Reports by Other Investigators Addressing Survival and/or Prognosis in Cancer Patients Treated with Recombinant Human Erythropoietin (rHuEpo):

- **Ludwig H et al (Ann Oncol 1993; 4:161-7)**: Forty two patients with various types of cancers were treated with rHuEpo for their anemia. The malignant diseases were: 18 multiple myeloma (MM), 10 myelodysplastic syndromes (MDS), 9 breast cancers and 5 colon cancers. The median time period of treatment with rHuEpo was 16 weeks. The study was designed to treat anemia. Response was defined as an increase of the initial hemoglobin (Hb) level by at least 2 g/dl. The response rates varied: 44.4% for breast cancer, 40% for colon cancer, 77.8% for MM, 10% for MDS. The median survival time of responders was 28.0 months as compared to only 9.2 months for non-responders

- **Rubins J (Ann Intern Med 1995; 122: 676-7)**: A clinical observation and a report on a single patient with metastatic renal (kidney) cell cancer (RCC), who had been treated with rHuEpo (for anemia) and unexpectedly experienced a very impressive response of the tumor too, with a significant regression of the metastases.

- **Morere JF et al (Prog Urol 1997; 7: 399-402)**: This was a phaseI/II French study designed to assess the antitumor effect of rHuEpo on metastatic renal cell cancer (RCC). Twenty patients with metastatic RCC, received rHuEpo (a relatively higher dose than usually given for anemia). All but one of the patients had received immunotherapy or chemotherapy prior to inclusion in the study. The results: One complete response (complete disappearance of the tumor and the metastases) for more than 12 months, one partial response (8 months), 2 minor responses, 10 cases of stabilization (the disease did not continue to progress) and 6 cases of progression were observed. In 5 patients, the duration of treatment was reduced before the 8 weeks initially defined because of tumour progression in one patient and because of Hb greater than 15 g/dl in 4 other patients.

- **Littlewood TJ et al (J Clin Oncol 2001; 19: 2865-74)**: This was a randomized, double-blind, placebo-controlled (phase III) clinical trial assessed the effects of epoetin alfa on transfusion requirements, hematopoietic parameters, quality of life, and safety in anemic cancer patients receiving nonplatinum chemotherapy. The study also explored a possible relationship between increased Hb and survival. Three hundred seventy five patients with solid or nonmyeloid hematologic malignances were randomized 2:1 to epoetin alfa 150-300u/Kg (n=251) or placebo (n=124), three times per week subcutaneously (sc) for 12-24 weeks. Results: Epoetin alfa, compared with placebo, significantly decreased transfusion requirements and increased Hb. Although the study was not powered for survival as an end point, Kaplan-Meier estimates showed a trend in overall survival favoring epoetin alfa, and a Cox regression analysis showed an estimated hazards ratio of 1.309 favoring epoetin alfa.

- **Lissoni P et al. (Anticancer Res 2001; 21: 777-9)**: A Phase II study of subcutaneous low-dose interleukin-2 plus erythropoietin in metastatic renal cell carcinoma progressing on interleukin-2 alone. The background for this trial is the high rate of failure with IL-2 treatment in patients with metastatic RCC, and the idea that a major reason for this resistance is high levels (and activity) of vascular endothelial growth factor (VEGF), which induces proliferation of new blood vessels, apparently serving the tumor. Data suggesting that Epo may modulate VEGF secretion and IL-2 biological activity led to this Italian study. On this basis, a study was planned with sc low-dose IL-2 plus rHuEpo in metastatic RCC, which had progressed on IL-2 alone. The study included 12 evaluable metastatic RCC patients. Results: A partial response (PR) and 4 stable diseases (SD) were achieved on IL-2 plus rHuEpo, whereas the other 7 patients had a progressive disease (PD). The authors concluded that "this preliminary study shows that the concomitant administration of Epo may allow a control of the neoplastic growth in advanced cancer patients progressing on IL-2 alone…".

- **Shasha D (Semin Hematol 2001; 38: Suppl 7; 8-15)**: This review summarizes and, in fact represents, a series of reports dealing with head and neck cancer. These investigators explain that anemia, which is associated with hypoxia (decreased oxygen supply) lead to reduced oxygen supply to the tumor making the tumor cells less sensitive to radiation therapy, the common treatment in this type of cancer. Several studies both in animal models as well as human patients, have shown that anemia correction by rHuEpo (or blood transfusion) is associated with better oxygenation to the tumor, leading to a better local control by radiation therapy and an improved prognosis.

- **Dunst J (Semin Oncol 2001; 28: Suppl 8: 42-8)**: This review basically is similar to the Shasha review on head and neck cancer, emphasizing the same point: Anemia correction (although should not be exagerated) allows a better local control of the tumor by radiotherapy, which is associated with a better prognosis.

- **Pangalis GA et al**: **(Haematologica 2002; 87: 500-6)**: Downstaging Rai stage III B-chronic lymphocytic leukemia patients with the administration of recombinant human erythropoietin. This phase II Greek clinical trial was designed to investigate the effectiveness of rHuEpo on disease-related anemia in patients with B-chronic lymphocytic leukemia (CLL) and to explore whether improvement of anemia could delay the initiation of antileukemic chemotherapy. Twenty five B-CLL patients with anemia were treated with rHuEpo. Patients were either on no treatment or on a standard regimen (for the CLL), and had at least Rai stage III disease. The Rai classification allows to define each CLL patients to have stage 0 through 4, reflecting the disease severity and prognosis. While Rai stage 0 patient is expected to live 10-12 years, the median survival of stage IV patients is less than 2 years. Results: Eighteen patients (72%) achieved complete Hb response and another 2 patients (8%) obtained partial Hb response. Six patients were down staged to Rai stage 0, 9 to Rai I and 4 to Rai II. At a median follow-up of 32 months only 4 of the responders required anti leukemic treatment. At the time of the report, the median survival of responders had not been reached, and 3-year

survival was 84%. The authors concluded that "rHuEpo was effective in downstaging Rai stage III B-CLL patients, and delayed the initiation of anti leukemic therapy".

- **Wallvik J et al. (Eur J Haematol 2002; 68: 180-5)**: This Swedish group reports its experience with a long-term follow-up of 68 MDS patients treated with rHuEpo. The median Hb response duration was 15 months. The median overall survival time from start of Epo treatment was 26 months, significantly longer for responders than for non-responders (49 vs 18 months, p=0.018).

- **Baz R et al: Recombinant human erythropoietin is associated with increased overall survival in patients with multiple myeloma (Acta Haematol 2007; 117: 162-7)**: Team from the Cleveland Clinic Myeloma Program analyzed their experience with Epo in MM patients. This retrospective analysis provides data on 292 MM patients enrolled on different protocols between 1997 and 2003, of whom 257 were followed for at least one month and 35 patients were excluded from the analysis because of missing information on rHuEpo treatment. Of the analyzed 222 patients, 127 MM patients were treated with rHuEpo for at least 1 month and their data were compared to the 95 MM patients who did not receive the hormone. On average, patients on rHuEpo were characterized by factors usually associated with poor prognosis and a shorter survival: older age, more advanced MM (higher SWOG stage), higher serum creatinine, lower serum Hb, higher beta2-microglobulin, lower platelet counts and a longer time from diagnosis to enrollment at the myeloma program (p<0.001 for all). After adjusting for age, months from diagnosis to enrollment, serum creatinine, Hb, platelet count and beta2-microglobulin, the use of rHuEpo was associated with improved overall survival (hazard ratio =0.6) in patients with SWOG stages II, III, and IV but not in patients with SWOG stage I. The authors concluded that "rHuEpo was associated with improved overall survival in this population of anemic MM patients with SWOG stages II, III and IV."

- **Jadersten M et al: Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome (J Clin Oncol 2008; 26: 3607-13)**: This recent study was designed to assess the effect of Epo plus Granulocyte-colony stimulating factor (G-CSF) treatment on survival and leukemic transformation in MDS. The multinational team compared the long-term outcome of patients with MDS treated with Epo plus G-CSF (n=121) with untreated patients (n=237) with MDS using multivariate Cox regression with delayed entry, for the first time adjusting for all major prognostic variables (WHO classification, karyotype, cytopenias, level of transfusion-need, age, and sex). Results: The erythroid (Hb) response rate to Epo plus G-CSF was 39% and the median response duration 23 months. In the multivariate analysis, treatment was associated with improved overall survival (hazard ratio 0.61). No link was found between Epo and G-CSF treatment and the rate of transformation from MDS to full acute leukemia. The authors emphasize that the inherent risk of leukemic evolution in MDS makes the current investigation highly relevant, in light of the recent reports of potential negative effects of Epo treatment on outcome in patients with cancer (see below). The group concluded that "treatment of anemia in

MDS with Epo plus G-CSF may have a positive impact on outcome in patients with no or low transfusion need, while not affecting the risk of leukemic transformation".