy study.

MD Anderson Cancer Center and Nektar Therapeutics announced a research collaboration that includes a phase I/II clinical study to evaluate NKTR-214, a CD122-biased cytokine designed to preferentially stimulate production of CD8-positive T cells.

CD122, which is also known as the Interleukin-2 receptor beta sub-unit, is a key signaling receptor that is known to increase proliferation of these effector T cells.

"We are certain that cytokines are an essential pillar of immunotherapy, along with checkpoint inhibitors, adoptive T cell therapy and cancer vaccines," said Patrick Hwu, Division Head of Cancer Medicine at MD Anderson. "Through clinical studies, we will explore this new cytokine's potential to preferentially activate an established target, the IL-2 receptor beta or CD122, in order to stimulate tumor cell killing within the tumor microenvironment."

The agreement covers a study to evaluate NKTR-214 in a variety of tumor types as a monotherapy and in combination with other therapies, including PD-1 pathway inhibitors. Nektar and MD Anderson expect to initiate the first dose-escalation clinical study later this year. The two organizations will also conduct translational research to identify predictive biomarkers that can be used in the future development of NKTR-214.