2. S115 Synopsis

Clinical Study Report Synopsis: Study H3E-EW-S115

Title of Study: Phase 2 Trial of Pemetrexed in Second Line Advanced/Metastatic Osteosarcomas	
Number of Investigators: This multicenter study included 12 principal investigators.	
Study Centers: This study was conducted at 12 study centers in 5 countries.	
Publication Based on the Study: Bin Bui N, Egerer G, Ferrari S, Comandone A, Cioffi A, Rassam H, Michel A, Ameryckx S, Weitckus S, and Duffaud F. Antitumor activity of pemetrexed (Pem) in second-line advanced/metastatic osteosarcomas: A multicenter phase 2 study. *J Clin Oncol*, 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2010;28(15)(suppl May 20): 10076.	
Length of Study: Date of first patient visit: 11 September 2007 Date of last patient visit: 30 June 2010	**Phase of Development:** 2
Objectives: The primary objective was to assess the antitumor activity of pemetrexed therapy, as measured by tumor response rate according to Response Evaluation Criteria in Solid Tumors (RECIST 1.0) in patients with advanced/metastatic osteosarcomas. Secondary objectives were as follows: • To assess the following efficacy variables: o duration of response for responding patients o progression-free survival (PFS) o time to treatment failure (TTTF) o overall survival (OS) • To examine the toxicity (evaluated with National Cancer Institute-Common Toxicity Criteria [NCI-CTC] version 3.0) and safety profile of study treatment • Correlation of disease outcome with pharmacogenomic analysis: MTAP gene deletion, FRα, and FPGS expression were correlated with the clinical data to determine the association between these factors and clinical outcome to treatment	
Study Design: Study H3E-EW-S115 is a Phase 2, open-label, multicenter, non-randomized, single-arm study of pemetrexed (500 mg/m^2 by intravenous [IV] infusion of 10 minutes) in patients with advanced or metastatic osteosarcomas. The treatment period is based on a 21-day cycle for pemetrexed. Treatment with pemetrexed was continued until disease progression or discontinuation from study treatment. During the post-study follow-up period, patients were followed with tumor response evaluation every 3 months until disease progression (for nonprogressive patients) or death. Study closure occurred as soon as 80% events had occurred (80% deaths) or all patients had a last (2-year) follow-up assessment, whichever came first, and until 30 days following discontinuation of study therapy of the last patient. The 80% deaths criterion was met for closure of this study.	
Number of Patients: Planned: 32 Treated (at least 1 dose): 32 active drug Completed: 32 active drug	

Diagnosis and Main Criteria for Inclusion:

- Men and women at least 18 years of age with a histological diagnosis of high-grade, locally advanced or metastatic osteosarcoma (World Health Organization classification), not amenable to surgery, radiation, or combined modality therapy with curative intent and with a life expectancy of at least 12 weeks.
- One prior chemotherapy regimen for advanced disease; neoadjuvant is not counted toward this requirement.
- Adequate bone marrow reserve, hepatic and renal function, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0,1, or 2.
- Prior radiation therapy was allowed to < 25% of the bone marrow if all toxicities had resolved and if radiation was completed at least 4 weeks before study enrollment.

Study Drug, Dose, and Mode of Administration:

Pemetrexed 500 mg/m^2 by IV infusion of 10 minutes.

Duration of Treatment:

Treatment with pemetrexed continued until disease progression or discontinuation from study treatment.

Variables:

Efficacy: Best response was determined from the sequence of responses assessed. For complete response (CR) or partial response (PR), best response was confirmed. A second assessment was performed ≥28 days and ≤ 42 days after the first evidence of response. Two objective status determinations of CR before progression were required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, were required for a best response of PR. Best response of stable disease (SD) was defined as disease that did not meet the criteria for CR, PR, or progressive disease (PD) and was evaluated at least one time, at least 6 weeks after the start of study treatment.

Overall survival time was defined as the time from the date of study enrollment to the date of death from any cause. For patients not known to have died as of the data cutoff date, OS was censored at the last contact date (last contact for patients in postdiscontinuation equaled the last known alive date in mortality status).

Progression-free survival time was defined as the time from the date of study enrollment to the first date of objectively determined PD or death from any cause. For patients not known to have died as of the data cutoff date and who did not have objective PD, PFS was censored at the date of the last objective progression-free disease assessment. For patients who received subsequent systemic anticancer therapy (after discontinuation from the study drug) prior to objectively determined disease progression or death, PFS was censored at the date of the last objective progression-free disease assessment prior to postdiscontinuation of chemotherapy.

Time to treatment failure (TTTF) was defined as the time from date of study enrollment to the first date of death from any cause, PD, or study treatment discontinuation due to any reason other than "protocol complete" or "satisfactory response." For patients who discontinued due to "protocol complete" or "satisfactory response," or for patients not known to have discontinued as of the data cutoff date, TTTF was censored at the last contact date.

A responder was defined as any patient who exhibited a confirmed CR or PR.

The duration of overall response (CR or PR) was defined as the time from the date when the measurement criteria were met for CR or PR (whichever status was recorded first) until the date of first observation of objective disease progression.

The duration of SD was defined as the time from the date of study enrollment to the date of first observation of disease progression or death due to any cause.

Safety: Investigators assessed the causality of any adverse event (AE) experienced by a patient and graded it using the NCI-CTC scale before each cycle and at 30 days and 90 days poststudy.

Pharmacogenomic: *MTAP* gene deletion and FRα and FPGS expression was planned to be correlated with the clinical data to determine the association between these factors and clinical outcome to treatment.

Statistical Evaluation Methods:

All patients who received at least 1 dose of study drug were qualified for the response analysis. A probability of less than 0.05 for achieving response in the targeted population was to be considered as unacceptable for warranting further investigation (null hypothesis). A probability of at least 0.2 for achieving response in the targeted population was to be considered for warranting further investigation (research hypothesis). Based on this assumption, a sample size of 32 eligible patients was needed to reject the null hypothesis with a power of approximately 80% and a significance level of 5% using a 2-sided exact binomial test.

Efficacy: The primary outcome measure was the tumor response rate. The estimate of the overall best response rate was given by:

Response Rate = Sum of # of PRs and # of CRs observed/Number of patients qualified for tumor response analysis.

The 2-sided exact binomial test was applied to evaluate the response rate. In addition, the 2-sided 95% exact binomial confidence intervals (CIs) are provided (Leemis and Trivedi 1996).

- Kaplan-Meier techniques were used to assess the time-to-event endpoints. For each variable, Kaplan-Meier curves were generated, and quartiles and point probabilities were calculated. Interval estimates were calculated using 95% CIs.
- Kaplan-Meier curves and quartiles for duration of response, if a sufficient number of responders is observed.

Analyses relating survival and PFS to potential prognostic factors were carried out using the Cox Regression Model.

Safety: Safety analyses included summaries of the incidence of laboratory and non-laboratory AEs by maximum CTC grade that occurred during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality. Additionally, the following safety-related outcomes are summarized:

- extent of exposure
- study treatment discontinuations due to AEs
- deaths during the study treatment period or within 30 days of the last dose of study treatment
- serious adverse events (SAEs) during the study treatment period or within 30 days of the last dose of study treatment
- treatment-emergent adverse events (TEAEs) during the study treatment period or within 30 days of the last dose of study treatment

Analyses for all safety data were done through 30 days after each patient's last dose of study treatment. Adverse events were also analyzed in this timeframe; that is, if an event started within 30 days of discontinuation from study treatment but after 30 days following the last dose of study treatment, it was not to be included.

Pharmacogenomic: Determination of *MTAP* gene copy and mRNA expression in the biopsy specimens was planned using real-time quantitative polymerase chain reaction (PCR) on genomic DNA and mRNA extracted from the tumor tissues, respectively. Interphase fluorescence in situ hybridization on tissue imprints was planned to assess copy number status of the chromosomal region spanning the *MTAP* locus to corroborate and complement the quantitative PCR assay.

Immunohistochemistry was planned to detect FRα and FPGS in tumor tissues. Slides were planned to be scored for level of expression using an established standard operating procedure.

The *MTAP* gene deletion and FRα and FPGS expression status was planned to be correlated with response and clinical outcome.

Summary:

Protocol Violations: In total, 47 significant protocol treatment violations were observed in 28 patients. Protocol violations included 11 protocol inclusion/exclusion criteria violations, 8 incorrect dose modifications, 7 incorrect dosing violations, and 21 protocol-specific violations. None were considered serious to affect the interpretation of the study results.

Patient Disposition, Baseline Demographics, and Characteristics: Between 11 September 2007 and 30 March 2009, 32 patients were enrolled (All Enrolled Population). There were no screen failures. Therefore, 32 patients received the study drug (Safety Population).

All 32 enrolled patients were included in the baseline demographics and characteristics analyses. Of the 32 patients, 20 were male and 12 were female. The overall age range was 18.6 years to 76 years (median age = 43.3 years). In total, 16 patients had an ECOG PS of 0, 14 patients had a PS of 1, and 1 patient had a PS of 2. All patients had histologically proven osteosarcoma. One patient (3.1%) was diagnosed with no targets lesions, 9 patients (28.1%) were diagnosed with 1 target lesion, 8 patients (25.0%) were diagnosed with 2 target lesions, 4 patients (12.5%) were diagnosed with 3 target lesions, 3 patients (9.4%) were diagnosed with 4 targets lesions, and 7 patients (21.9%) were diagnosed with 5 targets lesions. All patients were enrolled after at least 1 prior systemic therapy. Patients may have received more than 1 prior therapy. Systemic therapy included chemotherapy, biological therapy, and hormonal therapy. Table S115.2.1 summarizes the patient data on prior systemic therapy.

Table S115.2.1. Summary of Prior Systemic Therapy

	N = 32
Patients, n (%)	
Number of prior regimens	
Number of patients	**32**
1	11 (34.4)
2	9 (28.1)
3	9 (28.1)
4	1 (3.1)
5	2 (6.3)
Reasons for prior regimens	
Number of patients	**32**
Metastatic	25 (78.1)
Adjuvant / curative intent	19 (59.4)
Neoadjuvant	16 (50.0)
Best response of last prior regimen	
Number of patients	**32**
Complete response	1 (3.1)
Partial response	3 (9.4)
Stable disease	10 (31.1)
Progressive disease	15 (46.9)
Not applicable[a]	3 (9.4)

Abbreviations: N = total population size; n = number of patients with prior therapy.

a Patients may have received more than one prior therapy. Systemic therapy includes chemotherapy, biological therapy, and hormonal therapy.

b Best response of prior regimen is unknown.

Source: Accovion GmbH: 26AUG10 / 14:30 / ct_prior_syst_st.lst / ct_prior_syst_t.sas, Table 2.2.4.

Nine patients (28.1%) had prior radiotherapy, and 30 patients (93.8%) had prior surgery. Prior to the first dose of pemetrexed, all patients (100%) received vitamin B12 and folic acid supplements. Five patients (15.6%) received at least 1 blood transfusion.

Protocol Treatment: Protocol treatment analyses were performed on the safety population. The median number of cycles administered was 2.0 (range, 1 to 14). Fifteen patients (46.9%) had at least 1 cycle delay. Eight patients (28.6%) had a cycle delay in Cycle 2, 7 patients (58.3%) in Cycle 3, 2 patients (28.6%) in Cycle 4, 1 patient (16.7%) in Cycle 5, 1 patient (16.7%) in Cycle 6, 2 patients (40.0%) in Cycle 7, 1 patient (33.3%) in Cycle 9, and 1 patient (33.3%) in Cycle 10. Scheduling conflicts (defined as not being able to get an appointment for the patient on the exact planned date at the hospital) and adverse events were the main causes of cycle delay. One dose of pemetrexed was reduced in 2 patients (6.3%) due to 1 event of alanine aminotransferase increased and 1 event of obesity. The dose reductions occurred in Cycle 1 (1 event) and in Cycle 2 (1 event). The median duration of cycles was 21 days. The planned mean dose of pemetrexed was 166.7 mg/m^2/week, and the actual mean dose of pemetrexed was 153.8 ± 17.49 mg/m^2/week. The actual median cumulative dose of pemetrexed was 997.1 mg/m^2. The median pemetrexed relative dose intensity (RDI) for the entire study duration was 96.9% with a minimum RDI of 59.5% and a maximum RDI of 105.2%. Table S115.2.2 summarizes data on pemetrexed cycles received.

Table S115.2.2. Pemetrexed Cycles Received (Enrolled Population)

	Cycles						
	Cycle 1 (N = 32)	**Cycle 2 (N = 28)**	**Cycle 3 (N = 12)**	**Cycle 4 (N = 7)**	**Cycle 5 (N = 6)**	**Cycle 6 (N = 6)**	**Cycle 7 (N = 5)**
Actual Doses Pemetrexed (mg/m^2)							
Median	494.5	492.1	494.2	475.6	482.8	481.7	487.9
Minimum, Maximum	382, 520	370, 514	423, 528	423, 522	423, 520	423, 520	423, 524
Duration of Cycles Per Patient (days)							
Median	21.0	21.0	21.0	21.0	21.0	21.0	21.0
Minimum, Maximum	13, 40	14, 33	3, 30	21, 32	21, 22	21, 45	2, 21
	Cycles						
	Cycle 8 (N = 3)	**Cycle 9 (N = 3)**	**Cycle 10 (N = 3)**	**Cycle 11 (N = 3)**	**Cycle 12 (N = 2)**	**Cycle 13 (N = 2)**	**Cycle 14 (N = 1)**
Actual Doses Pemetrexed (mg/m^2)							
Median	487.9	487.9	487.9	487.9	494.9	493.4	497.2
Minimum, Maximum	460, 499	460, 499	460, 499	460, 502	491, 499	488, 499	497, 497
Duration of Cycles Per Patient (days)							
Median	21.0	21.0	22.0	21.0	21.0	20.5	20.0
Minimum, Maximum	21, 23	20, 23	21, 42	21, 27	21, 21	20, 21	20, 20

Abbreviations: N = total population size in the corresponding cycle.
Source: Accovion GmbH: 01DEC09 / 10:07 / ex_doseadmin_cyc_st.lst / ex_doseadmin_cyc_t.sas, Table 3.1.3

The distribution of patients that received further anticancer therapy after protocol treatment was determined using the all enrolled population. Eighteen of 32 patients (56.3%) received further anticancer therapy; of these, the majority received chemotherapy (15 patients [83.3%]).

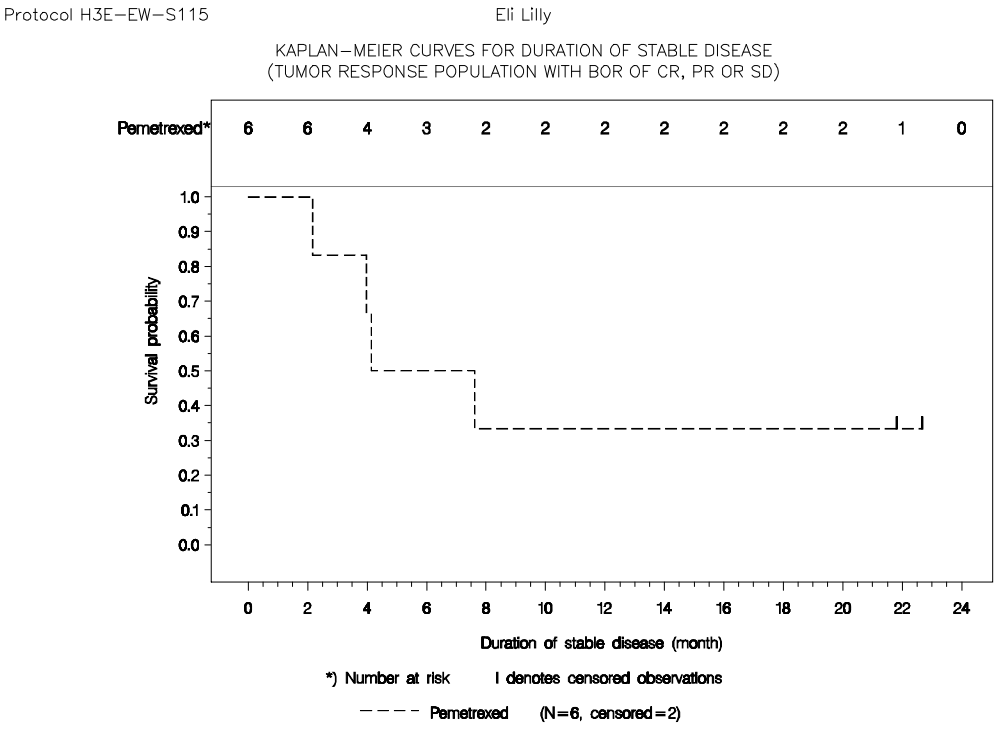
Efficacy: All efficacy analyses were performed on the all enrolled population of 32 patients (full analysis population).

Primary Analysis – Best Overall Tumor Response Rate

The best overall tumor response rate was 3.1%. The majority of patients experienced PD. As assessed by the investigator, 1 patient (3.1%) experienced PR, 5 patients (15.6%) experienced SD, 22 patients (68.8%) experienced PD, and 4 patients (12.5%) had an unknown overall tumor response (an unknown overall tumor response is reported since 3 patients died before the tumor assessment after Cycle 1 was performed, and 1 patient discontinued study treatment early without any tumor assessments performed).

Secondary Analysis – Duration of Stable Disease

The Duration of Stable Disease (DSD) was evaluated in the tumor response population, which included a total of 6 patients with best overall response (BOR) of CR, PR, and SD. Four patients (66.7%) had a DSD measured event, whereas 2 patients (33.3%) were censored. Overall median DSD was 5.9 months (95% CI, 4.0 to [NA]). The 6-month DSD rate was 50.0% (95% CI, 10.0 to 90.0), and the 1-year DSD rate was 33.3% (95% CI, 0.0 to 71.1). Figure S115.2.1 shows the total Kaplan-Meier curve for DSD in the tumor response population.



BOR = best overall response, CR = complete response, PR = partial response, SD = stable disease.
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Figure S115.2.1 Duration of stable disease (month) in patients receiving 500 mg/m^2 pemetrexed by intravenous infusion of 10 minutes.

The results of the primary endpoint show that only 1 patient responded to treatment. The duration of response for this patient (patient number 3203) is 224 days.

Progression-Free Survival

Twenty-eight patients (87.5%) had a PFS event, documented PD, or death, whichever occurred first. Four patients (12.5%) were censored due to an unknown death as of the data cut-off date with objective PD, or subsequent systemic anticancer therapy (after discontinuation from the study drug) prior to objective PD or death. These patients were censored at the date of the last objective progression-free disease assessment or the date of the last objective progression-free disease assessment prior to postdiscontinuation chemotherapy. Overall median PFS was 1.4 months (95% CI, 1.4 to 1.7) with a 3-month PFS rate of 17.2% (95% CI, 3.5 to 31.0) and a 6-month PFS rate of 6.9% (95% CI, 0.0 to 16.1). Figure S115.2.2 shows the total Kaplan-Meier curve for PFS in the full analysis population.

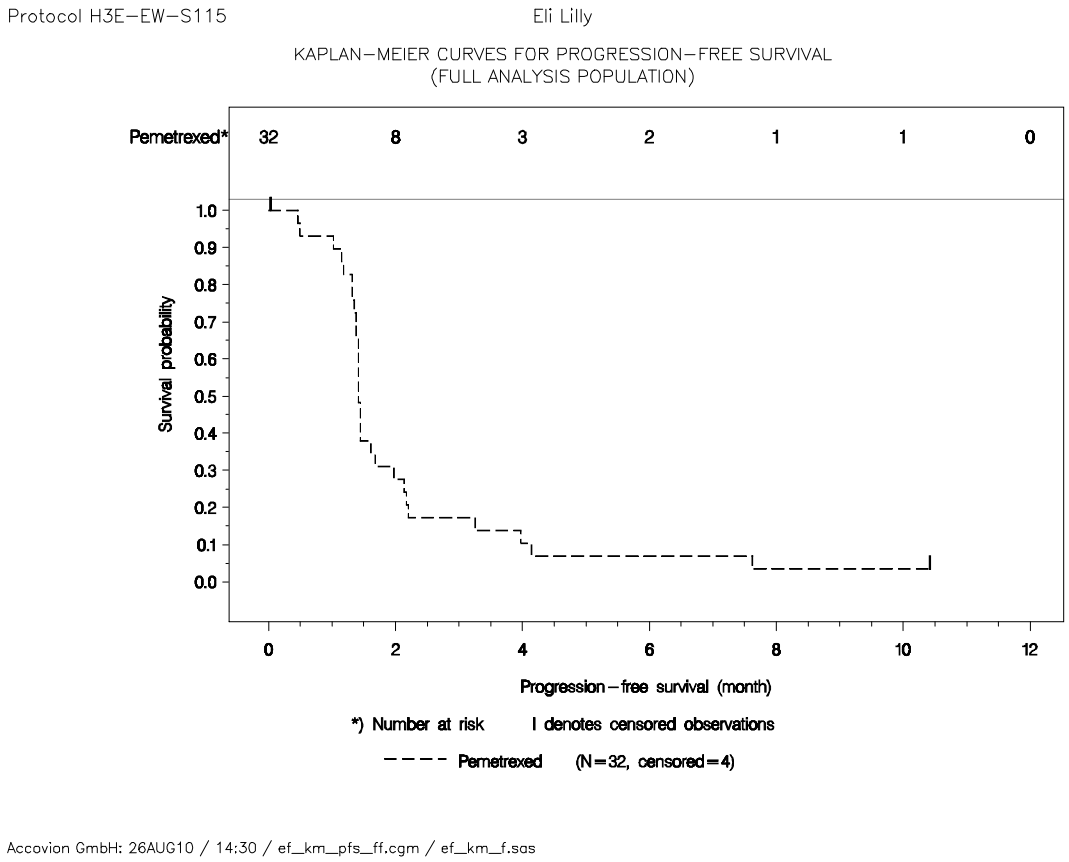

Figure S115.2.2 Progression-free survival (month) in patients receiving 500 mg/m2 pemetrexed by intravenous infusion of 10 minutes.

Time to Treatment Failure

TTTF was not analyzed because the results would be very similar to those obtained for PFS. Of the 32 patients in this study, only 4 had discontinuation as their event for TTTF; the remaining 28 had progression or death as their event.

Overall Survival Time

Twenty-six patients (81.3%) had events, and 6 patients (18.8%) were censored during the observation period. Median OS was 5.5 months (95% CI, 2.3 to 10.5). The survival rate at 6 months was 46.9% (95% CI, 29.6 to 64.2); at 1 year, the survival rate was 31.3% (95% CI, 15.2 to 47.3); and at 2 years, the survival rate was 21.9% (95% CI, 7.6 to 36.2). Figure S115.2.3 shows the total Kaplan-Meier curve for OS in the full analysis population.

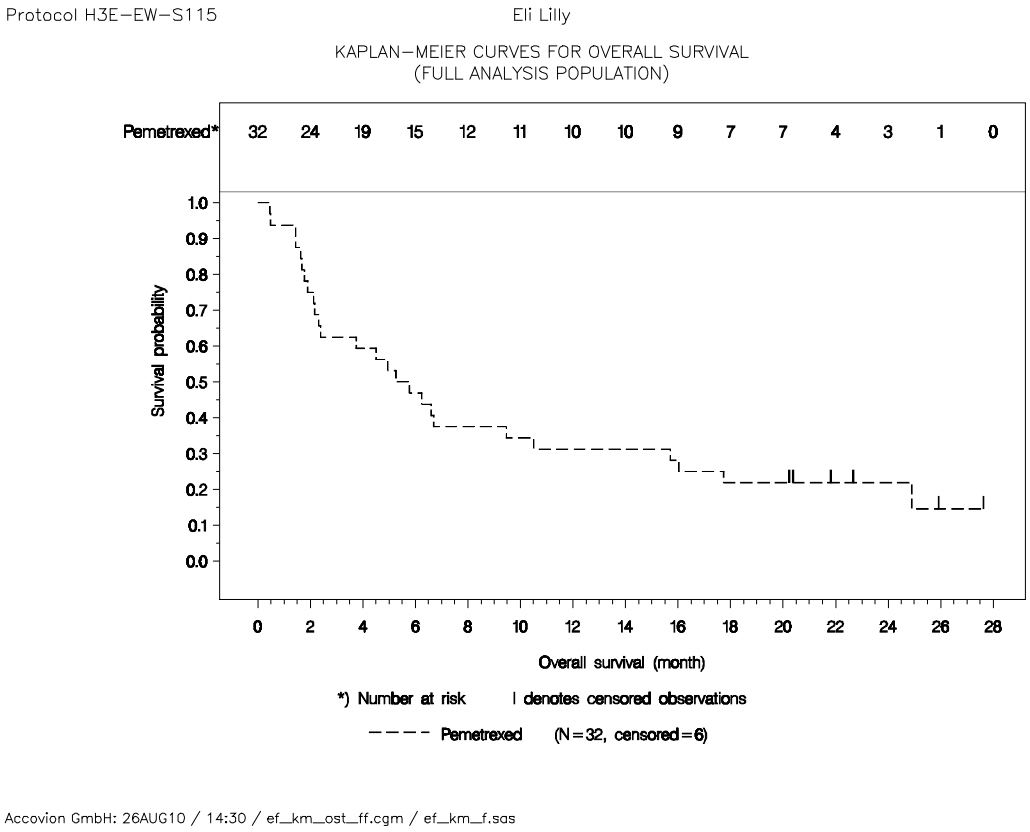

Figure S115.2.3 Overall survival (month) in patients receiving 500 mg/m^2 pemetrexed by intravenous infusion of 10 minutes.

Pharmacogenomic Analysis: The results of the primary endpoint show that only 1 patient responded to treatment; therefore, the response rate obtained did not meet the expectations required by the protocol. This part of the translational research was canceled upon the recommendation of the study team, and the correlation of clinical outcome (responders versus nonresponders) with the pharmacogenomic parameters was not performed.

Safety: All safety analyses were performed on all patients who received at least 1 dose of pemetrexed. Therefore, the safety population consisted of 32 patients.

Safety and Toxicity Analysis

Twenty-seven patients (84.4%) experienced at least 1 TEAE regardless of drug causality. Twenty-two patients (68.8%) experienced at least 1 possibly drug-related TEAE. A total of 19 patients (59.4%) experienced at least one Grade 3/4/5 TEAE regardless of causality. Twelve patients (37.5%) experienced a Grade 3/4/5 TEAE that was possibly drug-related. Ten patients (31.3%) experienced at least 1 serious TEAE regardless of causality, and 4 patients (12.5%) experienced at least 1 possibly drug-related serious TEAE. Seventeen patients (53.1%) experienced at least one Grade 3 or Grade 4 nonserious TEAE. Table S115.2.3 summarizes the distribution of Grade 3 and Grade 4 nonserious TEAEs reported by the investigator.

Table S115.2.3 Summary of Grade 3 and Grade 4 Non-Serious Treatment-Emergent Adverse Events (Safety Population [N = 32])

	N = 32	
System Organ Class/Preferred Term, n (%)	**Grade 3**	**Grade 4**
Patients with at least 1 event	13 (40.6)	4 (12.5)
Blood and lymphatic system disorders		
Anaemia	3 (9.4)[a]	0 (0.0)
Leukopenia	3 (9.4)[b]	0 (0.0)
Neutropenia	1 (3.1)[b]	1 (3.1)[b]
Febrile neutropenia	1 (3.1)[b]	0 (0.0)
Cardiac disorders		
Pericardial effusion	1 (3.1)	1 (3.1)
Gastrointestinal disorders		
Dyspepsia	1 (3.1)	0 (0.0)
General disorders and administration site conditions		
Asthenia	4 (12.5)[c]	0 (0.0)
Infections and infestations		
Respiratory tract infection	1 (3.1)	0 (0.0)
Urinary tract infection	1 (3.1)	0 (0.0)
Investigations		
Alanine aminotransferase, increased	3 (9.4)[b]	0 (0.0)
Blood alkaline phosphatase, increased	1 (3.1)	0 (0.0)
Transaminase, increased	1 (3.1)	0 (0.0)
Nervous system disorders		
Dizziness	1 (3.1)	0 (0.0)
Headache	1 (3.1)	0 (0.0)
Psychiatric disorders		
Anxiety	1 (3.1)	0 (0.0)
Reproductive system and breast disorders		
Erectile dysfunction	0 (0.0)	1 (3.1)
Respiratory, thoracic, and mediastinal disorders		
Acute respiratory distress syndrome	1 (3.1)	0 (0.0)
Dyspnea	1 (3.1)	0 (0.0)
Skin and subcutaneous tissue disorders		
Toxic skin eruption	0 (0.0)	1 (3.1)[b]

Abbreviations: N = total safety population size; n = number of patients with at least 1 event in the corresponding category.

[a] A total of 2 of 3 reported adverse events related to the study drug.
[b] Adverse event related to the study drug.
[c] A total of 3 of 4 reported adverse events related to the study drug.

Source: Accovion GmbH: 26AUG10 / 14:30 / ae_g345_ns.lst / ae_socpt_g345_t.sas,
Accovion GmbH: 26AUG10 / 14:30 / ae_dr_g345_ns.lst / ae_socpt_g345_t.sas, Table 5.1.6. and Table 5.1.7.

The most frequent serious TEAEs by system organ class (SOC) possibly related to study drug were in the SOCs of blood and lymphatic system disorders and general disorders and administration site conditions. Five serious TEAEs of febrile bone marrow aplasia, febrile neutropenia, thrombocytopenia, general physical health deterioration, and pyrexia were determined by the investigator to be related to the study drug. Table S115.2.4 summarizes all serious TEAEs.

Table S115.2.4. Summary of Serious Treatment-Emergent Adverse Events (Safety Population [N = 32])

System Organ Class/Preferred Term, n (%)	N=32
Patients with at least 1 event	10 (31.3)
Blood and lymphatic system disorders	
Febrile bone marrow aplasia	1 (3.1)[a]
Febrile neutropenia	1 (3.1)[a]
Thrombocytopenia	1 (3.1)[a]
Cardiac disorders	
Pericardial effusion	1 (3.1)
General disorders and administration site conditions	
General physical health deterioration	1 (3.1)[a]
Pyrexia	1 (3.1)[a]
Sudden death	1 (3.1)
Infections and infestations	
Device related infection	1 (3.1)
Sepsis	1 (3.1)
Staphylococcal infection	1 (3.1)
Injury, poisoning, and procedural complications	
Lumbar vertebral fracture	1 (3.1)
Nervous system disorders	
Nerve compression	1 (3.1)
Renal and urinary disorders	
Haematuria	1 (3.1)
Renal failure, acute	1 (3.1)
Ureteric obstruction	1 (3.1)
Urinary retention	1 (3.1)
Reproductive system and breast disorders	
Pelvic pain	1 (3.1)
Respiratory, thoracic, and mediastinal disorders	
Dyspnoea	1 (3.1)

Abbreviations: N = total safety population size; n = number of patients with at least one event in the corresponding category; TEAE = treatment emergent adverse event.

a Serious TEAE possibly related to study drug.

Source: Accovion GmbH: 26AUG10 / 14:30 / ae_sae.lst / ae_socpt_t.sas, Table 5.1.3.

During the study, 22 patients discontinued treatment due to progressive disease, 2 patients discontinued treatment due to physician decision, 1 patient discontinued treatment due to subject decision, and 1 patient discontinued due to an AE (asthenia). No patients discontinued due to a SAE. Six patients died on study drug therapy or within 30 days of study drug discontinuation. Four patients died due to study disease, and 2 patients died on therapy (1 patient due to a possibly drug-related AE of general physical health deterioration). No patients died within 30 days of study treatment discontinuation due to an AE.

CTCAE Grade 3/4 Laboratory Toxicities: In total, 14 patients (43.8%) experienced at least 1 laboratory toxicity of any grade. Nine patients (28.1%) with Grade 3 or Grade 4 laboratory toxicities. Table S115.2.5 summarizes Grade 3 and Grade 4 toxicities as reported by the laboratory.

Table S115.2.5. Summary of Grade 3 and Grade 4 Laboratory Toxicities by Maximum CTC Grade (Safety Population [N = 32])

	N=32	
Toxicity, n (%)	**Grade 3**	**Grade 4**
Patients with at least 1 event	7 (21.9)	2 (6.3)
Blood and lymphatic system disorders		
Anemia	3 (9.4)[a]	0 (0.0)
Leukopenia	3 (9.4)[b]	0 (0.0)
Neutropenia	1 (3.1)[b]	1 (3.1)[b]
Thrombocytopenia	0 (0.0)	1 (3.1)[b]
Investigations		
Alanine aminotransferase, increased	3 (9.4)[b]	0 (0.0)
Blood alkaline phosphatase, increased	1 (3.1)	0 (0.0)

Abbreviations: CTC = Common Toxicity Criteria; N = total safety population size; n = number of patients with events.

a A total 2 of 3 toxicities possibly related to study drug.

b Toxicity possibly related to study drug.

Source: Accovion GmbH: 26AUG10 / 14:30 / ae_grd_lr_all.lst / ae_pt_ctcgrd_t.sas ,
Accovion GmbH: 26AUG10 / 14:30 / ae_grd_lr_rel.lst / ae_pt_ctcgrd_t.sas, Table 5.1.11 and Table 5.1.12.

Conclusions:

- Efficacy: The primary outcome measure was the tumor response rate. The 3.1% response rate of pemetrexed as a second-line treatment in advanced or metastatic osteosarcoma did not meet expectations required by the protocol.
- Safety: The safety profile of pemetrexed in this study was expected and tolerated, similar to its safety profile when given as monotherapy.

References:

Leemis LM, Trivedi KS. A comparison of approximate interval estimators for the Bernoulli parameter. *Amer Stat*. 1996; 50:63-68.