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THE
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Cancer research news for clinicians

American Society of Hematology Meeting:

Phase III Study: Rituxan Improved PFS By 79% In Advanced Follicular Lymphoma

Genentech Inc. and Biogen Idec released data from a phase III study of Rituxan (rituximab) in patients with advanced follicular lymphoma who did not have symptoms of disease.

Based on results from previous studies that showed no benefit of immediate chemotherapy after diagnosis, asymptomatic patients are managed by a "watchful waiting" approach. Treatment for these patients usually does not begin until specific symptoms occur or their disease worsens.

This study showed that immediate administration of single-agent Rituxan (induction), followed by continued use of Rituxan (maintenance) delayed the

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2010 Year In Review:

ASCO Calls On NCI To Double Funding For Cooperative Group Clinical Trials

The American Society of Clinical Oncology has called on NCI to double funding for cooperative group clinical trials in the academic and community setting from its current level of $250 million to $500 million by 2015.

Funding for cooperative clinical research has been virtually flat since 2002, forcing NCI cooperative groups to limit patient enrollment in clinical trials. A recent ASCO survey found that one-third of Cooperative Group Program participants plan to limit participation in federally funded clinical trials as a result of inadequate patient reimbursement.

The recommendation was made in the society's "Clinical Cancer Advances 2010: ASCO's Annual Report on Progress Against Cancer," a review of the year's most important clinical cancer research. This year's report highlights 12 major advances and 41 notable advances, selected by a 14-person editorial board of oncologists.

"This year's Annual Report on Progress Against Cancer highlights those studies that have had the greatest impact on patient care," said Mark Kris, executive editor of the report. "Yet much work is still needed to advance clinical cancer research and care. We're on the verge of great discoveries, but we will not be able to speed the pace of progress without revitalizing the nation's clinical trial system."

ASCO's report also urges the cancer community to collaborate on implementing the recommendations laid out in the recent Institute of Medicine report, "A National Cancer Clinical Trials System for the 21st Century:

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Rituxan Prolonged PFS In Advanced Lymphoma

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need for chemotherapy or radiotherapy and decreased the risk of the disease worsening (progression-free survival or PFS), compared to watchful waiting. The safety profile was consistent with previous experience with Rituxan.

The data were presented at the annual meeting of the American Society of Hematology earlier this month in Orlando, Fla.

The phase III results showed that immediate use of Rituxan monotherapy as induction followed by maintenance when compared to watchful waiting, decreased the risk of needing additional therapy by 80 percent (hazard ratio of 0.20, 95 percent CI, 0.13-0.29, p= <0.001) and decreased the risk of their disease worsening (PFS) by 79 percent (based on a hazard ratio of 0.21, 95 percent CI, 0.15-0.29, p= <0.001).

The median time to initiation of new therapy (chemotherapy or radiotherapy) for patients managed by watchful waiting was 34 months and the median PFS was 23 months.

However, in patients given immediate Rituxan followed by maintenance, the median of these parameters was significantly longer (p= <0.0001) and has not been reached after four years. Serious adverse events Grade 3 or higher in patients treated with Rituxan in this study included infection (4 percent), allergy (3 percent), neutropenia (3 percent) and neutropenic sepsis (1 percent).

Sponsored by University College London Hospitals, this phase III study was an international, multicenter, randomized, trial that enrolled 462 patients with previously untreated asymptomatic Stage II-IV follicular lymphoma.

The trial compared the safety and efficacy profile of first-line induction followed by maintenance use of Rituxan alone (four weekly doses followed by maintenance doses once every two months for two years) compared to careful observation (i.e., watchful waiting). Patients were randomized to receive one of the following:

Arm A: No therapy/watchful waiting

Arm B: Rituxan alone (375mg/m2 weekly) for four cycles only (without maintenance Rituxan)

Arm C: Rituxan alone (375mg/m2 weekly) for four cycles followed by Rituxan maintenance, given once every two months for two years

Three years after the enrollment of the first patient, the Rituxan arm that did not include maintenance (Arm B) was closed because of emerging evidence of Rituxan efficacy in the maintenance setting. The trial was then amended to compare Rituxan maintenance following initial use of Rituxan alone to watchful waiting (Arm C compared to Arm A).

Rituxan, discovered by Biogen Idec, first received FDA approval in November 1997 for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. It was approved in the European Union under the trade name MabThera in June 1998. Rituxan is also approved for the treatment of NHL and chronic lymphocytic leukemia (CLL) as follows:

• Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy.

• Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent, after first-line CVP chemotherapy.

• Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

• Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).

Rituxan received FDA approval for RA in February 2006 and is currently indicated in combination with methotrexate in adult patients with moderately-to-severely active RA who have had inadequate response to one or more TNF antagonist therapies.

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Tasigna Shows Benefit Over Gleevec In Phase III Study for Ph+ CML In Chronic Phase

Novartis announced 24-month data showing that Tasigna (nilotinib) 150 mg capsules continues to surpass Gleevec (imatinib mesylate) tablets in the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase.

These new data, from the first phase III comparison of the two oral therapies as initial treatment for this blood cancer, were presented at the annual meeting of the American Society of Hematology.

With this longer-term follow-up at 24 months, first-line treatment with Tasigna at 300 mg twice daily was found to result in a lower incidence of progression to accelerated phase and blast crisis, compared to the standard approved dose of Gleevec 400 mg once daily. Patients receiving Tasigna also had a lower incidence of suboptimal response and treatment failure as defined by study criteria1.

These data also showed that Tasigna induced deeper and more durable complete cytogenetic response (CCyR) and major molecular response (MMR) compared to Gleevec, as well as a significantly higher rate of an even deeper response—a trace amount of 0.0032% or less of the Bcr-Abl protein that causes Ph+ CML, which is considered a complete molecular response (CMR).

Fewer patients taking Tasigna in the study discontinued treatment due to adverse events compared to Gleevec1. Tasigna and Gleevec were generally well tolerated.

"These 24-month phase III data extend the evidence of clinical benefit for newly diagnosed patients with chronic phase Ph+ CML treated with Tasigna, compared to Gleevec," said Timothy Hughes, ENESTnd study investigator and clinical professor at the University of Adelaide, Australia. "Now we can begin to evaluate the long-term treatment outcomes of patients who achieve and maintain deep reductions in Bcr-Abl on Tasigna."

Rates of MMR and CCyR remain statistically higher for Tasigna versus Gleevec at the 24-month minimum follow-up. MMR was achieved by 71% of patients taking Tasigna 300 mg twice daily and 67% of patients taking Tasigna 400 mg twice daily, compared to 44% of patients taking Gleevec by 24 months.

Durable MMR rates were statistically significantly higher in the Tasigna 300 mg twice daily and Tasigna 400 mg twice daily arms compared to Gleevec 400 mg once daily (42%, 39% and 21% respectively). Significantly more patients achieved CCyR in the Tasigna 300 mg and 400 mg arms compared to the Gleevec arm at 87% and 85% vs. 77% respectively by 24 months.

The US FDA and Swissmedic have approved Tasigna in this first-line indication. In September, Novartis received a positive opinion from the Committee for Medicinal Products for Human Use recommending European Commission approval for Tasigna for this indication. Regulatory submissions are under review in the European Union, Japan and other countries.

This year, Novartis also began a collaboration with molecular diagnostics company Cepheid to develop a new FDA cleared/approved Bcr-Abl test, which adheres to the International Scale. The goal of the collaboration is to help doctors more reliably monitor Ph+ CML patients. Cepheid and Novartis also will develop a next generation test, which is expected to enable even more sensitive testing, indicating the depth of a patient's response to tyrosine kinase inhibitors, including Tasigna and Gleevec. Currently there are no FDA cleared/approved tests to monitor for Bcr-Abl.

The clinical trial, ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients), is a phase III randomized, open-label, multicenter trial comparing the efficacy and safety of Tasigna versus Gleevec in adult patients with newly diagnosed Ph+ CML in chronic phase. It is the largest global randomized comparison of two oral therapies ever conducted in newly diagnosed Ph+ CML patients.

ENESTnd is being conducted at 217 global sites with 846 patients enrolled. Patients were randomized to receive Tasigna 300 mg twice daily (n = 282), Tasigna 400 mg twice daily (n = 281) or Gleevec 400 mg once daily (n = 283).

The primary endpoint was MMR at 12 months; the key secondary endpoint was durable MMR at 24 months (patients having MMR when evaluated at both 12 and 24 months)1. MMR was defined in the study as reduction in the level of the abnormal Bcr-Abl gene to less than or equal to 0.1% of the pretreatment level based on an internationally agreed standard. Planned follow-up is for five years. Patients on the Gleevec treatment arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to Tasigna via a protocol extension. These data, presented at ASH, were the 24-month minimum follow-up.

Results showed that fewer patients progressed to accelerated phase or blast crisis while on treatment with Tasigna at 300 mg twice daily (n = 2) and 400 mg twice daily (n = 3) versus Gleevec at 400 mg once

daily (n = 12)1 with 24 months of minimum follow-up demonstrating a significant improvement in disease control.

These data also showed that nearly three times more patients taking Tasigna 300 mg twice daily achieved CMR – defined as a trace amount of 0.0032% or less of the Bcr-Abl protein that causes Ph+ CML – with Tasigna 300 mg twice daily (n = 70) than with Gleevec (n = 25) by 24-months.

All patients had a minimum of 24 months of treatment or discontinued early; the median follow-up was 25 months. Overall, 75%, 78% and 68% of patients remained in the study on Tasigna 300 mg twice daily, Tasigna 400 mg twice daily and Gleevec 400 mg once daily, respectively.

Both Tasigna and Gleevec were generally well tolerated overall. Rates of discontinuation due to adverse events or laboratory abnormalities were 9% for Tasigna 300 mg twice daily, 13% for Tasigna 400 mg twice daily and 11% for Gleevec 400 mg once daily1. No patients treated with Tasigna in the study had prolongation of QT interval >500 milliseconds. No sudden deaths occurred in any of the treatment arms.

Bosutinib Vs. Imatinib Study Didn't Meet Primary Endpoint

Pfizer Inc said a significantly higher proportion of patients with newly diagnosed chronic myeloid leukemia who were treated with bosutinib (39 percent) experienced a major molecular response (MMR), a secondary endpoint, compared with patients treated with imatinib (26 percent) in the intent-to-treat population (p=0.002) of a phase III study.

However, the study did not meet its primary endpoint of superior complete cytogenetic response (CCyR) rate at one year versus imatinib (70 percent vs. 68 percent, respectively, [p=0.601]), in the ITT population.

These results are from a phase III study of the investigational compound bosutinib as a first-line treatment in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia, called the Bosutinib Efficacy and safety in chronic myeloid LeukemiA [BELA] study. These data were presented at an oral presentation at the annual meeting of the American Society of Hematology.

Preliminary data show that fewer patients who took bosutinib progressed to an advanced phase of the disease (n=4, 1.6 percent) compared to patients treated with imatinib (n= 10, 4.0 percent), and there were fewer deaths in the bosutinib arm (n=4, 1.2 percent) than in the imatinib arm (n= 10, 3.2 percent). Patients responding to bosutinib achieved CCyR faster than those responding to imatinib (13 weeks vs. 25 weeks, p<0.001).

A pre-specified exploratory analysis also showed that bosutinib produced a higher rate of CCyR at one year compared to imatinib when CCyR was assessed only in the evaluable patient population, 78 percent with bosutinib (n=219) compared to 69 percent with imatinib (n=241).

The evaluable population was different from the ITT population in that it included only those patients who received follow-up assessments for efficacy.

The most frequently reported all-grade drug-related adverse events with bosutinib were diarrhea (66 percent), nausea (27 percent), vomiting (25 percent), and rash (18 percent). The most frequent grade 3/4 adverse events with bosutinib included diarrhea (8 percent) and rash (2 percent), although no patients on the bosutinib arm discontinued therapy due to diarrhea. Gastrointestinal events associated with bosutinib had an early onset and usually subsided within the first four weeks of treatment. Most frequent grade 3/4 laboratory abnormalities with bosutinib included elevated ALT (21 percent), elevated AST (10 percent), and thrombocytopenia (7 percent).

More patients on bosutinib experienced serious adverse events (25.4 percent vs. 13.5 percent) and adverse events leading to discontinuation (19.4 percent vs. 5.6 percent) than on imatinib.

Adverse events leading to discontinuation were most frequently due to liver enzyme elevations in the bosutinib arm and neutropenia in the imatinib arm. There were no deaths in the study due to treatment-related adverse events.

The majority of patients on both treatment arms continued on study treatment after a median follow-up of 14 months.

"We are encouraged by these data, as they demonstrate early and meaningful response to bosutinib in patients with newly diagnosed CML. Given the length of time these patients are treated for CML, we need more therapeutic options to choose from since each patient is different and has different needs," said Carlo Gambacorti-Passerini, professor of internal medicine and director, clinical research unit, University of Milano Bicocca, San Gerardo Hospital, Monza, Italy, and a lead investigator of the BELA study. "Based on my experience with bosutinib, I feel it would be an important option for patients with CML."

The BELA study is a global, open label, multicenter trial of 502 adult patients randomized to receive either

bosutinib (n=250) or imatinib (n=252). The primary objective of the study was to compare the CCyR rate at one year between the bosutinib and imatinib arms in the ITT population. MMR rate at one year was a key secondary endpoint.

Although closed to enrollment, the study patients will continue to be followed for safety and efficacy outcomes.

Autologous BMT Equivalent To Allogeneic For Myeloma

Autologous hematopoeitic cell transplantation, or bone marrow transplantation using the patient's own stem cells, provides equivalent benefit as allogeneic transplantation, which uses donor stem cells, but without the latter's toxicity in the treatment of multiple myeloma, according to a multicenter study presented by a City of Hope researcher during the American Society of Hematology annual meeting in Orlando.

Amrita Krishnan, director of the City of Hope multiple myeloma program, is the lead author of the multicenter study that examined two types of stem cell transplantation in the treatment of standard risk multiple myeloma.

The Blood and Marrow Transplant Clinical Trials Network study investigated outcomes for patients who underwent two autologous transplants compared to patients who received one autologous transplant followed by an allogeneic transplant of stem cells from a sibling donor.

"We know that allogeneic transplants have demonstrated a lower risk of cancer relapse, but also a higher risk of mortality than autologous transplants, so the question has been 'what is the optimal kind of transplant to treat multiple myeloma?'" said Krishnan, who is also an associate professor in City of Hope's Department of Hematology & Hematopoietic Cell Transplantation. "The study shows that in standard risk patients, there is no added benefit to treatment with a reduced intensity allogeneic transplantation."

Between December 2003 and March 2007, the clinical trial enrolled more than 700 patients at 43 cancer centers in the U.S., with 436 patients receiving tandem autologous transplants and 189 receiving autologous-allogeneic transplants. The three-year progression free survival rate for tandem autologous transplants was 46 percent compared to 43 percent for autologous-allogeneic transplants. The overall survival rate after three years was 80 percent for tandem autologous versus 77 percent for autologous-allogeneic.

Non-Adherence To Protocol Explains Outcome Differences In Hispanic Children With ALL

Although great strides have been made in curing childhood acute lymphoblastic leukemia, there are disparities in overall outcomes in children of different races. City of Hope researchers observed that non-adherence to medication protocol is more prevalent among Hispanic children than non-Hispanic white children, and that non-adherence helps explain the ethnic differences in ALL outcomes.

"We had observed different treatment outcomes across ethnicities in our review of over 8,000 cases of acute lymphoblastic leukemia in which the children received uniform therapy," said Smita Bhatia, director of City of Hope's Center for Cancer Survivorship. "Children are required to take an oral medication at home for two years as part of ALL treatment. We hypothesized that non-adherence to oral chemotherapy would increase the risk of relapse, and that sociodemographic determinants of adherence would help explain the ethnic differences in outcome."

Bhatia is the lead author of the study presented at the American Society of Hematology annual meeting.

The team of researchers followed 332 Hispanic and non-Hispanic white patients under the age of 21 years who were diagnosed with ALL at 78 institutions who participate in the Children's Oncology Group. Patients were provided with special prescription bottles with microchips in their caps that could track dates and times the bottle was opened.

Patients were monitored monthly to assess the blood level of the chemotherapeutic agent. Of the 172 Hispanic patients, about 86 percent adhered to the treatment plan over the six-month course of the study, in comparison to about 93 percent of non-Hispanic white patients. Disease-free survival at the six year mark for Hispanic patients in the study was 81 percent and 94 percent for non-Hispanic white patients. An adherence level of 85 percent was critical for ensuring adequate survival rates. Analysis revealed that non-adherence to oral 6MP and patients' sociodemographic status explained the ethnic differences in survival.

"We found that most patients who missed doses said they simply forgot to take them or something interrupted their daily routine and only 5 percent skipped doses because of side effects," said Bhatia. "We believe that in addition to developing better treatments, we should focus on how to improve adherence to current oral chemotherapy by using a systematic, comprehensive

approach that is informed by the results of this study."

Bhatia has a similar study currently running that is examining adherence in African-American patients, who have the lowest survival outcomes among children with leukemia.

San Antonio Breast Cancer Symposium:

Afinitor Delayed Progression Compared To Tamoxifen Alone In Randomized Phase II Study

A new study shows that the addition of everolimus (Afinitor) to the hormonal therapy tamoxifen in patients with hormone-receptor positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer who have been previously treated with an aromatase inhibitor (AI) delays disease progression compared to tamoxifen alone.

The results were presented at the annual CTRC-AACR San Antonio Breast Cancer Symposium in San Antonio, Texas.

Findings from a randomized, phase II study of 111 patients showed the proportion of metastatic breast cancer patients without tumor progression at six months was 61.1% for those taking everolimus plus tamoxifen (95% confidence interval [CI], 46.9 to 74.1) versus 42.1% for patients treated with tamoxifen alone (95% CI, 29.1 to 55.9); p=0.045.

Disease progression was delayed by a median of 8.6 months in patients treated with the combination versus 4.5 months in patients treated with tamoxifen alone, with everolimus in combination with tamoxifen providing a statistically significant reduction in the risk of disease progression by 47% (hazard ratio=0.53 [95% CI, 0.35 to 0.81]; log-rank test: p=0.0026, exploratory analysis).

Side effects were generally manageable in both study arms. As of October 2010, there were 25 patient deaths in the tamoxifen arm versus nine in the everolimus plus tamoxifen arm (hazard ratio=0.32 [95% CI, 0.15 to 0.68]; log-rank test: p=0.0019).

This phase II trial is conducted by the Groupe d'Inve stigateurs Nationaux pour l'Etude des Cancers Ovariens et du sein (the French GINECO Group).

Everolimus is an investigational agent for the treatment of patients with breast cancer. Everolimus targets mTOR in cancer cells, a protein that acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism.

"The almost doubling of time to disease progression seen in the everolimus plus tamoxifen treatment arm reinforces the potential benefit of inhibiting mTOR to help overcome endocrine therapy resistance," said Thomas Bachelot, from Centre Léon Bérard in Lyon, France, and principal investigator of the study. "Based on these results, additional studies will evaluate the combination of everolimus with hormonal therapies as a second-line treatment for patients with HR+/HER2- metastatic breast cancer."

Breast cancer patients with advanced disease who become resistant to hormonal therapies have limited treatment options. Prior to these study findings, Novartis initiated a Phase III trial program called BOLERO (Breast cancer trials of OraL EveROlimus), which is the largest international Phase III clinical trial program to study an mTOR inhibitor in patients with locally advanced or metastatic breast cancer.

AZURE Trial: Zoledronic Acid Didn't Improve DFS In Stage II/III

Zoledronic acid did not improve disease free survival among women with stage II/III breast cancer according to results of the Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer (AZURE) trial, which was presented at the CTRC-AACR San Antonio Breast Cancer Symposium.

"In the larger population, we did not see a difference," said Robert Coleman, professor of medical oncology at the University of Sheffield in England.

However, among 1101 patients who were five years post-menopause, about 30 percent of the overall group, there was a 29 percent improvement in overall survival. Coleman stressed that this was a secondary outcome, so it could not be considered conclusive, but it did present the largest unanswered question.

"To see a survival advantage like this is quite remarkable, and the difference in outcome between this group and the younger population is unlikely to be a chance finding. We will clearly want to investigate further in this population," he said.

The AZURE trial included 3,360 patients with stage II/III breast cancer from 174 centers. Coleman and colleagues randomly assigned the patients to standard therapy or to standard therapy plus zoledronic acid. The primary outcome was disease free survival.

The researchers found no difference in disease free survival in the overall population.

"This will likely dissuade clinicians from giving adjuvant bisphosphonates on a routine basis to younger

women taking adjuvant chemotherapy because, although the drug is generally well tolerated, there is a small risk of osteonecrosis of the jaw," said Coleman.

The researchers identified 17 (1.1%) confirmed cases of osteonecrosis of the jaw over the duration of the study period.

Pediatric Cancer:

Survival For ALL Increased To 94 Percent In Recent Years

More effective risk-adjusted chemotherapy and sophisticated patient monitoring helped push cure rates to nearly 88 percent for older adolescents enrolled in a St. Jude Children's Research Hospital acute lymphoblastic leukemia treatment protocol and closed the survival gap between older and younger patients battling the most common childhood cancer.

A report online in the Dec. 20 edition of the Journal of Clinical Oncology noted that overall survival jumped 30 percent in the most recent treatment era for ALL patients who were age 15 through 18 when their cancer was found.

The study compared long-term survival of patients treated between 2000 and 2007 in a protocol designed by St. Jude investigators with those enrolled in earlier St. Jude protocols.

About 59 percent of older patients treated between 1991 and 1999 were cured, compared with more than 88 percent of children ages 1 through 14 treated during the same period.

But overall survival for older patients rose to almost 88 percent between 2000 and 2007, when long-term survival of younger patients soared to about 94 percent.

Nationally, about 61 percent of ALL patients age 15 to 19 treated between 2000 and 2004 were still alive five years later.

Not only did more patients in the recent treatment era survive, but Ching-Hon Pui, chair of the St. Jude Department of Oncology and the paper's lead author, said they are also less likely to suffer serious late treatment effects, including second cancers and infertility. That is because the regimen, known as Total XV, eliminated or dramatically reduced reliance on drugs associated with those side effects.

The protocol also replaced radiation of the brain with chemotherapy as a strategy for preventing relapse in the central nervous system and for reducing the risk of later neuro-cognitive problems. None of the adolescents suffered central nervous system relapses.

"Not only have we increased the cure rate, but we have also improved the long-term quality of life for our patients," Pui said.

Historically, individuals who develop ALL after age 14 were less likely to survive their disease than were younger patients. Older teenagers are more likely to have high-risk subtypes of the disease, their cancer cells are more likely to be resistant to current anti-cancer drugs and they tend to have more toxicity from therapy.

"The challenge is to get adolescents on the right amount of drug while avoiding toxicity. In Total XV we seem to have struck the right balance," said Mary Relling, chair of St. Jude Pharmaceutical Sciences Department and co-author of the research.

Glioblastoma:

TTF Increased Survival Compared To Chemotherapy

Data presented from a phase III randomized clinical trial for patients with recurrent glioblastoma tumors suggest that Tumor Treating Fields therapy may increase median survival time and improve quality of life scores compared to best standard of care chemotherapy.

Zvi Ram, chairman of the Department of Neurosurgery at Tel-Aviv Sourasky Medical Center, presented the data at the Society for Neuro-Oncology annual meeting.

Physicians delivered the investigational TTF therapy to patients in the study using the NovoTTF-100A, a portable, non-invasive medical device. Investigators conducted this phase III study under an approved IDE at 28 centers in the US, Europe, and Israel, enrolling 237 patients with glioblastoma tumors that had recurred or progressed after initial treatment.

Patients randomly received TTF therapy alone or an effective chemotherapy selected by physicians. "The study suggests that patients treated with TTF therapy, as defined in the protocol, lived significantly longer than patients treated with the currently available best chemotherapeutic regimens," said Ram. "Interestingly, younger patients and patients with better functional status appear to have an impressive survival advantage. In these patients the incidence of radiological tumor response to TTF therapy was double that seen in patients treated with chemotherapy. Most importantly, in addition to the survival benefit, treatment with TTF therapy was associated with significantly better quality of life compared to patients receiving chemotherapy."

Patients under the age of 60 who were able to maintain normal daily activities (KPS>80 percent) at the time of enrollment achieved a significant increase in median overall survival time (8.8 vs. 6.6 months, n=110, p< 0.01) and in the 1-year survival rate (35 percent vs. 20 percent, n=110, p< 0.01) when treated with TTF Therapy versus effective chemotherapies. TTF therapy also produced a significant increase in survival time for patients who had failed treatment with bevacizumab (Avastin; Roche) prior to enrollment (4.4 vs. 3.1 months, n=44, p< 0.02). Patients enrolled in the study also reported superior quality of life scores (EORTC QLQ-C30) across a range of lifestyle and symptom categories for TTF therapy compared to the chemotherapy-treated control group.

"The data presented at SNO further validate TTF therapy as a potential treatment option for patients with recurrent glioblastoma tumors," said Asaf Danziger, chief executive officer of Novocure, the trial sponsor. "The suggested improvement in quality of life scores reported by patients receiving TTF therapy is particularly important given the nature of this disease and the strong desire among patients and their caregivers to avoid the side-effects of chemotherapy and radiation."

TTF therapy has been shown in vitro to slow and reverse tumor cell proliferation by inhibiting mitosis, the process by which cells divide and replicate. The NovoTTF-100A device, which weighs about six pounds (three kilograms), creates a low-intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division.

Novocure is now sponsoring a second phase III study of TTF therapy at 26 centers in the US, Europe, and Israel. This study will enroll 283 patients with newly diagnosed glioblastoma tumors. Patients will be randomized (2 to 1) to receive TTF therapy and temozolomide (Temodar; Merck & Co) or temozolomide alone (the current best standard of care).

Novocure also recently reported results from a successful phase II trial that studied TTF therapy in combination with chemotherapy for advanced non-small cell lung cancer at the European Society of Medical Oncology Congress.

The NovoTTF-100A is an investigational device in the U.S. and has not been approved by the FDA for sale in the U.S. for any use. Results of this phase III trial for recurrent glioblastoma patients have been submitted in a premarket approval application, which is under review by FDA.

Cancer Prevention:

Randomized Trial Finds Sunscreen Use Cuts Risk Of Developing Melanoma

A randomized, prospective study of more than 1,600 adults in Australia found that regular use of sunscreen reduced the risk of developing melanoma by half, including a 73 percent drop in risk for invasive melanoma.

"Our results send a general message of reassurance," said Adele Green, acting director and professor of epidemiology at the Queensland Institute of Medical Research in Queensland, Australia, who led the work. "Most physicians would suggest sunscreen for protection against sunburn and against more common squamous skin tumors.

"This is the first trial of its kind evaluating sunscreen use against melanoma as an outcome" Green said. "These findings now provide some assurance to medical professionals, public health authorities and the public in general that sunscreen can offer some protection against melanoma."

While melanoma accounts for only 5 percent of skin cancer cases, it accounts for the majority of deaths from skin cancer. Sun exposure has long been associated with melanoma, but previous studies of sunscreen use and melanoma risk have been inconclusive, and the use of sunscreen as a preventative has been unclear.

Green and her co-workers randomly assigned 1,621 residents aged 25 to 75 in Nambour, Queensland, Australia, to daily or discretionary sunscreen use on the head and arms between 1992 and 1996. Participants also received beta carotene or placebo supplements during that period to see if their addition enhanced protection from skin cancers.

Investigators followed study subjects until 2006 through annual or biannual questionnaires that focused on new skin cancers, sunscreen use and average time spent outdoors, and monitored regional pathology laboratories and the Queensland Cancer Registry for new reported melanomas as well. They assessed both sun exposure and past skin cancers in both groups at the beginning of the trial and in the decade-long follow-up after the active trial ended, finding that sun exposure continued to be the same in both groups. They also found that those participants who had been randomized to use sunscreen daily were somewhat more likely to continue to do so after the trial than those in the other group.

In the 10 years after the five-year trial ended, the team identified 22 new melanomas in the discretionary

use group and 11 in the daily sunscreen use group—a 50 percent reduction. Of these new melanomas, they found 11 invasive melanomas in the discretionary group compared to only three among the daily sunscreen users, or 73 percent fewer. Beta carotene had no harmful or protective effects on melanoma.

Green said the dramatic differences were unexpected. "While we thought we might see some differences in early or superficial melanomas, we were especially surprised at the reduction in the more dangerous invasive melanomas," she said. "It appeared to be quite strong protection."

Green noted that previous studies had compared melanoma risk in individuals who chose to use sunscreen and those who did not, but the results were difficult to interpret. She stressed the importance of an intervention study where people were randomized to a protocol to use sunscreen regularly.

2010 Year in Review:
ASCO Highlights Advances In Clinical Cancer Research

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Reinvigorating the National Cancer Institute (NCI) Cooperative Group Program."

Research advances made this past year focus on progress against hard-to-treat cancers, reducing cancer recurrence, targeted therapies and personalized medicine, quality of life and new drug approvals. Highlights of this year's report include:

Reducing the risk of cancer recurrence: Researchers discovered that a three-week hypofractionated radiation therapy course was just as effective in preventing recurrence as the standard five-week course for women diagnosed with early-stage breast cancer.

Enhancing quality of life: Patients with advanced lung cancer who received standard chemotherapy coupled with palliative care immediately after diagnosis lived significantly longer and had a better quality of life than those who were treated with chemotherapy alone.

Advances in drug therapies: First-line treatment with FOLFIRINOX—a combination of the chemotherapy drugs 5-fluorouracil, leucovorin, irinotecan and oxaliplatin—resulted in better response rates, progression-free survival and overall survival for patients with advanced pancreatic cancer.

Addressing side effects: Researchers have found that the majority of patients (80 percent) undergoing chemotherapy for cancer suffer from sleep difficulties—a rate approximately two to three times higher than what is seen in the general population. This is a clear area where more awareness is needed so patients can get the additional help they need.

Improving progression-free survival in hard-to-treat cancer: Studies found that administering chemotherapy and bevacizumab (Avastin), followed by longer-term treatment with bevacizumab, was the most effective strategy for extending progression-free survival in patients with ovarian cancer.

Additional significant developments discussed in the report include:

• The discovery that a monoclonal antibody, ipilimumab, improves survival in patients diagnosed with advanced melanoma—a major advance for a very difficult-to-treat cancer.

• A study showing that the targeted drug crizotinib produces high response rates and shrinks tumors in many patients whose tumors harbor a specific gene mutation in the *ALK* gene.

• Findings from an early-stage trial of advanced melanoma showing that a novel gene-targeted therapy, PLX4032, caused tumors to shrink in a majority of patients with a specific *BRAF* gene mutation.

• A chemotherapy combination that was found to increase survival in elderly patients with advanced lung cancer, and is well-tolerated by these patients.

• A report issued by leading U.S. health and cancer organizations showing continued declines in cancer incidence and death rates over recent years.

• The FDA approvals of cabazitaxel (Jevtana) and sipuleucel-T (Provenge)—a therapeutic vaccine—for metastatic hormone-refractory prostate cancer.

The report is available at http://www.cancer.net/patient/Publications and Resources/Clinical Cancer Advances/CCA_2010.pdf.

The report and additional resources are posted on ASCO's patient Web site, at www.cancer.net/cca and published online in the Journal of Clinical Oncology.

Clinical Trials Approved By NCI CTEP Last Month

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

8305 A Phase 1 Study of Lenalidomide Maintenance Following Allogeneic Hematopoietic

Cell Transplantation in Patients with Select High Risk Hematological Malignancies, Ohio State University Medical Center. Andritsos, Leslie A. (614) 293-2268.

8609 A Phase 1 Dose-Escalation Study of ABT-888 (veliparib) in Combination with Carboplatin in HER2 Negative Metastatic Breast Cancer. Ohio State University Medical Center. Ramaswamy, Bhuvaneswari (614) 293-6401.

8695 Enhancement of Cetuximab-Induced Antibody-Dependent Cellular Cytotoxicity with Lenalidomide in Advanced Solid Tumors: a Phase I/IB Study. Ohio State University Medical Center. Otterson, Gregory A. (614) 293-2887.

8709 A Phase I Study of MK-2206 in Combination with Lapatinib in Refractory Solid Tumors Followed by Dose-expansion in Advanced HER2+ Breast Cancer, University of Wisconsin Hospital and Clinics. Tvaarwerk, Amye Juliet (608) 262-2837.

8803 A Phase 1 Study of Azacitidine in Combination with MEC (Mitoxantrone, Etoposide, Cytarabine) in Relapsed and Refractory Acute Myeloid Leukemia, Ohio State University Medical Center. Klisovic, Rebecca Bruner (614) 366-3802.

8828 Phase I Study of the Hsp90 Inhibitor, AT13387, in Adults with Refractory Solid Tumors, National Cancer Institute Developmental Therapeutics Clinic. Kummar, Shivaani (301) 435-5402.

ADVL1014 A Phase 1 Dose Escalation Study of Reolysin, a Replication Competent Reovirus, in Pediatric Patients with Relapsed or Refractory Solid Tumors, COG Phase 1 Consortium. Kolb, Edward Anders (302) 651-5567.

AMC-078 A Phase I Study of Vorinostat in Combination with Paclitaxel and Carboplatin in Solid Tumors (with Focus on Upper Aerodigestive Cancers) in Persons with HIV Infection, AIDS-Associated Malignancies Clinical Trials Consortium. Haigentz, Missak (718) 920-4826.

Phase II

8192 A Phase II Study of Vorinostat and Capecitabine in Recurrent and/or Metastatic Squamous Cell Carcinoma of Head and Neck and Nasopharyngeal Carcinoma, University Health Network-Princess Margaret Hospital. Chen, Xueyu Eric (416) 946-2263.

8540 Phase II Study of RO4929097 to Eradicate Residual Disease in Patients with Multiple Myeloma Post Single Autologous Stem Cell Transplant, Cancer Institute of New Jersey. Gharibo, Mecide Meric (732) 235-8776.

8692 A T1 Translational Multicenter Randomized Phase II Study of Temsirolimus Versus Cetuximab Plus Temsirolimus in Patients with Recurrent / Metastatic Head and Neck Cancer, Who Failed Prior EGFR Based Therapy, University of Chicago. Seiwert, Tanguy Y. (773) 702-2452.

8728 Phase II Study of MK-2206 in Patients with Relapsed Lymphoma, M D Anderson Cancer Center. Younes, Anas (713) 792-2806.

CALGB-10701 A Phase II Study of Dasatinib (Sprycel) as Primary Therapy Followed by Transplantation for Adults >/= 50 Years with Newly Diagnosed Ph+ Acute Lymphoblastic Leukemia by CALGB, ECOG, SWOG and NCIC CTG, Cancer and Leukemia Group B. Wetzler, Meir (716)845-8447.

CALGB-11001 A Phase II Study Incorporating Sorafenib into the Therapy of Patients >/= 60 Years of Age with FLT3 Mutated Acute Myeloid Leukemia, Cancer and Leukemia Group B. Uy, Geoffrey L. (314) 747-8439.

E2809 Phase II, Randomized Study of MK-2206 - Bicalutamide Combination in Patients With Rising PSA at High-Risk of Progression After Primary Therapy, Eastern Cooperative Oncology Group. Ferrari, Anna C. (212) 731-5389.

GOG-0227G A Phase II Evaluation of Brivanib in the Treatment of Persistent or Recurrent Carcinoma of the Cervix (BMS Study CA182-048), Gynecologic Oncology Group. Chan, John K. (415) 885-7561.

GOG-0230D A Phase II Evaluation of Pazopanib in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus, Gynecologic Oncology Group. Campos, Susana Maria (617) 632-5269.

RTOG 1012 Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer, Radiation Therapy Oncology Group. Berk, Lawrence B. (740)344-3100.

S1005 A Phase II Study of MK-2206 as Second Line Therapy for Advanced Gastric and Gastroesophageal Junction Cancer, Southwest Oncology Group. Ramanathan, Ramesh K. (480) 323-1350.

Phase III

NCIC CTG OV.21 A Phase II/III Study of Intraperitoneal Plus Intravenous Chemotherapy Versus IV Carboplatin Plus Paclitaxel in Patients with Epithelial Ovarian Cancer Optimally Debulked at Surgery Following Neoadjuvant Intravenous Chemotherapy, National Cancer Institute of Canada Clinical Trials Group. Mackay, Helen Jane (416) 846-2253.