# Relapse Speed Predicted Neuroblastoma Survival

Major Finding: INSS stage 4 patients had a 5-year survival of 8%, compared with 52% for those who were stage 1, 2, 3, or 4S.

**Data Source:** A retrospective analysis of children in the International Neuroblastoma Risk Group database.

**Disclosures:** The study was supported by the Little Heroes Pediatric Cancer Research Foundation, the Forbeck Foundation, and a grant from the National Institutes of Health, Dr. London and her associates reported no conflicts of interest.

### BY PATRICE WENDLING

From the annual meeting of the AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO – Time to relapse is highly predictive of overall survival post relapse in children with neuroblastoma, according to an analysis of 2,266 children in the International Neuroblastoma Risk Group database.

The analysis identified other factors prognostic of overall survival post relapse as well as a small proportion of relapsed patients who are salvageable, Wendy B. London, Ph.D., reported at the meeting.

Currently, clinicians do not know how to identify which patients are more likely to re-

spond to postrelapse therapy and have difficulty in interpreting time to relapse because neuroblastoma is a heterogeneous disease, she said.

The median time to relapse among the 2,266 children was 13.2 months, with a wide range from 1 day to 11.4 years.

All told, 73% of children who relapsed were aged 18 months or older, 72% were International Neuroblastoma Staging System (INSS) stage 4, and 33% had amplified MYCN oncogene expression.

Overall survival at 5 years was 20%.

It was not possible to categorize time to relapse using a simple 1-year cutoff, said Dr. London, director of biostatistics at Children's Hospital Boston.

The risk of death was about the same for children who relapsed within the first 6 months as it was for those who relapsed at 18-24 months. The risk of death was highest in those who relapsed between 6 and 18 months.

All three groups had a significantly higher risk of death, compared with patients who relapsed after 36 months (P less than .001).

The association between time to relapse and overall survival appears to be driven by stage 3, 4, and MYCN-amplified patients, Dr. London said.

In a survival tree regression analysis that adjusted for time to relapse, disease stage was identified as the most highly significant variable for survival post relapse. INSS stage 4 patients had a 5-year survival of 8%, compared with 52% for those who were stage 1, 2, 3, or 4S.

"Aggressive disease that advances unhindered by treatment has a highly predictable time course and ultimate death; we already knew this, but now we're able to describe it quantitatively," she said.

Upon further analysis, three cohorts emerged as salvageable after relapse:

- ▶ Patients who are stage 4, with nonamplified MYCN, and less than 18 months of age.
- ▶ Patients who are stage 1, 2, 3, or 4S with MYCN amplification.
- ▶ Patients who are stage 1, 2, 3, or 4S with nonamplified MYCN and undifferentiated grade histology.

Patients who had stage 4 disease and MYCN amplification had a 5-year survival of 4%, compared with 12% for stage 4 patients with nonamplified MYCN.

Time to first relapse as a predictor of survival is important for two reasons, said Dr. Andrew Pearson, chair of pediatric oncology at the Institute of Cancer Research and the Royal Marsden Hospital in London, who was invited to discuss the findings. It can be used to stratify and/or describe patients in early clinical trials and to identify a salvageable population post relapse.

"In the past, I'm sure that some agents have had a negative response in early clinical studies because a group of very poor prognosis patients were included,'

The study findings will also be utilized by the International Neuroblastoma Risk Group, which is nearing completion of Continued on following page

## **BETASERON®**

(INTERFERON BETA-1b) FOR SCILON

### BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

NOIDCATIONS AND USAGE

Belaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

WARNINGS
Depression and Suicide
Belaseron (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Betaseron, Patients treated with Betaseron should be advised to report immediately any symptoms of depression and/or suicidal idealino to their prescribing physicians. If a patient develops depression, cessation of Betaseron therapy should be considered. In the four randomized controlled studies there were three suicides and the stage and the suicide and four suicide attempts among the 1532 patients in the Betaseron treated groups compared to one suicide and four suicide attempts among the 965 patients in the placebo groups.

arus nour surcure attempts among the 965 patients in the placebo groups.

Injection Site Necrosis
Injection Site Paccrosis (SN) has been reported in 4% of patients in controlled clinical trials (see ADVERSE REACTIONS). Typically, injection site records occurs within the first four months of the party, although post-marketing reports have been received of ISN occuring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic leasions are placially three ner or less in diameter had lespectate the temperature of the state been reported. Generally the necrosis has extended only to subcutaneous fat. However, there are also reports of necrosis extending to and including fascia overlying muscle. In some lessions where biopsy results are available, vascullits has been reported. For some lesions were biopsy results are available, vascullits has been reported. For some lesions were biopsy results are available, vascullits has been reported. For some lesions of bring the proported to the control of the proported for some lesions of the fine treatment was begun. In most cases healing on the severity of the necrosis at the time treatment was begun. In most cases healing was associated with scarring. Some patients have experienced healing of necrotic skin lesions while Betaseron therapy continued; others have not Whether to discontinue therapy following a single store of necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron after rijection site necrosis has occurred, Betaseron should not be administered to the continued until healing occurs. Injection Site Necrosis

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated, particularly if injection site necrosis has occurred.

Anaphylaxis
Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic
reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria
(see ADVERSE REACTIONS).

Albumin (Human), USP
This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS Information for Patients
All patients should be instructed to carefully read the supplied Betaseron Medication Guide.
Patients should be cautioned not to change the dose or schedule of administration without medical consultation.

Palients should be cautioned not to crainge the duse or surrounce or common advantage.

Patients should be made aware that serious adverse reactions during the use of Bebaseron have been reported, including depression and suicidal ideation, injection site necrosis, and anaphytaxis (see WARNINGS). Patients should be advised of the symptoms of depression or suicidal ideation and be lold to report them immediately to their physician. Patients should be advised to the symptoms of allergic reactions and anaphytaxis. Patients should be advised to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their Bebaseron therapy.

Patients should be informed that flu-flue symptoms are common following initiation of therapy with Bebaseron. In the controlled clinical trials, antipyretics and analgesics were permitted for relief of these symptoms. In addition, gradual dose titration during initiation of Bebaseron treatment may required fluid like symptoms (see DOSAGE AND ADMINISTRATION).

Female patients should be cautioned about the abortificcient potential of Bebaseron (see

### Instruction on Self-injection Technique and Procedures

Instruction on Self-injection Technique and Procedures
Patients should be instructed in the use of aseptic technique when administering Betaseron.
Appropriate instruction for reconstitution of Betaseron and methods of self-injection should be provided, including careful review of the Betaseron Medication Guide. The first injection should be performed under the supervision of an appropriately qualified health care professional.
Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be advised of the importance of rotating areas of injection with each dose, to minimize the likelihood of severe injection site reactions, including necrosis or localized infection, (see Picking an Injection Site section of the Medication Guide).

Laboratory Tests
In addition to those laboratory tests normally required for monitoring patients with multiple soleross, complete blood and differential while blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Carcinogenesis. Mulagenesis, and Impairment of Fertility
Carcinogenesis. Interferon beta-1b has not been tested for its carcinogenic potential in animals.
Mulagenesis: Betaseron was not mulagenic when assayed for genotoxibility in the Ames
bacterial test in the presence or absence of metabolic activation. Interferon beta-1b was not
mulagenic to human peripheral blood lymphocytes in vitro, in the presence or absence of
metabolic inactivation. Betaseron treatment of mouse BALBo-313 cells did not restore
in increased transformation frequency in an in vitro model of humor transformation.

Impairment of fertility: Studies in normally cycling, female rhesus monkeys at doses up to 0.33 mg/kg/day (32 times the recommended human dose based on body surface area.

body surface dose based on 70 kg female) had no apparent adverse effects on eith menstrual cycle duration or associated hormonal profiles (progesterone and estradi when administered over three consecutive menstrual cycles. The validity of extrapolitic doses used in animal studies to human doses is not known. Effects of Betaseron on normologiciling human females are not known.

oycling human temales are not known.

Pregnancy — Teratogenic Effects

Pregnancy — Category C: Belassorn was not teratogenic at doses up to 0.42 mg/kg/day when given to pregnant female rhesus monkeys on gestation days 20 to 70. However, a dose related abortification and the season monkey when Interferon beta-1b was administered at doses ranging from 0.028 mg/kg/day to 0.42 mg/kg/day (28 to 40 times administered at doses ranging from 0.028 mg/kg/day to 0.42 mg/kg/day (28 to 40 times the recommended human dose based on body surface area comparison). The validity of extrapolating doses used in animal studies to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reposted in patients (n=4) who participated in the Batsearon RRMS clinical trial. Belaseron given to thesus monkeys on gestation days 20 to 70 did not cause teralogenic directs, however, it is not known if teralogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant women. If the patient should be apprised of the potential hazard to the tetus and it should be recommended that the patient discontinue therapy.

Nursian Mothers

Nursing Mothers
It is not known whether Betaseron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Betaseron, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

Pediatric Use Safety and efficacy in pediatric patients have not been established.

Geriatric Use
Clinical studies of Betaseron did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. ADVERSE REACTIONS

AVENSE REACTIONS

In all studies, the most serious adverse reactions with Betaseron were depression, suicidal ideation and injection site necrosis (see WARNINGS). The incidence of depression of any severity was approximately 30% in both Betaseron-freated patients and placebo-freated patients. Anaphylaxis and other allergic reactions have been reported in patients using Betaseron (see WARNINGS). The most commonly reported adverse reactions were lymphopenia (lymphocytess-1500/mm³), injection site reaction, astheria, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions were lymphopenia (lymphocytes-1500/mm³), injection site reaction, astheria, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Betaseron, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leuktopenia, increased liver enzymes, astheria, hypertonia, and mysatheria.

Because clinical triais are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical triais of Betaseron cannot be directly compared to rates in clinical triais of other drugs, and may not reflect the rates observed in pactice. The adverse reaction information from clinical triais does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Betaseron in the four placebo controlled triais.

identifying the adverse events that appear to be related to drug use and for approximating rates. The data described below reflect exposure to Betaseron in the four placebo controlled trials of 1407 patients with MS treated with 0.25 mg or 0.16 mg/m², including 1261 exposed for greater than one year. The population encompassed an age range from 18 – 65 years. Suby-four percent (64%) of the patients were lemale. The precentages of Caucasian, Black, Asian, and Hispanic patients were 94.8%, 3.5%, 0.1%, and 0.7%, respectively. The safety profiles for Betaseron-treated patients with SPMS and RRMS were similar. Clinical experience with Detaseron-treated patients with SPMS and RRMS were similar. Clinical experience with Detaseron in the populations (patients with cancer, HIV positive patients, etc.) provides additional data regarding adverse reactions; however, experience in non-MS populations may not be fully applicable to the MS population. Table 2 enumerates adverse events and laboratory abnormalities that occurred among all patients treated with 0.25 mg or 0.16 mg/m? Betaseron every other day for periods of up to three years in the our placebo controlled trials (Study 14-4) at all nicitorice that was at least 2.0% more than that observed in the placebo patients (System Organ Class, MedDRA v. 8.0).

Adverse Reactions and Laboratory Abnormalities		
System Organ Class MedDRA v. 8.0 * Adverse Reaction	Placebo (N=965)	Betaseron (N=1407)
Blood and lymphatic system disorders		
Lymphocytes count decreased (< 1500/mm³) ×	66%	86%
Absolute neutrophil count decreased (< 1500/mm <sup>3</sup> ) ×	5%	13%
White blood cell count decreased (< 3000/mm <sup>3</sup> ) ×	4%	13%
Lymphadenopathy	3%	6%
Nervous system disorders		
Headache	43%	50%
Insomnia	16%	21%
Incoordination	15%	17%
Vascular disorders		
Hypertension	4%	6%
Respiratory, thoracic and mediastinal disorders	•	
Dyspnea	3%	6%
Gastrointestinal disorders		
Abdominal pain	11%	16%
Hepatobiliary disorders		
Alanine aminotransferase increased (SGPT > 5 times baseline)×	4%	12%
Aspartate aminotransferase increased (SGOT > 5 times baseline)×	1%	4%
Skin and subcutaneous tissue disorders		
Rash	15%	21%
Skin disorder	8%	10%
Musculoskeletal and connective tissue disorders		
Hypertonia	33%	40%
Myalgia	14%	23%
Renal and urinary disorders		
Urinary urgency	8%	11%
Reproductive system and breast disorders	•	
Metrorrhagia*	7%	9%
Impotence**	6%	8%
General disorders and administration site condit	ions	•
Injection site reaction (various kinds) 0	26%	78%
Asthenia	48%	53%
Flu-like symptoms (complex)§	37%	57%

## Table 2 Adverse Reactions and Laboratory Abnormalities System Organ Class MedDRA v. 8.0 \* Adverse Reaction Betaseron (N=1407) 0%

- 1 cliction site reaction (various kinds)" comprises all adverse events occurring at the ction site (except injection site necrosis), i.e. the following terms: injection site injection, injection site hemorrhag, injection site hypersensitivity, injection site amation, injection site mass, injection site pain, injection site edema and injection site of the site
- audpris. Hike symptom complex" denotes flu syndrome and/or a combination of at least two from fever, chills, myalgia, malaise, sweating.

Injection Site Reactions
In four controlled clinical trials, injection site reactions occurred in 78% of patients
receiving Betaseron with injection site recrosis in 4%. Injection site inflammation
(42%), injection site pain (16%), injection site hypersensitivity (4%), injection site
necrosis (4%), injection site mass (2%), injection site edema (2%) and non-specific
reactions were significantly associated with Betaseron freatment (see WARNINGS and
PRECAUTIONS). The inodence of injection site reactions lended to decrease over time.
Approximately 96% of patients experienced the event during the first three months of
treatment, compared to approximately 40% at the end of the studies.

Flu-Like Symptom Complex
The rate of flu-like symptom complex
The rate of flu-like symptom complex was approximately 57% in the four controlled clinical trials. The incidence decreased over time, with only 10% of patients reporting flu-like symptom complex at the end of the studies. For patients who experienced a flu-like symptom complex in Study 1, the median duration was 7.5 days.

symptom complex in Study 1, the median duration was 7.5 days.

Laboratory Abnormalities
In the four clinical trials, leukopenia was reported in 18% and 6% of patients in Betaseronand placebo-freated groups, respectively. No patients were withdrawn or dose reduced for
neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced
leukopenia and were dose-reduced. Other abnormalities included increase of SGPT to
greater than five times baseline value (12%), and increase of SGPT to
greater than five times baseline value (12%), and increase of SGPT to
times baseline value (4%). In Study 1, two patients were dose reduced for increased hepatic
enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and
3, 1.5% of Betaseron patients were dose-reduced or interrupted treatment for increased
hepatic enzymes. In Study 4, 1.7% of patients were withdrawn from treatment to
increased hepatic enzymes, two of them after a dose reduction. In Studies 1-4, nine (0.6%)
patients were withdrawn from treatment with Betaseron for any laboratory abnormality,
including four (0.3%) patients following dose reduction. (see PRECAUTIONS,
Laboratory Tests).

Menstrual Irresul

Mensional Irregularities
In the four clinical trials, 97 (12%) of the 783 pre-menopausal females treated with Bebaseron and 79 (15%) of the 528 pre-menopausal females treated with placebo reported menstrual disorders. One event was reported as severe, all other reports were mild to moderate severity. No patients withdrew from the studies due to menstrual irregularities.

moderate seventy. No patients withdrew from the studies due to menstrual irregularities.

Postmarketing Experience
The following adverse events have been observed during postmarketing experience with Betaseron and are classified within body system categories:
Blood and lymphatic system disorders: Anemia, Thrombocytopenia
Endocrine disorders: Hypothyroidism, Hyperthyroidism, Thyroid dysfunction
Metabolism and nutrition disorders: Hypocalecnia, Hyperuricenia, Triglyceride increased. Anorexia, Weight decrease
Psychiatric disorders: Contuision, Depersonalization, Emotional lability
Nenous system disorders: Ataxia, Convulsion, Paresthesia, Psychotic symptoms
Cardiac disorders: Cardiomyopathy
Vascular disorders: Deep vein thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders: Bronchospasm, Pneumonia
Gastronitestinal disorders: Parceattis, Vomitting
Hepatlobilary disorders: Hepatitis, Gamma GT increased
Skin and subculeaneous tissue disorders: Proritus, Skin discoloration, Urticaria

respaceurally usorders: repatitis, Gamma G1 increased Skin and subcutaneous tissue disorders: Pruritis, Skin discoloration, Urticaria Renal and urinary disorders: Urinary tract infection, Urosepsis General disorders and administration site conditions: Fatal capillary leak syndrome\*. "The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

has been associated with the development of this syndrome. Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to Betaseron during Study 1. In patients receiving 0.25 fing every other days 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. In Study 4, neutralizing activity was measured every 6 moniths and at end of study. At individual visits after start of herapy, activity was observed in 16.5% up to 25.2% of the Betaseron treated patients. Such neutralizing activity was measured at least once in 75 (29.9%) out of 251 Betaseron patients who provided samples during treatment phase; of these, 17 (22.7%) converted to negative status later in the study.

negative status later in the study.

Based on all the available evidence, the relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Betaeron using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MAA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, triming of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to betaseron with the incidence of antibodies to the mischalling. Anaphylactic reactions have rarely been reported with the use of Betaseron.



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## **NEUROSCIENCE TODAY, NEUROLOGY TOMORROW**

# Drug Combo May Prevent Glioblastoma Recurrence

amma-secretase inhibitors could play an important role in augmenting the effectiveness of temozolomide chemotherapy for glioblastoma multiforme if the results obtained in recent in vitro, ex vivo, and in vivo experiments are supported in future studies.

Although temozolomide (TMZ) has increased the 2-year survival rate of patients with glioblastoma multiforme (GBM) when it is used in combination with surgical resection and radiotherapy, some cells still escape treatment in most patients and contribute to local tumor recurrence. Gamma-secretase inhibitors (GSIs) are an attractive therapeutic option because they have been found in previous studies to stop both glioblastoma cell growth and the formation of glioblastoma neurospheres by blocking the Notch

signaling pathway, which is commonly overexpressed in glioblastoma cells, wrote Candace A. Gilbert and her colleagues at the University of Massachusetts, Worcester (Cancer Res. 2010 Aug. 10 [doi:10. 1158/0008-5472.CAN-10-1378]).

Before Ms. Gilbert and her associates tested the combination of TMZ and a GSI in vivo, they tested TMZ alone, a GSI alone, and both together on neurosphere cultures derived from patients' GBMs. Although GSI treatment alone decreased Notch pathway signaling and reduced neurosphere formation, it could not stop the proliferation of GBM cells and the formation of secondary neurospheres. And although treatment with TMZ alone and combined treatment with TMZ and a GSI yielded similar decreases in initial neurosphere formation, cultures treated with the combination recovered to a smaller size, and there were fewer of them than was the case for those treated with TMZ alone. When these neurosphere cultures were dissociated to single cells and replated, the cells that underwent combination treatment formed far fewer secondary neurospheres than did those treated with only TMZ. Treatment with both drugs also led to significantly fewer cells in each neurosphere that were capable of self-renewal.

Further in vitro experiments of the combination of drugs showed that a single dose of a GSI could reduce neurosphere recovery and the formation of secondary neurospheres only when the GSI was administered 24 hours after TMZ, in comparison with TMZ alone.

When the tumor cells were treated and then injected subcutaneously into immunocompromised mice, the researchers observed palpable tumor growth in very few mice that received cells treated with TMZ and a GSI (tumor latencies, 43-96 days), compared with tumor growth in all mice that received cells treated with a GSI alone (latencies, 3-16 days) and growth in nearly all mice that received cells treated with TMZ alone (latencies, 25-43 days).

In another group of immunocompromised mice, tumor cells that were injected subcutaneously were allowed to grow to 150 mm<sup>3</sup>. Ms. Gilbert and her associates found that the xenografts were completely eliminated in half of immunocompromised mice by an intraperitoneal injection of TMZ followed by ingestion of a GSI mixed into their food supply. The mice also survived free of a palpable tumor until they were euthanized at 150 days. The remaining half of the mice that received the combination treatment showed tumor progression at a mean of 26 days.

All tumor masses progressed (doubled in size) in mice that received only TMZ.

"Because Notch activity is associated with GBM stem cell function and survival, and the cells that survive TMZonly treatment are capable of self-renewal and tumor initiation, it is probable that the cells targeted by TMZ plus GSI treatment possess a cancer stem cell phenotype," the researchers wrote.

They suggested that the variability of response to combined treatment in the in vivo studies could have been due to a TMZ concentration that was not "high enough to induce a cell cycle arrest in all the cells capable of recovery, which could hinder GSI enhancement," or a "slight variability" in food consumption.

The need for only a single dose of a GSI to enhance TMZ therapy is beneficial, the researchers noted, because GSIs can cause cytotoxicity in the gastrointestinal tract. They found no change in the weight of the mice during combined treatment.

'These studies suggest a role for TMZ plus GSI therapy to reduce recurrences in patients with low tumor burden after surgical resection of the bulk tumor," wrote the investigators, who acknowledged that they ultimately need to include radiation in their treatment schedule to see how it contributes to combination therapy with TMZ and

The National Institutes of Health and the CVIP Technology Development Fund funded the research. The investigators had no conflicts of interest to disclose.

Research report by Managing Editor, Jeff

## A Springboard to Future Treatments

Since 2005, the treatment standard for GBM has been concomitant TMZ with radiotherapy followed by adjuvant TMZ. This treatment showed slightly increased overall survival, compared with radiotherapy alone. However, the most striking finding in support of this treatment was the 2-year survival rate of 26.5%, which was higher than any prior

treatment regimen had shown. The time to progression on the aforementioned regimen is about 6 months, which points to the refractory and aggressive nature of this tumor. Despite the progress made with up-front therapy, researchers in the field con-

tinue to struggle with how to prevent tumor recurrence, and we remain limited in our treatment options for recurrent disease.

Thus far, bevacizumab has been the only agent approved by the Food and Drug Administration for use in the setting of recurrent GBM. Studies are currently underway to assess the up-front efficacy of using bevacizumab with radiotherapy and TMZ. Given the dismal prognosis for this patient population, novel agents are needed not only to augment upfront therapy to prevent recurrence but also to provide further treatment options in the recurrent setting.

Ms. Gilbert and colleagues conducted an eloquent study using a novel GSI to assess influence on neurosphere replication in the pre-, adjunct, and post-TMZ treatment periods. The remarkable in vitro and in vivo data suggest that GSI and TMZ act together to halt neurosphere replication, and that administering a GSI after TMZ may have the maximum impact in affecting neurosphere repopulation. These data sug-

gest that GSIs may indeed have an impact on glioblastoma recurrence and time to progression.

As the authors point out, future studies to assess the total impact of the GSI in the GBM population will need to incorporate irradiation in addition to TMZ

to reflect a more accurate sense of the full effect and toxicity of the GSI. Toxicity was measured in this study by rodent weight; according to the data provided, it seemed well tolerated with TMZ. The authors suggest that GSIs may also improve the impact of irradiation, which may further reduce treatment toxicity. This study certainly provides a springboard for considering future directions in the use of GSIs and may indeed provide further treatment options for this patient population, in whom options are greatly needed.

ALYX B. PORTER, M.D., is a neurooncologist at the Mayo Clinic in Arizona. She has no relevant disclosures.

Continued from previous page

standardized international criteria for eligibility and response for phase II studies in neuroblastoma, he said.

In multivariable analysis, factors at diagnosis that were independently predictive of overall survival post relapse were stage 4 (hazard ratio, 6.9); stage 3 (HR, 4.3); stage 4S (HR, 3.5); MYCN amplification (HR, 2.4); age less than 18 months (HR, 1.6); and time to relapse less than 12 months (HR, 2.0) – all with a P value less than 0.0001, Dr. London said.

Time to relapse was predictive of survival post relapse in patients with stage 1, stage 2, or no MYCN amplification, but it was not independently predictive,

## Time to Relapse Useful for Determining Trial Eligibility

gression and progression-free survival

are considered.

The observation that time to retional end points such as time to prolapse predicts survival in neuro-

ease and especially when nontradi-

blastoma is made possible by the analysis of a large international collaborative database. Given the unique biology of neuroblastoma and the extreme clinical heterogeneity that impacts its natural history despite therapy and initial response to therapy, this finding will be important as new agents become

available for investigation in this dis-

enriching patient populations for some degree of biological homogeneity is important, not only for the purpose of accurately defining activity of a spe-

cific investigational agent

In addition, refining and

in this specific disease, but also for potentially identifying a group of patients with relapsed disease who may be candidates for

more conventional or standard salvage therapy approaches. This will also aid in defining eligibility criteria and estimating accrual requirements for investigational approaches.

GREGORY H. REAMAN, M.D., is chair of the United States-based Children's Oncology Group. He is also a professor of pediatrics at George Washington University School of Medicine and Health and member of the Division of Hematology-Oncology at the Children's National Medical Center, both in Washington.