

## 2. JMHW Synopsis

### Clinical Study Report Synopsis: Study H3E-MC-JMHW

<b>Title of Study:</b> A Phase II Study of Pemetrexed in Children with Recurrent Malignancies	
<b>Number of Investigators:</b> This multicenter study included 40 principal investigators.	
<b>Study Centers:</b> This study was conducted at 40 study centers in 2 countries.	
<b>Publication Based on the Study:</b> Warwick AB, Malempati S, Krailo MD, Melemed AS, Adamson PC, Blaney S. Phase II trial of pemetrexed in children with refractory solid tumors: A Children's Oncology Group study. <i>J Clin Oncol.</i> 2010;28(suppl 15):7s. Abstract 9535.	
<b>Length of Study:</b> Date of first patient entered: 25 September 2007 Date of last patient completed: 03 February 2010	<b>Phase of Development:</b> 2
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"> <li>to estimate the response rate to pemetrexed administered intravenously (IV) every 21 days in children with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral primitive neuroectodermal tumor (PNET), rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high-grade glioma</li> <li>to further define and describe the toxicities of pemetrexed</li> </ul> <b>Secondary:</b> <ul style="list-style-type: none"> <li>to examine the relationship between the presence of the C677T polymorphism of the methylene tetrahydrofolate reductase (MTHFR) gene and toxicity of patients being treated with pemetrexed</li> <li>to examine the relationship between the presence of a polymorphism in the thymidylate synthase (TS) gene and/or gene promoter and toxicity of patients being treated with pemetrexed</li> <li>to examine the relationship between response and tumor expression of the enzymes TS, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, reduced folate carrier, folylpolyglutamate synthase, and gamma-glutamyl hydrolase as well as methylthioadenosine phosphorylase deletion status</li> </ul>	
<b>Study Design:</b> This was a multicenter, open-label study of pemetrexed every 21 days in children and adolescents with recurrent solid tumors. Target tumor types were osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma (measurable disease), neuroblastoma (metaiodobenzylguanidine [MIBG]+ evaluable disease), ependymoma, medulloblastoma/supratentorial PNET, and non-brainstem high-grade glioma. This study had a 2-stage design with an initial enrollment of 10 patients with each tumor type. If at least 1 partial or complete response was observed within a tumor type, an additional 10 patients with that tumor type could have been enrolled.	
<b>Number of Patients:</b> Planned: Minimum = 80 (10/tumor type); Maximum = 160 (20/tumor type) Enrolled and Treated (at least 1 dose): 72	

**Diagnosis and Main Criteria for Inclusion:** Patients must have been less than 22 years of age when originally diagnosed with the malignancy to be treated on this protocol. Patients must have had a histologic verification of one of the of the following tumors (no other histology is eligible):

- osteosarcoma
- Ewing sarcoma / peripheral PNET
- rhabdomyosarcoma
- neuroblastoma (measurable disease)
- neuroblastoma (MIBG+ evaluable disease)
- ependymoma
- medulloblastoma/supratentorial PNET
- non-brainstem high grade glioma

Patients must have had measurable disease; however, patients with neuroblastoma who did not have measurable disease but had MIBG+ evaluable disease were eligible. The patient's disease state must be one for which there was no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients must have had an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy, and have had adequate organ function.

Patients were excluded from the study if they were receiving other anticancer agents or investigational drugs. Patients were excluded if they had a prior allergic reaction to mannitol, received prior treatment with pemetrexed, or received growth factors within 7 days of enrollment (14 days for Neulasta®). Patients with central nervous system tumors who were not on a stable or decreasing dose of dexamethasone or other corticosteroid for 7 days prior to enrollment on this study were excluded. Also, patients were also excluded for uncontrolled infection, pleural effusions, or ascites.

**Study Drug, Dose, and Mode of Administration:**

Pemetrexed 1910 mg/m<sup>2</sup> (or 60 mg/kg if patient < 12 months old) was to be administered as a 10-minute IV infusion once every 21 days.

**Duration of Treatment:**

Patients could be treated up to 17 cycles (51 weeks).

**Variables:**

Efficacy: Overall response rate (complete response [CR] + partial response [PR]).

Safety: Common Terminology for Adverse Events (CTCAE) ratings, adverse events, dose adjustments, and exposure.

**Statistical Evaluation Methods:**

Efficacy: Response rates were calculated as the percentage of patients who were enrolled and received at least 1 dose of pemetrexed whose best response was a CR or PR, and the confidence intervals were to be constructed according to the method of Chang and O'Brien.

Safety: Toxicity tables were constructed to summarize the observed incidence by severity and type of toxicity for patients who were enrolled and received at least 1 dose of pemetrexed.

**Summary:**

Seventy-two patients were enrolled and received at least 1 dose of study drug. The majority of the patients were White and the majority of the patients were males. The median age was 11.5 years (range was 3 to 23 years). Most patients had Karnofsky Performance Score of 90 and Lansky Play Score of at least 90. The most common reason for treatment discontinuation was progressive disease.

None of the 72 treated patients had a partial or complete response. Five patients had a best overall tumor response of stable disease defined as 2 determinations of stable/no response or better before progression, but not qualifying as CR or PR. Four patients were not evaluable for response assessment.

The median number of cycles was 1 cycle (range 1-13 cycles). There were no dose delays or omissions. One patient received 1 cycle of therapy at a reduced dose, while a second patient received 2 cycles of therapy at a reduced dose. The patients received more than 99.0% of the planned doses of study drug.

The most commonly reported all grade toxicities regardless of causality were leukocytes (48.5%), neutrophils/granulocytes (47.3%), hemoglobin (45.9%), platelets (40.3%), and lymphopenia (27.8%). Other frequently reported all grade toxicities were alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (47.2%), and aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) (40.2%), fatigue (32.0%), and nausea (23.7%). Similar results were observed for toxicities possibly related to study drug.

The most commonly reported Grade 3 or 4 toxicity regardless of causality was neutrophils/granulocytes (30.6%). Other commonly reported Grade 3 or 4 toxicities were hemoglobin (18.1%), leukocytes (16.7%), platelets (16.7%), ALT/SGPT (15.3%), and lymphopenia (12.5%). Similar results were observed for toxicities possibly related to study drug.

The most frequent adverse events requiring expedited reporting were infection with normal absolute neutrophil count (ANC) or Grade 1 ANC (8.33%), death with no associated CTCAE term (6.94%), and febrile neutropenia (5.56%).

There were 3 deaths within 30 days after the last dose of study drug due to progressive disease. These were not considered possibly related to study treatment. There were no deaths at any time considered to be possibly related to study treatment.

**Conclusions:** Pemetrexed is approved in combination with cisplatin for the treatment of unresectable malignant pleural mesothelioma and in combination with cisplatin for first-line treatment of advanced nonsquamous non-small cell lung cancer (NSCLC). Pemetrexed as monotherapy is also approved for the treatment of advanced nonsquamous NSCLC following prior chemotherapy and for the maintenance treatment of patients with locally advanced or metastatic nonsquamous NSCLC whose disease has not progressed after 4 cycles of platinum-based first-line chemotherapy. These are tumor types not typically seen in the pediatric population and currently pemetrexed is not indicated for the treatment of any pediatric tumors.

Seventy-two pediatric patients with recurrent malignancies were treated with pemetrexed 1910 mg/m<sup>2</sup> once every 21 days. The patients had one of the following tumor types: osteosarcoma, Ewing's sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma (measurable or MIBG+ evaluable), ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high-grade glioma. It was anticipated that 10 patients would be enrolled in each tumor stratum, including 10 each in neuroblastoma (measurable disease) and neuroblastoma (MIBG+ evaluable). A total of 11 patients were enrolled in the 2 neuroblastoma strata, and after assessing the data on these 11 patients, both of the neuroblastoma strata were closed. Subsequently, based on a Data Safety Monitoring Board recommendation, the rhabdomyosarcoma stratum was closed after 9 patients had been enrolled in this group. Both of these decisions reflect the difficulty in enrolling patients with relatively rare pediatric solid tumors to Phase 2 trials. In this Phase 2 study, there were no responders in any tumor type, either complete or partial, to pemetrexed and 5 patients were noted to have stable disease for at least 4 cycles of therapy.

The dose of pemetrexed determined in the pediatric Phase 1 study was 1910 mg/m<sup>2</sup>. This is in contrast to the label dose of 500 mg/m<sup>2</sup> for mesothelioma and advanced nonsquamous NSCLC used in adults. In the pediatric population, the most common toxicities seen regardless of causality, including all grade toxicities and Grade 3-4 toxicities, were hematological. The most common all grade nonhematological toxicities

were liver function abnormalities, fatigue, and nausea. The most common Grade 3-4 nonhematologic toxicity regardless of causality was the elevation of ALT/SGPT. The most frequent adverse event requiring expedited reporting was infection with normal ANC or Grade 1 ANC. The frequency of hematological and transaminase elevation was higher than seen in adult studies, which may at least in part be due the higher dose of pemetrexed used in this study.

There were no deaths that were considered possibly related to study treatment; however, 3 deaths within 30 days of last dose of study drug did occur and were attributed to progressive disease.

Pemetrexed was not efficacious in the pediatric tumors studied, and no safety concerns were identified; no unexpected toxicities were identified. and no deaths occurred related to study treatment.