National Veterans Affairs Monograph
Darbepoetin (Aranesp®)
February 2002

Introduction:

Majority of patients with chronic renal failure (CRF) develop normocytic normochromic anemia [1,2]. CRF patients include patients with progressive renal insufficiency, patients with chronic allograft dysfunction, and patients already on dialysis [2]. These patients develop anemia from several factors but the main cause is due to a decrease in the production of erythropoietin leading to a hormone-deficient state. CRF patients may also develop iron deficiency anemia secondary to blood loss during hemodialysis [1].

Effects of anemia in CRF patients are associated with several physiologic disorders. Cardiovascular effects include left ventricular hypertrophy- a high predictor of ischemic heart disease, decreased tissue oxygen delivery and utilization leading to angina, cardiac failure, and death [7]. Partial correction of the anemia is postulated to cause improvement in tissue oxygenation, and reduced cardiac workload. Patients on maintenance hemodialysis have a higher mortality (estimated 3.5 times higher) than the general population [8]. Although normalization of hemoglobin in this population does not lead to a regression of left ventricular dilation or hypertrophy, it may prevent its development [7]. In predialysis patients, normalization of hematocrit was found to be associated with significant regression of left ventricular hypertrophy and did not adversely affect blood pressure control or renal function.

In addition to cardiovascular effects, anemia is also responsible for chronic fatigue, loss of appetite, cognitive and physical impairments, sleeping disorders, depression and impaired immune response in the CRF patient population [2-7]. The target range of hemoglobin and hematocrit (as recommended by the National Kidney Foundation) ranges from 33% to 36% and 11g/dL to12g/dL respectively [2]. Raising hematocrit and hemoglobin levels significantly improves the quality of life and physical and psychological well-being of patients by improving energy levels, social and sexual functioning, depression, appetite and sleeping disorders [3-7].

Patients with malignant diseases such as cancer also develop anemia often characterized as anemia of chronic disease. These patients develop anemia mainly from erythroid hyperplasia of the bone marrow, slightly decreased bone marrow survival, decreased reticulosytosis, hypoferremia, and inappropriately low serum erythropoietin. Other causative factors include mucosal bleeding, nutritional deficiencies, hemolysis, tumor infiltration into the bone marrow and certain chemotherapeutic agents such as cisplatin [9]. Correction of anemia leads to reduced transfusion requirements, improved functional capacity and quality of life in patients independent of tumor response in patients either receiving or not receiving chemotherapy [9,10].

Erythropoetin alpha or rHuEPO (recombinant human erythropoietin) is currently the treatment of choice for anemia due to chronic renal failure. It is used off-label as a treatment for chronic anemia associated with cancer. rHuEPO is developed using DNA recombinant technology and has been found to be identical to endogenous erythropoietin with the same physiochemical, immunological and pharmacological properties as endogenous erythropoietin[10]. Darbepoetin, a newly developed novel erythropoeisis stimulating protein (NESP), was currently approved for treatment of anemia associated with CRI. Darbepoetin is produced in Chinese hamster ovary cells (CHO) through recombinant DNA technology much like rHuEPO. It has a half-life that is three-fold longer than erythropoietin alpha and may be dosed less frequently compared to the latter.

Pharmacology:

Erythropoietin is released by the peritubular cells in the kidneys in response to hypoxia and is the primary growth factor that stimulates erythropoiesis, the process by which red blood cells are made. Oligosaccharide chains (sialic acid residues) help stabilize this hormone and prevent its rapid removal from the system. Erythropoetin is then desialyated and cleared via galactose receptors in the liver. In patients with chronic renal failure, endogenous erythropoietin is not produced sufficient enough to meet the body's demands. This results in anemia. Cancer patients on the other hand, develop anemia from different factors as mentioned previously. Erythropoietin binds to the erythropoietin receptor on erythroid progenitor cells stimulating their proliferation and differentiation into mature red blood cells. The hormone also inhibits the apoptosis of red blood cells thereby prolonging the life of erythrocytes [(1-10)].

Darbepoetin is a 165-amino acid protein that stimulates erythropoiesis through the same mechanism as endogenous erythropoietin. Darbepoetin contains five N-linked oligosaccharide chains whereas erythropoietin alfa contains only three of such chains. The two additional sialic acid residues on Darbepoetin increases the molecular weight and prolongs its half-life by constantly binding to the erythropoietin receptor leading to more frequent erythropoiesis [(1-10)].

Pharmacokinetics:

In Chronic Renal Failure Patients:

	Darbepoetin		Erythropoietin	
Route of Administration	IV	SC	IV	SC
Distribution	60 mL/kg	NA	NA	NA
Metabolism	NA	NA	Unknown	Unknown
Elimination	1.6 ± 0.3 mL/h/kg	4.0 ±0.3 mL/h/kg	NA	NA
Half-life	21 hrs	49 hrs	4-13 hrs	NA
Bioavailability	100%	30-50%	100%	NA
Protein Binding	NA	NA	NA	NA
Time to peak	NA	24-72 hrs	NA	5-24 hrs

*Difference in Pharmacokinetic Parameters between dialysis patients and predialysis patients were not specified.

In Oncology Patients‡:

	Darbepoetin		Erythropoietin	
Route of Administration	IV	SC	IV	SC
Distribution	NA	NA	NA	NA
Metabolism	NA	NA	Unknown	Unknown
Elimination	NA	3.70	NA	NA
Half-life	13.1-25.3 hours†	32.6-49.7 hours	4-13 hours	16.3-25 hours
Bioavailability	NA	NA	NA	NA
Protein Binding	NA	NA	NA	NA
Time to peak	NA	86.1 hours	NA	NA

†IV Data was based on CRF patients undergoing dialysis.

‡ Data refers to oncology patients receiving chemotherapy.

FDA Approved Indications and Off-label Uses

Darbepoetin is indicated for the treatment of anemia associated with chronic renal failure in patients either on or not on dialysis. It may be used off-label for the treatment of chronic anemia associated with cancer.

Current VA National Formulary Status

Non-formulary status

Dosage and Administration

Darbepoetin is approved as a single weekly injection IV or SC. Doses are adjusted based on hemoglobin and hematocrit levels. The time to response varies from 2-6 weeks due to the time required to stimulate erythropoeisis and red blood cell half-life. In addition, predialysis patients may also be more responsive to Darbepoetin and may require lower maintenance doses than patients already established on dialysis. However hemoglobin levels should be monitored weekly until the patient has been stabilized with target hemoglobin levels of ≤12g/dL in all patients.

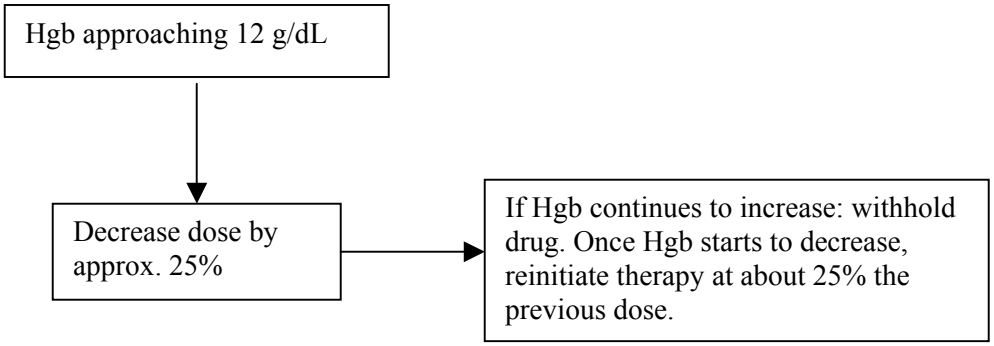
Several factors may be attributed to the lack of response or failure to maintain a hemoglobin level within the recommended dosing range. These include folic acid or Vitamin B_{12} deficiencies, infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis. Safety and efficacy of patients with underlying hematologic diseases has not been established.

- Starting Dose:
  - For Correction of Anemia: 0.45 mcg/kg body weight IV or SC once weekly.
  - For Conversion from Epoetin Alpha (r-HuEPO) to Darbepoetin (NESP):
    - Doses should be titrated to maintain target hemoglobin
    - Darbepoetin should be administered less frequently.

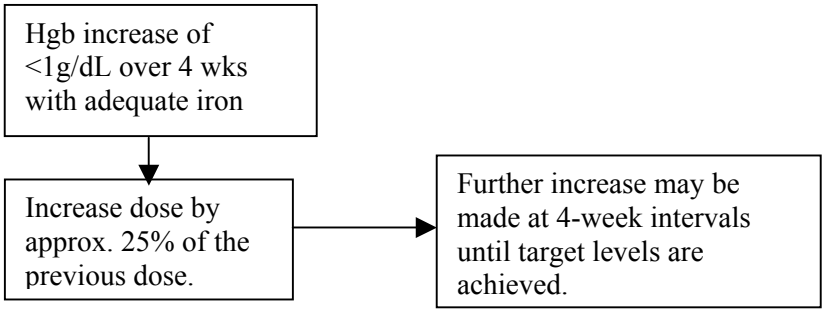
- Dose Adjustment:

  Due to patients' response variability, doses should be individualized to achieve and maintain a target hemoglobin level of ≤12 g/dL. Hemoglobin levels should be measured weekly for at least 4 weeks after every dose adjustment to ensure that levels have stabilized. After such time, hemoglobin and hematocrit levels should be monitored at regular intervals.

  A. Hemoglobin approaching target levels:



B. Hemoglobin **not** approaching target levels:



- Maintenance Dose:
  Doses may be adjusted based on above algorithm to maintain a target hemoglobin of ≤12 g/dL.

- Preparation/Administration/Storage:
  - Do not shake bottle. This may denature the protein.
  - Do not use parenteral products that contain particulate matter or are discolored.
  - Darbepoetin should not be diluted.
  - Do not coadminister Darbepoetin in other drug solutions.
  - Darbepoetin is packaged in single-use vials with no preservatives. Discard any unused portions. Do not pool unused portions.
  - Protect from light.
  - Store at 2-8° C (36 - 46° F). Do not freeze.

Dosage Forms Available:

Darbepoetin is available in single-dose vials of 25, 40, 60, 100 or 200 mcg. Two formulations containing different excipients are as follows:

- Polysorbate solution
  This contains the following substances:
  - 0.05 mg of polysorbate 80
  - 2.12 mg of sodium phosphate monobasic monohydrate
  - 0.66 mg sodium phosphate dibasic anhydrous
  - 8.18 mg sodium chloride in Water for Injection, USP with a pH 6.0± 0.2.
- Albumin Solution
  This contains the following substances:
  - 2.5 mg (human) albumin
  - 2.23 mg sodium phosphate monobasic monohydrate
  - 0.53 mg sodium phosphate dibasic anhydrous
  - 8.18 mg sodium chloride in Water for Injection, USP with a pH 6.0± 0.3.

Adverse Effects (Safety Data):

The most *severe* adverse reactions associated with Darbepoetin were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmias. The most *common* adverse reactions were infection (includes sepsis, bacteremia, pneumonia, peritonitis, and abscess), hypertension, hypotension, myalgia, headache, and diarrhea. The most frequently reported adverse reactions resulting in clinical intervention i.e. discontinuation or adjustment of dose, were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

Warnings:

Cardiovascular Events:

The incidence of cardiovascular events, including death, increases with higher hemoglobin and hematocrit levels. Increases in hemoglobin greater than 12 g/dL during a two week period were associated with an increase in incidence for cardiac arrest, neurologic events, exacerbation of heart failure and hypertension, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload and edema. Patients with existing cardiovascular problems should be monitored carefully to maintain a hemoglobin level not to exceed 12 g/dL.

Hypertension:

Darbepoetin is contraindicated in patients with uncontrolled hypertension. It is recommended to first control the patient's blood pressure first before initiating therapy with Darbepoetin. Approximately 40% of patients who received Darbepoetin required initiation or adjustment of antihypertensive medications. Such patients with poorly controlled blood pressure should be monitored closely.

Seizures:

Patients with CRF who participated in clinical trials of Darbepoetin and rHuEPO have experienced seizures. It is recommended that the patient be closely monitored for neurologic symptoms during the first several months. A decrease in Darbepoetin doses is further recommended if the increase in hemoglobin levels exceeds 1.0 g/dL within a 2 week period.

Thrombotic Events:

Vascular thrombotic events such as vascular access thrombosis, venous thrombosis, and pulmonary emboli have occurred at an annual rate of 0.22 events per patient year in hemodialysis patients during Darbepoetin therapy. These results were similar to rHuEPO in these trials.

Albumin:

Darbepoetin formulated with albumin carries very minimal risk of viral transmission. A theoretical risk of Creutzfeld-Jakob disease is considered extremely rare. No reports of either incidence have yet been reported.

Immunogenicity:

Although the incidence of developing antibodies to Darbepoetin has not been established, the protein content of the moiety still contains a potential for developing immunogenicity. Assays performed in the 1534 patients who participated in the Darbepoetin trials were not detected. However, assay sensitivity and specificity may not be adequate to detect lower titers of antibodies. Erythrocyte aplasia associated with antibodies to erythropoietin have been reported on rare occasions during clinical trials with rHuEPO. Due to the similarity of Darbepoetin to rHuEPO, a theoretical possibility exists. Other rare reports of potentially serious allergic reactions to Darbepoetin include skin rash and urticaria. These symptoms have reoccurred when Darbepoetin was rechallenged. Therefore, therapy with Darbepoetin must be discontinued immediately and appropriate therapy administered should an anaphylactic reaction occur.

Table 1. Adverse effects related to Darbepoetin and Erythropoetin Alpha [11,12]

	Darbepoetin	Epoetin Alpha
Pain at injection site	7%	NA
Body as a whole		
Peripheral Edema	11%	9%
Fatigue	9%	9%
Death	7%	0%
Asthenia	5%	7%
Cardiovascular		
Hypertension	23%	24%
Hypotension	22%	NA
Cardiac Arrhythmias/ Cardiac Arrest	10%	NA
Angina/ Cardiac Chest Pain	8%	7%
Thrombosis Vascular Access	8%	7%
Congestive Heart Failure	6%	NA
CNS/PNS		
Headache	16%	16%
Dizziness	8%	7%
Gastrointestinal		
Diarrhea	16%	9%
Vomiting	15%	8%
Nausea	14%	11%
Musculoskeletal		
Arthralgia	11%	11%
Resistance Mechanism		
Infection	27%	NA
Respiratory		
Upper Respiratory Infection	14%	NA
Dyspnea	12%	NA
Cough	10%	NA
Bronchitis	6%	NA
Skin and Appendages		
Pruritis	8%	7%

*Data from package insert of each separate drug

Table 2. Incidence of other Significant Events[11,12]

Event	Darbepoetin	Epoetin Alpha
Acute Myocardial Infarction	2%	0.4%
Seizure	1%	1.1%
Stroke	1%	0.4%
Transient Ischemic Attack	1%	0.4%

*Data from package insert of each separate drug

Contraindications:

Darbepoetin is contraindicated in patients with uncontrolled hypertension and/or known hypersensitivity to the active ingredients or excipients of the drug.

Drug Interactions:

No formal drug interaction studies of Darbepoetin have been performed.

Efficacy Measures:

To ensure patients are responding adequately to therapy, various parameters need to be monitored regularly. These include the following:

- Hemoglobin,
- Hematocrit
- Reticulocyte counts
- Need for transfusions
- Blood Pressure
- Iron parameters:
  - serum iron
  - total iron binding capacity
  - Percent transferring saturation
  - serum ferritin

Clinical Trials:

A. Review of data in predialysis patients

Citation	Locatelli F, Olivares J, walker R, Wilkie M, Jenkins B, Dewey C, Gray SJ, on behalf of the European/Australian NESP 980202 Study Group. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. Kidney International 2001; 60:741-747 [(14)].
Study Goals	To determine whether NESP is effective for the treatment of anemia associated with CRI patients not yet on dialysis.
Methods	• Study Design: ➢ Multicenter, randomized, open-label ➢ Patients were randomized to receive NESP or rHuEPO in 3:1 ratio. ➢ NESP was administered SC at a starting dose of 0.45 µg/kg once weekly and rHuEPO SC 50 U/kg twice weekly. ➢ Doses were adjusted by 25% to maintain a Hgb level of 11.0 – 13.0 g/dL. ➢ Length of study: 24 weeks • Data Analysis: ➢ Per-protocol analysis of efficacy ➢ Descriptive statistics were used to determine differences between groups. ➢ Study had enough power (n=166).
Criteria	• Inclusion criteria ➢ 18 years of age or older diagnosed with CRI ➢ rHuEPO naïve within 12 weeks of first trial dose ➢ Hgb <11.0 g/dL ➢ Serum Vit. B_{12} or folate levels above the upper limit of normal. ➢ Serum ferritin levels ≥100 µg/L. ➢ CrCl <30 mL/min. ➢ Patients had not have blood transfusions or androgen therapy within 8 wks of the first planned trial dose. • Exclusion Criteria: ➢ Uncontrolled hypertension (DBP > 100 mmHg) ➢ CHF (NYHA Class III or IV) ➢ Hematologic disorders that could cause anemia ➢ Systemic inflammation or inflammatory disease or other disorders that could interfere with the response of NESP or rHuEPO.

Results:

Patient Demographics:

	NESP (n=129)	rHuEPO (n=37)
Sex		
Men	70 (54%)	19 (51%)
Women	59 (46%)	18 (49%)
Race		
Asian	3 (2%)	1 (3%)
Black	3 (2%)	0 (0%)
White	123 (95%)	36 (97%)
Mean Age in years (SD)	60.4 (15.0)	60.6 (15.7)
Primary Cause of renal failure		
Diabetes	32 (25%)	8 (22%)
Hypertension	15 (12%)	1 (3%)
Glomerulonephritis	24 (19%)	10 (27%)
Polycystic kidney disease	6 (5%)	2 (5%)
Other urologic	5 (4%)	0 (0%)
Other	32 (25%)	11 (30%)
Unknown	15 (12%)	5 (14%)
Hemoglobin (g/dL)	9.3 (1.0)	9.8 (1.1)
Serum Ferritin (mcg/L)	168 (30-1420)	151 (31-899)
Creatinine Clearance (mL/min)	15.7 (6.6)	15.7 (6.4)

	NESP	rHuEPO
Hgb response after 24 week period	93%	92%
Median time to achieve a hemoglobin response	7 weeks	7 weeks
Increase in mean Hgb concentration after initial 4 weeks	1.38 g/dL	1.40 g/dL
Patients who did not require dose adjustment	35%	32%
Weekly dose at the time of Hgb response	0.46 µg/kg	100 U/kg
Median Dose at week 24	0.34 µg/kg	56.9 U/kg
% of patients with dose reductions to levels below starting dose at week 24	68%	70%
Patients who required transfusion	5%	8%
Patients who experienced at least one adverse effect	83%	65%
Incidence of hypertension	32%	22%
Incidence of peripheral edema	13%	11%
Reported deaths	4%	3%
Patients who received IV iron	77%	81%
Patients who received oral iron	52%	51%

Efficacy Measure	A hemoglobin response was defined as an increase of ≥ to 1.0 g/dL from baseline and a concentration ≥11.0 g/dL
Critique	• Strengths ➢ Patients were randomized in the study. ➢ Study methods and results were clearly stated. ➢ Comparison between the two drugs was done extensively. • Limitations ➢ The study was sponsored by Amgen. ➢ An open-label design could encourage investigators and patients to favor EPO. ➢ Different dosing frequency between the two drugs does not allow for equal basis of comparison. ➢ Exclusion criteria for uncontrolled hypertension defined by diastolic blood pressure was not appropriate. ➢ Efficacy trial was not designed to compare superiority between the two drugs. ➢ IV and SC data were not separated. ➢ Unequal number of subjects and baseline characteristics between the two groups.
Conclusion	• NESP safely and effectively corrects and maintains hemoglobin concentrations at a reduced dosing frequency relative to rHuEPO in patients with CRI.

Citation (Abstract)	M Suranyi, Walker R, Jackson L, Feaster J, Mc-Dermott, Vitak A. Novel Erythropoiesis Stimulating Protein (NESP) Administered Once Every Week Corrects Anemia in Patients with Chronic Renal Insufficiency (CRI) [15].
Study Goals	To evaluate the effectiveness of fixed doses of NESP administered subcutaneously (SC) once every other week for the treatment of patients with CRI.
Methods	• Patients received a starting dose of 0.75 µg/kg of NESP subcutaneous once every other week. • Calculated NESP dose was rounded to the nearest fixed dose of the eleven dose strengths used in the study (i.e. 10, 15, 20, 30, 40, 50, 60, 80, 100, 130 and 150 µg). • Doses were adjusted either a step up or down the list of fixed doses to achieve a ≥1.0 g/dL but <3.0 g/dL rise in Hgb. • Doses were also adjusted to maintain a Hgb concentration of 11.0 to 13.0 g/dL. • After target levels were achieved, doses were adjusted based on two consecutive out of range Hgb concentrations. • If Hgb was >14.0 g/dL, NESP was withheld and restarted at the next lower dose when Hgb falls back to < 13.0 g/dL. • Primary Endpoints of the study: ➢ Proportion of patients achieving a Hgb response (defined as two consecutive Hgb concentrations within the target range of 11.0 to 13.0 g/dL. • Secondary Endpoints: ➢ Dose of NESP at the time of Hgb response. ➢ Time to reach Hgb response. ➢ Change in Hgb level from baseline over 4 week intervals. ➢ Safety was evaluated by monitoring adverse events and rate of rise in Hgb. • Duration of the study: 10 weeks.

Criteria	• Inclusion Criteria ➢ ≥18 years of age ➢ Diagnosis of CRI (not yet on dialysis) ➢ CrCl <30 mL/min (based on Cockcroft-Gault formula) ➢ Hemoglobin <11.0 g/dL ➢ No r-HuEPO therapy within 12 weeks ➢ Iron replete (transferring saturation ≥ 20% or serum ferritin ≥100 µg/dL) ➢ No red blood cell transfusion or androgen therapy within 8 weeks of study drug administration.

Results

Patient Demographic and Baseline Characteristics

	NESP (n= 23)
Sex	
Men	11 (48%)
Women	12 (52%)
Race	
Caucasian	16 (70%)
Asian	5 (22%)
Other	2 (8%)
Age (years)	67 (18-85)
Weight (kg)	66.6 +/- 14
Hemoglobin (g/dL)	9.83 +/- 0.73
Transferrin Saturation (%)	26 (18.0 - 84.0)
Serum Ferritin (mcg/L)	406.4 (130.6 - 1200.0)
Creatinine Clearance (mL/min)	16.2 (10-30)
Primary Cause of Renal Insufficiency	
Glomerulonephritis	6 (26%)
Diabetes	4 (17%)
Hypertension	2 (9%)
Other	10 (43%)
Unknown	1 (4%)

Efficacy Results:

- Median time to achieve a Hgb response was 6 weeks (range: 0-17 weeks).
- Mean increase in Hgb over the initial 4 weeks of treatment was 1.37 g/dL (± 0.81).

	NESP
Number of patients achieving a Hgb Response	22
Proportion Achieving Hgb Response (95% CI)	96%
Median Fixed Dose (mcg/QOW)	50
Mean Dose (mcg/QOW)	56
Dose Adjustment	
Patients requiring no dose change	13 (57%)
Patients requiring a dose change	10 (44%)

Safety Results:

- None of the patients experienced an increase of >3.0 g/dL in their Hgb levels over 4 weeks.
- 11 patients (48%) had Hgb levels >14 g/dL and had the drug withheld. 7 of these 11 patients' Hgb levels returned to <13 g/dL within a median time of 4 weeks (range: 2-6 wks).

		Incidence of Adverse Events Occurring in ≥ 5% of the Patients	NESP (n = 23)
		Upper Respiratory Infection	5 (42%)
		Peripheral Edema	2 (9%)
		Headache	2 (9%)
		Urinary Tract Infection	2 (9%)
		Dyspnea	2 (9%)
		Pruritus	2 (9%)
Conclusions	• NESP administered in fixed doses once every other week is equally safe and effective for the treatment of anemia in patients with chronic renal insufficiency. • Extending the dosing interval may simplify the management of CRI patients.		
Critique	• Strengths ➢ Dose and drug administration were individualized to the patients. • Limitations ➢ Not enough patients (n=23) ➢ No control group. ➢ Study design was not specified. ➢ Abstract form offers little information. ➢ Duration of the study (10 weeks) is not long enough to evaluate safety of the drug.		

Review of data in dialysis patients

Citation (Abstract)	Vanrenterghem Y, Barany P, Mann J, on behalf of the European/Australian NESP 970200 Study Group. Novel Erythropoiesis Stimulating Protein (NESP) Maintains Hemoglobin (Hgb) in ESRD Patients When Administered Once Weekly or Once Every Other Week [16].
Study Goals	To determine if NESP is safe and effective in maintaining Hgb when administered at a reduced frequency compared to EPO.
Methods	• Study Design ➢ Randomized controlled study ➢ Before randomization, patients were receiving EPO IV or SC once a week (n= 101), twice a week (n=177) and thrice a week (n=244). ➢ Patients were randomized (1:2) to continue EPO at the same dose, frequency, and route or receive NESP at the equivalent dose given once a week to once every other week with the same route of administration. ➢ NESP and EPO doses were titrated to maintain a Hgb level between 9-13 g/dL and within a -1.0 to +1.5 deviation from baseline Hgb for up to 52 weeks. ➢ Duration of the study: 52 weeks ➢ Evaluation period: 24 – 32 weeks • Data Analysis ➢ Mean ± SD

Criteria	• Inclusion Criteria ➢ Patients on hemodialysis or peritoneal dialysis ➢ Hemoglobin levels between 9.5 to 12.5 g/dL • Efficacy Measure ➢ Primary endpoint was a change in Hgb levels between baseline and at the end of the study period (wks 24-32).
Results	• Mean change in Hgb level between baseline and evaluation was -0.03 (± 0.80) g/dL for NESP and -0.06 (± 0.87) g/dL for EPO. (P>0.05) • 97% of NESP patients assigned to once weekly dosing and 95% NESP patients on once every other week dosing were successfully managed at these reduced dose frequencies • Maintenance of Hgb level, weekly dose requirement and frequency of dose changes in NESP and EPO groups were similar regardless of route of administration. • Adverse events, withdrawals from the study and deaths were similar between the two treatment groups. • No antibodies to NESP or EPO were detected.
Conclusions	• NESP maintains Hgb levels as effectively as EPO, providing benefits for both patients and health care providers through less frequent dosing.
Critique	• Strengths ➢ Randomized, controlled study allows more equal basis for comparison. ➢ Greater number of patients. • Limitations ➢ The study was sponsored by Amgen. ➢ Abstract form allows little information. ➢ Detailed information of how the study was done could not be presented in the abstract. ➢ Unequal number of patients in each arm of the study. ➢ Equivalent dose between Darbepoetin and rHuEPO was not stated. ➢ Dose of both Darbepoetin and rHuEPO throughout the abstract was not mentioned. ➢ The study does not address the comparison with the same dosing frequency between the NESP and EPO. ➢ Resulting data from both routes of administration (IV or SC) as well as routes of dialysis (peritoneal vs hemodialysis) were not separated.

Citation (Abstract)	Nissenson AR, Swan SK, Lindberg JS, Soroka SD, McDermott-Vitak AD, Wang C, Picarello N, Beatey R. Novel Erythropoiesis Stimulating Protein (NESP) Safely Maintains Hemoglobin Concentration Levels in Hemodialysis Patients as Effectively as R-HuEPO when Administered Once Weekly [17].
Study Goals	To determine is NESP is safe and effective in maintaining Hgb when administered at a reduced frequency compared with r-HuEPO
Methods	• Double-blind randomized study comparing IV NESP and rHuEPO • 507 patients were randomized (1:2) to receive IV NESP once weekly and two placebo twice weekly or IV rHuEPO thrice weekly. • Doses of both treatment groups were adjusted to maintain a Hgb level within -1.0 to +1.5 g/dL of their baseline levels and between 9.0 to 13.0 g/dL during

	the study. • Duration of the study: 28 weeks • Primary endpoint of the study: Change in Hgb levels between the baseline and evaluation period.
Criteria	• None stated
Results	• Mean change from baseline Hgb and upon evaluation was 0.16 (± 0.97 g/dL) for NESP group and 0.0 (± 1.0 g/dL) in the rHuEPO group. • Difference in mean change from baseline Hgb concentration during the evaluation period was 0.16 g/dL (95% CI: -0.06, 0.38). • Percentage of patients with unstable Hgb concentrations (35% NESP, 38% EPO) and frequency of dose changes were similar between the treatment groups. • Adverse events, deaths, and withdrawals were similar between the two groups
Conclusions	NESP maintains Hgb as safely and effectively as r-HuEPO while providing the benefit for both patients and healthcare providers through less frequent dosing.
Critique	• Strengths ➢ Double-blind and randomized study. • Limitations ➢ Limited information from the abstract form. ➢ IV data only. ➢ Equivalent dose between Darbepoetin and rHuEPO was not stated ➢ Dose of both Darbepoetin and rHuEPO throughout the abstract was not mentioned.

Citation (Abstract)	Graf H, Lacombe JL, Braun J, Gomes da Costa AA, and the European/ Australian NESP 980140/194 Study Group. Novel Erythropoiesis Stimulating Protein (NESP) Effectively Maintains Hemoglobin (Hgb) When Administered at a Reduced Dose Frequency Compared with Recombinant Human Erythropoietin (r-HuEPO) in ESRD Patients [18].
Study Goals	To determine if NESP is safe and effective for maintaining Hgb then administered at a reduced frequency compared with r-HuEPO
Methods	• Study Design ➢ 703 patients on hemodialysis and peritoneal dialysis with baseline Hgb between 9.5 – 12.5 g/dL were switched from r-HuEPO to NESP with the same route of administration at an equivalent dose to r-HuEPO (200 U r-HuEPO = 1 µg NESP. ➢ Patients receiving once a week of r-HuEPO were switched to once every other week of NESP. ➢ Patients receiving two to three times a week of r-HuEPO were switched to once a week of NESP. ➢ NESP dose was titrated to maintain Hgb levels between 9.0 – 13.0 g/dL.
Criteria	None stated
Results	• Mean change in Hgb levels from baseline to week 36 was -0.08 g/dL (95% CI, -0.29, -0.12). • Median weekly dose of NESP on study was equivalent to the weekly dose of r-HuEPO at study enrollment.

	• 96% of NESP patients were managed at a reduced dose frequency with 89% on a dosing of once every other week. • There is no evidence of dose- or time-dependence with chronic SC dosing, or serum accumulation of NESP over time. • Adverse event profile of NESP was similar between that associated with r-HuEPO therapy.
Conclusions	NESP safely and effectively maintain Hgb in chronic renal failure patients when switched from rHuEPO to NESP. Less frequent dosing with NESP may confer a clinical advantage for both patients and healthcare providers.
Critique	• Strengths ➢ Large number of patients. ➢ Study assessed result for a longer period of time (36 weeks) • Limitations ➢ Open-label study ➢ Equivalent dose between Darbepoetin and rHuEPO was not stated ➢ Dose of both Darbepoetin and rHuEPO throughout the abstract was not mentioned. ➢ Data from both route of dialysis were not separated. ➢ Number of patients receiving NESP IV or SC were not mentioned.

Citation (Poster)	Vanrenterghem Y, Jadoul M, Foret M, Walker R. Aranesp (Darbepoetin Alfa) Administered at a Reduced Frequencies (once every three weeks and once every four weeks) by the Subcutaneous or Intravenous Route Maintains Hemoglobin levels in Dialysis Patients [19].
Study Goals	• To evaluate the efficacy of subcutaneous (SC) and intravenous (IV) Aranesp administered at frequencies of once every 3 weeks and once every four weeks in patients with chronic kidney disease (CKD) on dialysis. • To evaluate the safety and tolerability of these Aranesp dosing regimens.
Methods	• Study Design ➢ Multi-center, Open label study. ➢ Aranesp starting dose for once every three-week administration was three times the average weekly dose at the time of enrollment. Starting dose for the once every four week administration was four times the average weekly dose during the once every three week evaluation period. ➢ Patients previously receiving once every other week of Aranesp were switched to once every three weeks for a period of 15 weeks. ➢ After 15 weeks, dose adjustments were made to maintain a hemoglobin target range of -1.0 to +1.5 g/dL of their mean baseline level and between 10.0 to 13.0 g/dL. ➢ Dose adjustments were made when two consecutive hemoglobin values were outside the patient's target range. ➢ Dose adjustments were made in 25% to 50% increments. ➢ An evaluation period of 4 weeks was allotted for dose adjustments. ➢ At the end of the 4 week evaluation period, dosing regimen was switched to once every 4 weeks. ➢ Patients were given Aranesp at once every 4 week for the duration of the 16 weeks titration period, after which was followed by a 4 week evaluation period for dose adjustments.

<table>
<tr><td></td><td>

The protocol required the dose interval to be decreased if the Aranesp dose increased by 100%. The protocol required the dose interval to be increased if the Aranesp dose decreased by 75% of the baseline value.
If the hemoglobin increased to >14.0 g/dL, Aranesp was withheld until the hemoglobin decreased to 12.0 g/dL. Aranesp was then restarted at 50% of the dose administered prior to withholding the drug.

• Data Analysis:

95% Confidence Interval was used to determine the statistical significance of the results.

</td></tr>
<tr><td>Criteria</td><td>
• Inclusion Criteria

≥18 years of age
Currently receiving stable Aranesp therapy administered SC or IV once every other week in a long-term treatment protocol.
Mean hemoglobin concentration between 10.0g/dL and 13.0 g/dL.
Iron replete (serum ferritin ≥ 100µg/dL)

• Exclusion Criteria

RBC transfusion within 12 weeks prior to screening period.

</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th colspan="3">Patient Demographics and Baseline Characteristics</th></tr>
<tr><td></td><td>Every 3 Wks (n=34)</td><td>Every 4 Wks (n=28)</td></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>Male</td><td>21 (61%)</td><td>19 (69%)</td></tr>
<tr><td>Female</td><td>13 (39%)</td><td>9 (31%)</td></tr>
<tr><td>Race</td><td></td><td></td></tr>
<tr><td>White</td><td>28 (82%)</td><td>24 (85%)</td></tr>
<tr><td>Black</td><td>3 (9%)</td><td>2 (7.5%)</td></tr>
<tr><td>Other</td><td>3 (9%)</td><td>2 (7.5%)</td></tr>
<tr><td>Age (years)</td><td>64.1± 17</td><td>66.4 ± 17</td></tr>
<tr><td>Mean Baseline Hgb (g/dL)</td><td>11.3 ± 0.7</td><td>11.4 ± 0.7</td></tr>
<tr><td>Dialysis Modality</td><td></td><td></td></tr>
<tr><td>Hemodialysis</td><td>33 (97%)</td><td>27 (96%)</td></tr>
<tr><td>Peritoneal dialysis</td><td>1 (3%)</td><td>1 (4%)</td></tr>
<tr><td>Route of administration</td><td></td><td></td></tr>
<tr><td>IV</td><td>15 (44%)</td><td>11 (39%)</td></tr>
<tr><td>SC</td><td>19 (54%)</td><td>17 (61%)</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>
<u>Study Endpoints</u>
• Primary

Percentage of patients who successfully maintained their mean hemoglobin ≥10 g/dL with reduced dosing frequencies during the evaluation period.

• Secondary
</td></tr>
</table>

- Changes in mean hemoglobin concentration over time.
- Change in average weekly dose of Aranesp over time.
- Safety and tolerability of Aranesp.

Efficacy and Safety Results

- 34 patients started Aranesp at a dosing frequency of once every three week. 32 patients completed the evaluation period. 28 of the 32 successfully maintained their target hemoglobin concentration.
- 28 patients started Aranesp at once every four weeks. 26 reached the evaluation period while only 22 patients completed it. 19 of the 22 patients successfully maintained their target hemoglobin.
- 2 patients in the once every three week and 3 patients in the once every four week dosing frequency increased their dose per protocol. These patients were able to maintain their target hemoglobin successfully with the increased dosing frequency.
- Percentage of successful patients maintaining target hemoglobin

Every three weeks	
All (N= 32)	87.5% 95% CI: (71%, 96.5%)
IV (N=14)	78.6%
SC (N=18)	94.4%
Every four weeks	
All (N=22)	86.4% 95% CI: (65%, 97%)
IV (N=9)	100%
SC (N=13)	76.9%

- Mean change in Hgb (g/dL) between baseline and evaluation periods

	Baseline	Evaluation	Changes
	(Mean ± SD)	(Mean ± SD)	(Mean [95% CI])
Once every 3 wks			
All (N=28)	11.4 ± 0.7	11.3 ± 0.9	-0.08 (-0.39, 0.24)
IV (N=11)	11.2 ± 0.7	11.1 ± 1.1	-0.13 (-0.57, 0.31)
SC (N= 17)	11.5 ± 0.7	11.4 ± 0.9	-0.04 (-0.51, 0.43)
Once every 4 wks			
All (N=19)	11.5 ± 0.8	11.2 ± 0.6	-0.27 (-0.59, 0.04)
IV (N=9)	11.2 ± 0.8	11.1 ± 0.6	-0.08 (-0.44, 0.28)
SC (N=10)	11.7 ± 0.8	11.3 ± 0.7	-0.45 (-1.00, 0.11)

- Percent changes in dose between baseline and evaluation periods

	Percent Change (Mean [95% CI]
Once every 3 wks	
All (N= 28)	13% (0%, 28%)
IV (N= 11)	23% (-9%, 67%)
SC (N= 17)	8% (-4%, 21%)
Once every 4 wks	
All (N=19)	34% (0%, 80%)
IV (N=9)	57% (-11%, 176%)
SC (N=10)	16% (-17%, 63%)

	• All adverse events were consistent as expected for patients with chronic kidney disease. • Hypertension was the only adverse event related to the treatment. • One case of death was reported which (in the investigator's opinion) was not related to Aranesp. • There were no reports of withdrawals due to adverse events. <u>Drop-outs/ Unsuccessful cases</u> • 2 of the 32 patients who started on the once every three week frequency dosing did not complete the evaluation period. These patients were unsuccessful at maintaining this dosing frequency due to a >100% increase in dose (per protocol). • 2 of the 28 patients who were started on the once every four week dosing frequency were terminated prior to the evaluation period. One was lost to follow-up, the other due to kidney transplant. • 3 of the 26 patients who reached the evaluation period were unsuccessful at maintaining every four week dosing due to >100% increase in dose (per protocol).
Conclusion	• Aranesp administered at reduced frequencies of once every three weeks and once every four weeks maintains hemoglobin safely and effectively in dialysis patients. • Reducing the dosing frequency to once every four weeks will further simplify management of anemia in chronic kidney diseases for both patients and health care providers.
Critique	• Strength ➢ Study design similar to a cross-over study. • Limitations ➢ Data between the two modes of dialysis were not separated. ➢ Absence of rHuEPO or placebo group as a control group for comparison of efficacy. ➢ Patients were given higher doses did not compared to the approved starting dose of 0.45 µg/kg once weekly. ➢ Rationale for dose determination for once every three weeks and once every four weeks was not justified. ➢ Increased incidence of hypertension in patients receiving NESP was not discussed.

Review of data in cancer patients:

A. Patients not currently receiving chemotherapy

Citation	Smith RE, Jaiyesmi IA, Meza LA, Tchkmedyian NS, Chan D, Griffith H, Brosman S, Bukowski R, Murdock M, Rarick M, Saven A, Colowick AB, Gayko U, Glaspy J. Novel Erythropoiesis stimulating protein (NESP) for the treatment of anemia of chronic disease associated with cancer. British Journal of Cancer 2001 Supplement 1 (84): 24-30. [20]
Study	• To assess the safety of NESP when administered subcutaneously once a week to

Goals	patients with chronic anemia not receiving chemotherapy. • To determine the clinically effective doses of NESP and to begin to characterize a dose response relationship. • To assess the effects of NESP in the health-related quality of life in these patients.
Methods	• Study Design ➢ Open-label, dose-escalation, dose finding study ➢ NESP given subcutaneously once a week in doses of 0.5, 1.0, 2.25, or 4.5 µg/kg/week. ➢ Doses were given at the same day of the week for 12 weeks. ➢ Weekly CBCs, blood chemistry, serum iron, iron-binding capacity, ferritin and transferrin saturation were drawn. ➢ Antibody testing was done monthly. ➢ Patients were allowed to receive RBC transfusions when indicated and transfusions were given to patients when their Hgb fell below ≤8.0 g/dL ➢ A follow-up period (with the same standard tests and observations) was started immediately after the last dose of the study was given, and continued for 4 weeks. ➢ Health-related quality of life questions with the FACT-G and FACT-Anemia scale were completed by the patients every 2 weeks throughout the 16-week study. • Dose Adjustments ➢ NESP was decreased to the next lower dose if the patient's hemoglobin was above 13.0 g/dL. ➢ NESP was withheld if the Hgb value was >15.0 g/dL for men or >14.0 g/dL for women. ➢ Only one dose reduction per patient could be made.
Criteria	• Inclusion Criteria ➢ Patients must be at least 18 years old ➢ Diagnosis of non-myeloid malignancy and anemia ➢ Not currently receiving or planning to receive cytotoxic chemotherapy or external beam radiotherapy within 16 week of the study. ➢ Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 ➢ Platelet count ≥50× 10^9/L ➢ Anemia predominantly due to cancer or previous treatment with chemotherapy or radiotherapy. ➢ Adequate stores of iron ➢ Adequate renal and liver function • Exclusion Criteria ➢ Primary or metastatic malignancy involving the central nervous system ➢ Active bleeding or hemodialysis ➢ Received red blood cell transfusions within 16 days of enrollment in the study. ➢ Unstable medical condition ➢ Presence of a primary hematologic disorder that could cause anemia.

Results

Patient Baseline Characteristics	NESP (mcg/kg/week)				
	0.5 mcg/kg/week	1.0 mcg/kg/week	2.25 mcg/kg/week	4.5 mcg/kg/week	All NESP
	n=6	n=33	n=18	n=30	n=87
Age, years					
Mean (SD)	53.2 (8.6)	69.7 (13.5)	71.1 (9.5)	74.0 (9.1)	70.3 (12.0)
Sex, n (%)					
Female	5 (83.3%)	14 (42.4%)	8 (44.4%)	12 (40.0%)	39 (44.8%)
Male	1 (16.7%)	19 (57.6%)	10 (55.6%)	18 (6.0%)	48 (55.2%)
Primary Site of disease, n(%)					
Breast	4 (66.7%)	9 (27.3%)	4 (22.2%)	7 (23.3%)	24 (27.6%)
Lung		1 (3.0%)	2 (11.1%)	2 (6.7%)	5 (5.7%)
Gastrointestinal		2 (6.1%)	2 (11.1%)	4 (13.3%)	8 (9.2%)
Gynecologic		1 (3.0%)		1 (3.3%)	2 (2.3%)
Genitourinary	1 (16.7%)	11 (33.3%)	4 (22.2%)	12 (40.0%)	28 (32.2%)
Other solid tumor	1 (16.7%)	3 (9.1%)		1 (3.3%)	5 (5.7%)
Lymphoid malignancy		6 (18.2%)	6 (33.3%)	3 (10.0%)	15 (17.2%)
ECOG, n (%)					
0	2 (33.3%)	11 (33.3%)	8 (44.4%)	7 (23.3%)	28 (32.3%)
1	3 (50.0%)	17 (51.5%)	8 (44.4%)	18 (60.0%)	46 (52.9%)
2	1 (16.7%)	5 (15.2%)	2 (11.1%)	5 (16.7%)	13 (14.9%)
Hgb, g/dL					
Mean (SD)	9.60 (1.53)	9.80 (0.91)	9.80 (1.14)	10.05 (0.94%)	9.87 (1.01)
Median	9.65	9.9	10.05	10.45	10.1
Min, Max	7.4, 11.4	7.3, 11.0	7.4, 11.2	7.8, 11.4	7.3, 11.4
Endogenous EPO, mU/mL					
Mean (SD)	65.71 (80.41)	45.68 (42.48)	56.48 (49.04)	41.76 (56.77)	48.30 (50.65)
Median	29.73	31.05	36.79	26.01	29.9
Min, Max	12.0, 206.6	12.0, 180.7	12.0, 163.9	12.0, 278.5	12.0, 278.5

- N= 87 patients (who received at least one dose)
- 78% of patients completed the study
- Reasons for not completing the study include: death (3%), adverse events (2%) and

	miscellaneous (1%-4% each) • Efficacy Endpoints ➢ Efficacy was assessed by a hemoglobin response defined as a ≥2.0 g/dL increase from baseline hemoglobin levels within 28 days without transfusions. ➢ Feasibility, reliability and validity of the quality of life questionnaire (FACT-Figure) was also assessed. ➢ Health-related quality of life was analyzed by Hgb response at the end of the 12 weeks. • Data Analysis ➢ Mean and 95% Confidence Interval. • Dose Adjustment ➢ Patients who had their dose reduced due to a rapid increase in Hgb: ○ 0.5 µg/kg/wk: n=0 ○ 1.0 µg/kg/wk: n=10 (30%) ○ 2.25 µg/kg/wk: n= 3 (17%) ○ 4.5 µg/kg/wk: n= 6 (20%) ➢ Patients who had their dose withheld because of Hgb values per protocol: ○ 0.5 µg/kg/wk: n=0 ○ 1.0 µg/kg/wk: n=0 ○ 2.25 µg/kg/wk: n=6 (33%) ○ 4.5 µg/kg/wk: n=11 (37%) • Safety results ➢ 86 (99%) of the patients reported at least once adverse reaction. ➢ Most frequent adverse reaction reported were fatigue, asthenia, fever, peripheral edema, pain, and influenza-like symptoms. ➢ 9 (10%) of these adverse reactions were treatment related. ➢ 20 (23%) patients reported serious adverse events that were not treatment related. ➢ 5 patients (6%) died during the study. These were determined to be due to disease progression and not treatment related. ➢ No antibodies to NESP were detected. ➢ No unexpected trends were seen such as to suggest a drug-related adverse effect. ➢ There were no dose-related relationships to correlate with the occurrence of adverse events. • Efficacy results ➢ The study shows a dose-dependent relationship between NESP and the proportion of patients achieving a Hgb response. ➢ Percentage of patients who had a response rate: ○ 1.0 µg/kg/wk: 61%; 95% CI= 42%, 77% ○ 2.25 µg/kg/wk: 67%; 95% CI=41%, 87% ○ 4.5 µg/kg/wk: 83%; 95% CI= 65%, 94% ➢ Percentage of patients who achieved a Hgb correction: ○ 1.0 µg/kg/wk: n= 61%; 95% CI=42%,77% ○ 2.25 µg/kg/wk: n=72%; 95% CI= 47%, 90% ○ 4.5 µg/kg/wk: n=80%; 95% CI=61%, 92%

➢ Change from baseline Hgb and red blood cell transfusion

	0.5 µg/kg/wk	1.0 µg/kg/wk	2.25 µg/kg/wk	4.5 µg/kg/wk
Change from baseline Hgb at wk 4. Mean (95% CI)	-0.10 g/dL (-1.08, 0.88)	0.68 g/dL (0.22, 1,14)	0.84 g/dL (0.22, 1.46)	1.26 g/dL (0.85, 1.67)
Change from baseline Hgb at the end of treatment. Mean (95% CI)	1.45 g/dL (-0.52, 3.42)	1.71 g/dL (0.91, 2.52)	2.63 g/dL (1.54, 3.71)	2.91 g/dL (2.17, 3.65)
RBC transfusions from wk 5 to the end of treatment.				
Number of patients (n)	1	8	3	2
Percent of patients (95% CI)	17% (0.64)	24% (11, 42)	17% (4,41)	7% (1,22)

- Health-related Quality of life findings:

	Hgb <0 g/dL	Hgb 0 to 2 g/dL	Hgb >2 g/dL
FACT-Fatigue			
Mean	-5.2	6.9	9.0
Median	-2.5	4.5	7.0
SD	10.7	9.7	10.8
Quartiles	-8.0, 0.0	1.0. 11.0	2.0, 15.0
Range	-27.0, 10.0	-3.0, 31.0	-10.0, 36.0
n	10	10	46

Conclusions

- Increasing doses of NESP corresponded with increased efficacy.
- NESP was safe and well-tolerated at doses from 0.5 to 4.5 µg/kg/wk when given weekly by subcutaneous injection
- NESP when administered once weekly over 12 weeks increased Hgb levels ≥2.0 g/dL over baseline in 60% of all patients treated at each dose tested

Critique

- Strengths
  - ➢ Dose escalation allowed to determine the most effective and safe dose for the patient.
  - ➢ Appropriate tests were done to determine efficacy of the drug.
  - ➢ Data from the different groups were specified individually and not grouped together.
- Limitations
  - ➢ Data does not apply to cancer patients receiving chemotherapy or radiotherapy.
  - ➢ Open-label study evokes bias from both patients and physicians.
  - ➢ Randomization of patients into groups and criteria to determine the patients' dose was not specified.
  - ➢ Absence of a control group.

	➢ Data on adverse events were not elaborated. ➢ Different baseline patient characteristics and unequal number of patients in the different arms of the study.

Citation (Abstract) and (Poster)	Smith R, Meza L, Tchekmedyian S, Chan D, Jaiyesimi I, Fleishman A, Gayko U, Colowick A, Glaspy J, and the NESP 990111 Study Group. An Open-Label, dose-finding study of Novel Erythropoiesis stimulating protein (NESP; Darbepoetin alfa, Aranesp) Administered by Subcutaneous (SC) Injection for the Treatment of Anemia in Patients with Chronic Anemia of Cancer. Abstract 1320. European Journal of Cancer October 2001; (37) Suppl 6:355.[21]
Study Goals	• To assess the safety of Darbepoetin administered subcutaneously once weekly in patients with chronic anemia of cancer. • To determine the clinically effective dose (CED) of Darbepoetin in this setting during the 12-week treatment phase. • To assess the administrative feasibility and timing of patient self-reported health-related quality of life (HRQOL) Surveys.
Methods	• Study Design ➢ Open-Label, Dose finding study. ➢ Patients were given Darbepoetin 0.5, 1.0, 2.25 or 4.5 µg/kg/week. ➢ Duration of study: 12 weeks ➢ At the end of the treatment period, patients were observed for 4 weeks after the last dose of Darbepoetin. ➢ Study drug was held if the patient's hemoglobin increased to >15.0 g/dL (for men) or 15.0 g/dL (for women). Therapy was restarted at 50% the previous dose once Hgb levels decreased to ≤13.0 g/dL. • Data Analysis ➢ Kaplan-Meier Curve was used to plot the Hemoglobin response. ➢ 95% Confidence Interval
Criteria	• Inclusion Criteria ➢ Hgb ≤ 11.0 g/dL ➢ Patients are diagnosed with non-myeloid malignancy ➢ Patients are not receiving or plan to receive any form of cytotoxic chemotherapy or external beam radiation within 16 wks after enrollment. ➢ Patients have not received chemotherapy or rHuEPO therapy within 8 wks of enrollment. ➢ Life expectancy >3 months with an ECOG performance status of 0 to 2. ➢ Adequate liver and renal function. ➢ No iron deficiency ➢ < 2 RBC transfusions within 4 weeks or no transfusion within 16 days of enrollment.
Results	• Patient Baseline Characteristics

	1.0	2.25µg/kg/week	4.5
Patients (n)	33	33	30
Age (years) Mean (SD)	69.7 (13.5)	70.2 (11.0)	74.0 (9.1)
Sex			
Women	14 (42%)	17 (52%)	12 (40%)
Primary Site of Disease			

Primary Site of Disease			
Genitourinary	12 (36%)	9 (27%)	12 (40%)
Breast	9 (27%)	10 (30%)	7 (23%)
Lymphoid	6 (18%)	6 (18%)	8 (27%)
Other	6 (18%)	6 (18%)	8 (27%)
Disease Stage			
I/II	11 (33%)	4 (12%)	7 (24%)
III/IV	21 (63%)	27 (82%)	21 (70%)
Unknown	1 (3%)	2 (6%)	2 (7%)
Baseline Hgb (g/dL) Mean (SD)	9.80 (0.91)	9.62 (1.12)	10.05 (0.94)
Baseline Endogenous EPO (mU/mL) Mean (SD)	48.84 (52.29)	67.00 (76.28)	37.82 (53.38)

- Efficacy Results

	1.0 µg/kg/week	2.25µg/kg/week	4.5µg/kg/week
Patients (n)	33	33	30
RBC transfusions from wks 5-12, n % of n (95% CI)	8 36% (10,62%)	4 14% (1,26%)	2 7% (0, 17%)
Change in Hgb from baseline to end of treatment. Mean (SD) g/dL	1.66 g/dL (2.22)	2.07 g/dL (2.14)	2.91 g/dL (1.99)
Hgb response/ n % of n (95%CI)	20 68% (50, 86)	19 67% (49, 84)	24 86% (73, 100)
Time to Hgb response (median no. of weeks)	8	6	7
Hgb correction/n % of n (95% CI)	20 65% (47,82)	19 67% (49,84)	24 86% (73,100)
Time to Hgb correction (median no. of weeks)	8	8	5

- The mean change in Hgb from baseline to the end of treatment appears to be Dose-dependent.
- The incidence of Red Blood cell transfusions (from week 5 to the end of treatment) decrease at the higher doses.
- Health related quality of life results showed at least a 25% to 50% improvement in FACT-Fatigue Scale Scores.
- Type and frequency of adverse events in patients receiving Darbepoetin are consistent with those expected from patients with cancer.
- Most frequently reported side effects include fatigue, arthralgia, asthenia, constipation, and nausea.

Conclusions

- The lowest clinically effective dose was determined to be 1.0 µg/kg/wk
- Darbepoetin appears to be effective and well tolerated at doses of 1.0 to 4.5 µg/kg/wk.
- Greater than 65% of patients achieved a greater hemoglobin response in all Darbepoetin groups with up to 92% in the 4.5µg/kg/wk group.

	• Results appear to be dose dependent with a mean change in Hgb ranging from 1.66 to 2.91 g/dL. • RBC transfusion rates ranged from 7% to 36% and were lowest at the 4.5µg/kg/wk group.
Critique	• Strengths ➢ Efficacy measure were comprehensive ➢ Dosing was tailored to the patient's individual response. • Limitations ➢ An open-label study could be biased. ➢ Unequal number of patients in each group. ➢ Increase in Hgb levels up to 15g/dL is not within the accepted range of the NKF-DOQI guidelines.

B. Patients currently receiving chemotherapy

Citation (Poster)	Glaspy J, Jadeja J, Justice G, Kessler J, Richards D, Schwartzberg L and the Darbepoetin alfa 980290 Study Group, O'Bryne J, Armstrong S, Colowick A. Randomized Active-Controlled Phase ½ Dose-escalation study of Darbepoetin Alfa Every 2 Weeks in Patients with Solid Tumors. [22]
Study Goals	• To evaluate the effect of Darbepoetin alfa at once weekly and once every two weeks dosing schedules in patients receiving multicycle chemotherapy. • To determine the clinically effective dose and schedule of Darbepoetin alfa in this setting. • To assess the administrative feasibility and timing of a patient self-reported, health-related, quality of life (HRQOL) questionnaire.

<table>
<tr><td>Methods</td><td>Study Design:
Randomized, Active controlled.
Hemoglobin response defined as an increase of at least 2.0 g/dL from the baseline hemoglobin in the absence of any RBC transfusion on that day during the preceding 26 days.
Proportion of patients achieving a hemoglobin response was determined using the Kaplan-Meier method.
HRQOL was assessed using the Functional Assessment of Cancer Therapy Fatigue (FACT-Fatigue Scale).
Part A:
Patients were randomized to receive either 0.5, 1.0, 1.5, 2.25, or 4,5 µg/kg/week of Darbepoetin or 150 U/kg three times a weeks of rHuEPO
Duration of part A: 12 weeks.
Darbepoetin patients remained at randomized doses while rHuEPO patients either doubled the dose due to inadequate Hgb response or remained at the randomized doses.
Part B:
Patients were randomized to receive either 3.0, 5.0, 7.0 or 9.0 µg/kg/q2 weeks or rHuEPO 40,000 units once a week.
Darbepoetin patients remained at randomized doses while rHuEPO patients either increased the dose if the change in Hgb levels was <1.0g/dL, or remained at the randomized doses.
Duration of part B: 12 weeks.</td></tr>
<tr><td>Criteria</td><td>Inclusion Criteria:
Anemic (Hgb ≤11.0 g/dL)
Solid tumors
Receiving cyclic chemotherapy
>6 month life expectancy
ECOG performance status of 0 to 2
Adequate renal and liver function.
No more than 2 RBC transfusions within 4 weeks of randomization.
Not iron deficient.
No rHuEPO therapy within 8 weeks of randomization.</td></tr>
<tr><td>Results</td><td>Demographics and Baseline Characteristics-Part A<table>
<tr><td></td><td>rHuEPO</td><td>Darbepoetin</td></tr>
<tr><td>Patients</td><td>53</td><td>216</td></tr>
<tr><td>Age (years)</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>57.8 (14.5)</td><td>61.9 (11.9)</td></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>Women</td><td>38 (72%)</td><td>146 (68%)</td></tr>
<tr><td>Primary Site of Disease</td><td></td><td></td></tr>
<tr><td>Breast</td><td>15 (28%)</td><td>64 930%)</td></tr>
<tr><td>Lung</td><td>11 (21%)</td><td>40 (19%)</td></tr>
<tr><td>Gastrointestinal</td><td>12 (23%)</td><td>41 (19%)</td></tr>
</table></td></tr>
</table>

Gynecologic	6 (11%)	27 (13%)
Other	9 (17%)	44 (20%)
Baseline Hgb (g/dL)		
Mean (SD)	10.0 (0.9%)	9.9 (0.9)

Demographics and Baseline Characteristic of Part B

	rHuEPO	Darbepoetin
Patients	32	126
Age (years)		
Mean (SD)	63.9 (12.3)	64.3 (12.0)
Sex		
Women	22 (69%)	82 (64%)
Primary Site of Disease		
Breast	6 (19%)	29 (23%)
Lung	7 (22%)	31 (24%)
Gastrointestinal	13 (41%)	36 (28%)
Gynecologic	1 (3%)	16 (13%)
Other	5 (16%)	16 (13%)
Baseline Hgb (g/dL)		
Mean (SD)	9.7 (1.2)	9.8 (1.0)

Efficacy Results: Part A

- Hgb response was similar between rHuEPO and Darbepoetin at Doses 1.5 and 2.25 µg/kg/week.
- rHuEPO dose was doubled for non-responders while no dose increases was made for Darbepoetin at week 8.

Efficacy Results: Part B

- rHuEPO dose was doubled for non-responders while no dose increases was made for Darbepoetin at week 6.
- Time to Hgb response appears to decrease with increasing Darbepoetin doses.

Health-Related Quality of Life (HRQOL) for Parts A and B

Changes in Hgb (g/dL)	Patients Number (%)		Change in FACT-F Score (95% CI)	
	Darbepoetin	rHuEPO	Darbepoetin	rHuEPO
<0	62 (19%)	14 (18%)	-1 (-5.2)	0.5 (-3,11)
0 to <1	73 (22%)	15 (19%)	0 (-1,1)	3 (0,18)
1 to <2	66 (20%)	14 (18%)	2 (-1,8)	-1 (-6,8)
2 to <3	55 (17%)	20 (25%)	4 (1,10)	5.5 (-5,11)
3	73 (22%)	16 (20%)	16 (20%)	4.5 (1,16)

Conclusions

- Greater than 54% of patients in all Darbepoetin dose groups in the every-two0week dosing schedule achieved a Hgb response.
- Decrease in fatigue was associated with increasing Hgb concentration.
- A reduction in the frequency of injections from once weekly dosing to every-two-week dosing resulted in no apparent loss of efficiency for Darbepoetin.

	• Darbepoetin appears to be well tolerated when dosed once weekly or every two weeks. • The type and frequency of adverse events in patients receiving Darbepoetin are consistent with those experienced by patients with solid tumors receiving chemotherapy and comparable to those patients receiving rHuEPO.

Citation (Abstract and Poster)	Glapsy J, Jadeja JS, Justice G, Kessler J, Richards D, Schwartzberg L, Rigas J, Kuter D, Harmon D, Prow D, Demetri G, Gordon D, Arseneau J, Saven A, Hynes H, Boccia R, O'Bryne R J, Colowick AB. A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anemia in patients receiving multicycle chemotherapy. [(23)]
Study Goals	To assess the safety and efficacy of NESP administered subcutaneously once per week to patients with solid tumors who were receiving multicycle chemotherapy for up to 12 weeks.
Methods	• Study Design ➢ Ongoing phase 1-2 multicenter, open-label, sequential dose-escalating study. ➢ Patients received one of 3 doses of NESP: 0.5, 1.5, or 2.25 µg/kg/wk subcutaneously. ➢ Duration of the study = 12 weeks. ➢ N= 107 ➢ Patients were monitored for vital signs and CBC every week. ➢ ECOG status and blood chemistries were measured at various times throughout the study. ➢ NESP was withheld if the Hgb levels increased to >15.0 g/dL (for men) and >14.0 g/dL (for women). ➢ NESP was restarted at the next lowest dose level or reduced by 50% if the patient was already taking the lowest dose once Hgb levels decrease to ≤ 13.0 g/dL. • Data Analysis ➢ Kaplan-Meier method was used to determine the proportion of patients achieving a Hgb response.
Criteria	• Inclusion Criteria ➢ 18 years of age ➢ Patients have a solid tumor and had at least 12 additional weeks of cyclic chemotherapy planned. ➢ Presence of anemia (Hgb ≤ 11.0 g/dL) primarily due to their cancer or chemotherapy. ➢ Adequate serum folate and Vitamin B_{12} levels ➢ Adequate renal and hepatic functions. • Exclusion Criteria ➢ Overt bleeding or hemolysis ➢ Primary or metastatic malignancy of the central nervous system. ➢ Had received more than two red blood cell transfusions within 28 days before the start of the study. ➢ Had received any red blood cell transfusions within 2 weeks of the start of the study. ➢ Had received rHuEPO therapy within 8 weeks of start of study or any previous treatment with NESP. ➢ Pregnancy, breastfeeding, or not using any adequate method of birth control.

	➢ History of seizure disorders ➢ Active cardiac disease, hypertension or a primary hematologic disorder as the cause of the present anemia.
Results	Patient Baseline Characteristics

	0.5 µg/kg/wk (n=13)	1.5 µg/kg/wk (n=35)	2.25 µg/kg/wk (n=59)	All (n=107)
Age, years Mean (SD)	61.3 (13.3)	62.5 (12.2)	61.8 (10.3)	62.0 (11.2)
Sex, n (%)				
Female	9 (69.2%)	25 (71.4%)	42 (71.2%)	76 (71.0%)
Male	4 (30.8%)	10 (28.6%)	17 (28.8%)	31 (29.0%)
Primary disease site, n (%)				
Breast	2 (15.4%)	11 (31.4%)	18 (30.5%)	31 (29.0%)
Lung	1 (7.7%)	2 (5.7%)	11 (18.6%)	14 (13.1%)
Gastrointestinal	3 (23.1%)	9 (25.7%)	14 923.7%)	26 (24.3%)
Gynecologic	5 (38.5%)	4 (11.4%)	4 (4.8%)	13 (12.1%)
Genitourinary		4 (11.4%)	1 (1.7%)	5 (4.7%)
Other solid tumor	2 (15.4%)	5 (14.3%)	11 (18.6%)	18 (16.8%)
ECOG performance, n(%)				
0	3 (23.1%)	12 (34.3%)	21 (35.6%)	36 (33.6%)
1	7 (53.8%)	22 (62.9%)	33 (55.9%)	62 (57.9%)
2	2 (15.4%)	1 (2.9%)	5 (8.5%)	8 (7.5%)
Hgb (g/dL)				
Mean	9.82 (1.03)	9.72 (1.07)	9.97 (1.01)	9.87 (1.03)
Median	9.70	9.70	10.10	10.00
Endogenous EPO, mU/mL	8.3, 11.4	7.0, 11.5	6.9, 12.0	6.9, 12.0
Mean (SD)	50.14 (36.28)			
Median	44.30	37.52 (22.84)	46.13 (45.32)	43.80 (38.48)
Min, max	12.0, 123.2	31.76	29.80	31.76

- Primary Endpoint of the study was the safety of NESP which was assessed by the occurrence of adverse events and antibody formation.
- A hemoglobin response was determined as an increase in Hgb levels of ≥2.0 g/dL from baseline in the absence of red blood cell transfusions in the previous 28 days throughout the 12 weeks treatment period.

Safety Results:

- Most common reasons for early termination of the study include death and withdrawal of consent.
- 6 patients died (6%) and 6 (%) withdrew from the study due to adverse events.
- 5 most commonly reported adverse events were:
  - ➢ Fatigue (44%)
  - ➢ Nausea (32%)

<table>
<tr><td></td><td>

Diarrhea (29%)
Vomiting (25%)
Anorexia (21%)

• 16 patients reported adverse events that were treatment related:

Injection site pain (7%)
Fever (2%)
Pain (2%)
Limb pain (2%)

• 28 (26%) patients reported a serious adverse event.
• No antibodies were detected.

Efficacy Results:
<table>
<tr><td></td><td>0.5 µg/kg/wk</td><td>1.5µg/kg/wk</td><td>2.25µg/kg/wk</td></tr>
<tr><td>Subjects treated (n)</td><td>13</td><td>35</td><td>59</td></tr>
<tr><td>Hgb response</td><td></td><td></td><td></td></tr>
<tr><td>No. of patients</td><td>3</td><td>12</td><td>29</td></tr>
<tr><td>Kaplan Meier % (95% CI)</td><td>23 (0, 46)</td><td>44 (25,63)</td><td>52 (39,66)</td></tr>
<tr><td>Maximum change from baseline Hgb (g/dL)</td><td></td><td></td><td></td></tr>
<tr><td>Through week 4, mean (95% CI)</td><td>0.26 (0.04, 0.48)</td><td>0.63 (0.40, 0.86)</td><td>0.82 (0.60, 1.04)</td></tr>
<tr><td>Through entire treatment, mean (95% CI)</td><td>1.24 (0.72, 1.75)</td><td>1.73 (1.21, 2.25)</td><td>2.15 (1.77, 2.52)</td></tr>
<tr><td>RBC transfusions from wk 5 to end of treatment</td><td></td><td></td><td></td></tr>
<tr><td>No. of patients</td><td>2</td><td>7</td><td>7</td></tr>
<tr><td>% of patients (95% CI)</td><td>15 (2, 45)</td><td>20 (8, 37)</td><td>12 (5, 23)</td></tr>
<tr><td>Dose of study drug received</td><td></td><td></td><td></td></tr>
<tr><td>Number</td><td>13</td><td>35</td><td>59</td></tr>
<tr><td>Mean</td><td>0.48</td><td>1.51</td><td>2.07</td></tr>
<tr><td>SD</td><td>0.05</td><td>0.01</td><td>0.31</td></tr>
<tr><td>Median</td><td>0.50</td><td>1.51</td><td>2.24</td></tr>
<tr><td>Q1, Q3</td><td>0.50, 0.51</td><td>1.50, 1.52</td><td>1.88, 2.25</td></tr>
<tr><td>Min, Max</td><td>0.36, 0.51</td><td>1.47, 1.54</td><td>1.27, 2.29</td></tr>
</table>
• 67 (63%) patients completed the 12 week treatment are the following 4 weeks of observation period.
</td></tr>
<tr><td>Conclusions</td><td>
• NESP is safe when administered to oncology patients with anemia undergoing chemotherapy.
• Adverse event profile was expected from this population of patients receiving chemotherapy.
• NESP seems safe at all doses tested
</td></tr>
<tr><td>Critique</td><td>
• Strengths

Results were comprehensive

• Limitations

Lack of control group
Drop-out rates were not presented.
An open-labeled study could be biased

</td></tr>
</table>

<table>
<tr><td>Citation (Abstract and Poster)</td><td>Kotasek D, the ARANESP™ 980291 Study Group, Berg R, Poulsen E, Colowick A. Randomized, double-blind, placebo-controlled, phase I/II dose finding study of Aranesp administered once every three weeks in solid tumor patients. Abstracts of the 42nd Annual Meeting of the American Society of Hematology, December 1-5 2000, The Moscone Center, San Francisco, CA.</td></tr>
<tr><td>Study Goals</td><td>• To assess the safety and efficacy of ARANESP administered by subcutaneous injection once every three weeks in patients with solid tumors receiving multicycle chemotherapy.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Multi-center, randomized, double-blind, placebo controlled, sequential, dose escalation study.
➢ Total number of patients who participated in the study: n=131
➢ Patient were randomized in a 4:1 ration to receive Aranesp (4.5, 6.75, 9.0, or 13.5 µg/kg) or placebo. This was administered subcutaneously once every 3 weeks on day 1 of the first cycle of chemotherapy after randomization.
➢ Duration of the study was 12 weeks.
➢ Aranesp was withheld if patients experience any of the following:
o Dose-limiting toxicity
o Hgb concentration >15.0 g/dL (for men) or >14.0 g/dL (for women). Once Hgb levels have decreased to ≤13.0 g/dL, the drug is restarted with the next lowest dose or reduced to 50% if the patient was already receiving the lowest dose.</td></tr>
<tr><td>Criteria</td><td>• Inclusion Criteria
➢ Hgb ≤ 11.0 g/dL
➢Solid Tumors
➢Receiving cyclic chemotherapy
➢≥ 6 month life expectancy
➢ECOG performance status of 0 to 2
➢Adequate liver and renal function
➢Iron replete
➢No more than 2 red blood cell transfusions within 4 weeks of randomization.
➢No rHuEPO therapy within 8 weeks of randomization.</td></tr>
<tr><td>Results</td><td>• Patient Baseline Characteristics
<table>
<tr><td></td><td>Placebo</td><td>4.5 µg/kg</td><td>6.75µg/kg</td><td>9.0 µg/kg</td><td>13.5 µg/kg</td><td>All Aranesp</td></tr>
<tr><td>Patients Treated</td><td>32</td><td>32</td><td>17</td><td>46</td><td>36</td><td>131</td></tr>
<tr><td>Age (yrs) Mean (SD)</td><td>58.4 (10.1)</td><td>59.1 (12.9)</td><td>59.1 (9.6)</td><td>56.8 (11.3)</td><td>57.0 (11.5)</td><td>57.7 (11.5)</td></tr>
<tr><td>Sex Women</td><td>21 (66%)</td><td>24 (75%)</td><td>11 (65%)</td><td>28 (61%)</td><td>27 (75%)</td><td>90 (69%)</td></tr>
<tr><td>Primary Site of Disease</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Breast</td><td>6 (19%)</td><td>8 (25%)</td><td>4 (24%)</td><td>7 (15%)</td><td>11 (31%)</td><td>30 (23%)</td></tr>
<tr><td>Lung</td><td>7 (22%)</td><td>4 (13%)</td><td>4 (24%)</td><td>13 (28%)</td><td>4 (11%)</td><td>25 (19%)</td></tr>
</table></td></tr>
</table>

GI	9 (28%)	6 (19%)	1 (6%)	7 (15%)	9 (25%)	23 (18%)
Gynecologic	6 (19%)	7 (22%)	4 (24%)	11 (24%)	11 (31%)	33 (25%)
Genitourinary	1 (3%)	4 (13%)	2 (12%	5 (11%)	1 (3%)	12 (9%)
Head and Neck	-	1 (3%)	-	-	-	1 (1%)
Soft Tissue Sarcoma	-	1 (3%)	-	-	-	1 (1%)
Other Solid Tumor	3 (9%)	1 (3%)	2 (12%)	-	-	6 (5%)
Baseline Hgb (g/dL) Mean (SD)	9.82 (1.09)	10.22 (0.89)	9.82 (1.11)	9.91 (0.99)	9.91 (0.99)	9.92 (1.01)

- Efficacy Results
  - Incidence of Red Blood Cell Transfusions at the End of Treatment Phase

	Placebo	4.5 µg/kg	6.75 µg/kg	9.0 µg/kg	13.5 µg/kg
Pts Treated	32	32	17	46	36
Pts w/ RBC Transfusion	14	7	4	11	9
Proportion of Pts w/ RBC transfusion (95% CI)	44% (26%, 62%)	22% (9%, 40%)	24% (7%, 50%)	24% (13%, 39%)	25% (12%, 42%)

  - Mean Change in Hgb Appears Dose-Dependent

	Placebo	4.5 µg/kg	6.75 µg/kg	9.0 µg/kg	13.5 µg/kg
Patients included in the Analysis	32	32	15	43	36
Mean	0.02	0.38	0.96	0.98	1.43
95% CI	(-0.49, 0.53)	(-0.04, 0.80)	(0.12, 1.80)	(0.50, 1.46)	(0.94, 1.92)

- Safety Results
  - Frequency and nature of adverse events in patients receiving Aranesp are consistent with patients receiving cytotoxic chemotherapy.

Conclusions

- This study showed that Aranesp appears to be well tolerated.
- There appears to be a dose-dependent response in patients achieving a Hgb response as well as a mean change in Hgb concentration.
- There is a reduced incidence of red blood cell transfusions in patients receiving Aranesp.
- Dose linearity was observed with no evidence of accumulation over time.

Critique

- Strengths
  - A randomized double-blinded placebo controlled study
- Limitations
  - The study did not compare Aranesp directly with rHuEPO.
  - No data was shown regarding adverse events experienced by the patients.
  - A hemoglobin response criteria was not defined.

Citation (Abstract)	Hedenus M, Hansen S, Dewey C, Watson D, Colowick A, Osterborg A, 9. Study Group. A Randomized, Blinded, Placebo-Controlled, Phase II, Dose-Finding Study of Novel Erythropoiesis Stimulating Protein (NESP) in Patients with Lymphoproliferative Malignancies. Abstract 1569. American Society of Clinical Oncology Thirty-Seventh Annual Meeting. May 12-15, 2001. Proceedings of ASCO, vol 20, pt. 1 of 2.
Study Goals	• To assess the relationship between darbepoetin alfa dose and Hgb response in patients with lymphoproliferative malignancies receiving chemotherapy. • To investigate the effect of darbepoetin alfa on red blood cell (RBC) transfusions and Hgb concentrations. • To investigate the safety of darbepoetin alfa in this setting.
Methods	• Study Design ➢ Randomized, Blinded , Placebo-Controlled study. ➢ Patients were randomized by a 1:2:2:1 ratio to receive Darbepoetin 1.0, 2.25, or 4.5µg/kd or placebo SC once a week. ➢ Duration of the study = 12 weeks. ➢ Decrease 50% of the dose if patients' Hgb increased ≥2.0 g/dL.
Criteria	• Inclusion Criteria ➢ Diagnosed with lymphoproliferative malignancies (except high-grade non-Hodgkin's lymphoma). ➢ Hgb ≤ 11.0 g/dL ➢ Receiving chemotherapy for at least 12 weeks. ➢ ≥ 6 month life expectancy ➢ ECOG performance status of 0 to 2 ➢ Adequate renal and liver function ➢ No iron deficiency ➢ No more than 2 RBC transfusions within 4 wks of randomization. ➢ No rHuEPO therapy within 8 wks of randomization.

Results

• Patient Baseline Characteristics

	Placebo	1.0 µg/kg	2.25µg/kg	4.5µg/kg	All NESP	Total
No. of Pts.	11	11	22	22	55	66
Sex						
Men	2 (18%)	7 (64%)	14 (64%)	14 (64%)	35 (64%)	37 (56%)
Age (yrs)						
Mean	60.1	61.2	66.7	66.3	66.2	65.2
SD	17.5	16.2	15.0	8.2	13.0	13.9
Primary Tumor Type						
Chronic Lymphocytic Leukemia	2 (18%)	2 (18%)	1 (5%)	7 (32%)	10 (16%)	12 (18%)
Hodgkin's Disease	3 (27%)	3 (27%)	4 (18%)	1 (5%)	8 (15%)	11 (17%)
Multiple Myeloma	3 (27%)	3 (27%)	6 (27%)	6 (27%)	15 (27%)	18 (27%)
Non-Hodgkin's	3	2	5 (23%)	4 (18%)	11	14

Lymphoma	(27%)	(18%)			(20%)	(21%)
Waldenstrom's Macroglobuminemia	0 (0%)	1 (9%)	6 (27%)	4 (18%)	11 (20%)	11 (17%)
Baseline Serum EPO (mU/mL)						
Mean	58.89	65.29	210.41	70.72	125.51	114.40
SD	42.15	64.73	343.66	59.49	230.17	211.92
Baseline Hgb (g/dL)						
Mean	9.54	9.74	9.40	9.70	9.59	9.58
SD	0.95	0.82	1.25	0.85	1.02	1.00

- A hemoglobin response was defined as an increase of ≥2 g/dL from baseline.
- A hemoglobin correction was defined as a Hgb concentration ≥ 12g/dL in the absence of RBC transfusion in the preceding 4 weeks.

	Placebo (n=11)	1.0 µg/kg (n=11)	2.25µg/kg (n=22)	4.5 µg/kg (n=22)
Pts. with Hgb response (95% CI)	9% (0, 41%)	45 % (17, 77%)	55% (32, 76%)	59% (36, 79%)
Pts with Hgb correction (95% CI)	18% (2, 52%)	55% (23, 83%)	45% (24, 68%)	59% (36, 79%)
Pts with RBC transfusion (wks 5-12) (95% CI)	45% (17, 77%)	27% (6, 61%)	27% (11, 50%)	14% (3, 35%)
Mean (SD) Hgb change (Baseline to wk 12)	1.1g/dL (0.60)	1.69g/dL (1.76)	1.72 g/dL (1.26)	2.26 g/dL (1.59)

- NESP significantly increases the proportion of patients achieving a hemoglobin response.
- NESP reduces the time to reach a hemoglobin response during the treatment phase.
- Mean change in Hgb from baseline at the end of the treatment period was ≥1.5 g/dL for all NESP groups.
- NESP appears to reduce the incidence of red blood cell transfusion compared with placebo.
- No unexpected trends in severity, incidence, or clinically significant differences in terms of adverse events from placebo.
- Adverse events reported in ≥15% of the patients:
  - Nausea
  - Fatigue
  - Fever
  - Peripheral Edema
  - Vomiting
  - Constipation
  - Abdominal Pain
  - Back Pain
  - Upper Respiratory Infection
  - Dyspnea
  - Diarrhea
- The type and frequency of adverse events in patients receiving NESP are consistent with those experienced by patients with lymphoproliferative malignancies receiving chemotherapy.
- Incidence of adverse reactions was comparable to placebo.
- The most frequently reported adverse event includes nausea, fatigue and fever.
- No antibodies to NESP were detected.

	• NESP was well tolerated.
Conclusion	• Darbepoetin administered at doses of 1.0 to 4.5 µg/kg in patients with lymphoproliferative malignancies showed greater rates of Hgb response and Hgb correction. • Mean change in baseline Hgb was greater than 1.5 g/dL in all patients receiving Darbepoetin. • Darbepoetin showed a lesser incidence of RBC transfusions • Darbepoetin appears to be well-tolerated in this patient population.
Critique	• Strengths ➢ Study design. • Limitations ➢ Limited information due to the abstract and poster format. ➢ Number of patients who completed the trial was not stated.

Citation (Abstract and Poster)	Pirker R, Vansteenkiste J, Gateley J, Yates P, Colowick A, Musil J, NESP 980297 Study Group. A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Novel Erythropoiesis stimulating protein (NESP; Darbepoetin alfa; ARANESP) in Patients undergoing Platinum-treatment for lung cancer. Abstract 981. European Journal of Cancer Oct 2001 Vol.37, Suppl 6: 264.
Study Goals	• To compare the efficacy of Darbepoetin alfa with placebo in the treatment of anemia in patients with lung cancer receiving multicycle platinum-containing chemotherapy.
Methods	• Study Design ➢ Double-Blind, Placebo Controlled, Randomized study ➢ 320 patients were randomized in a 1:1 ration to receive 2.25 µg/kg of NESP or placebo subcutaneously once a week for 12 weeks.
Criteria	• Inclusion Criteria: ➢ Hgb ≤ 11.0 g/dL ➢ Diagnosis of Lung cancer ➢ Patients are receiving platinum-containing chemotherapy. ➢ ≥6 month life expectancy ➢ ECOG performance status of 0 to 2. ➢ Adequate renal and liver function ➢ No iron deficiency ➢ No more than 2 RBC transfusions within 4 wks of randomization. ➢ No rHuEPO therapy within 8 wks prior to randomization.
Results	• Patient Baseline Characteristics

	Placebo	Darbepoetin	Total
Patients	158	156	314
Sex			
Men	116 (73%)	111 (71%)	227 (72%)
Race			
White	158 (100%)	156 (100%)	314 (100%)
Hgb (g/dL) Mean (SD)	9.93 (1.01)	10.28 (1.08)	10.11
Serum endogenous EPO	65.97	51.10 (71.72)	58.71
Small-cell Lung Cancer	44 (28%)	48 (31%)	92 (29%)

	Small-cell Lung Cancer	44 (28%)	48 (31%)	92 (29%)
	Limited Disease	19 (12%)	16 (10%)	35 (11%)
	Extensive Disease	25 (16%)	32 (21%)	57 (18%)
	Non-small cell lung Cancer	114 (72%)	108 (69%)	222 (71%)
	Stage I	2 (1%)	2 (1%)	4 (1%)
	Stage II	2 (1%)	2 (1%)	4 (1%)
	Stage III	48 (30%)	29 (19%)	77 (25%)
	Stage IV	62 (39%)	75 (48%)	137 (44%)
	ECOG Performance Status			
	0	23 (15%)	22 (14%)	45 (14%)
	1	98 (62%)	109 (70%)	207 (66%)
	2	37 (23%)	24 (15%)	61 (19%)
	>2	0 (0%)	1 (1%)	1 (0%)

- Primary Endpoints
  - RBC transfusion after the first month of therapy- week 5 to the end of the treatment phase (EOTP).
- Other Endpoints:
  - RBC transfusion from wk 1 to EOTP.
  - Number of units of RBC transfused.
  - Hematopoetic response which is defined as a $\geq$ 2 g/dL increase in Hgb or a $\geq$ 12g/dL Hgb concentration in the absence of RBC transfusion within the past 28 days.
  - Health-related quality of life as assessed by the Functional Assessment Cancer Therapy-Fatigue (FACT- Fatigue) scale.
  - Safety evaluation was done using assessment of adverse events, hospitalization, antibody development to Darbepoetin and progression-free survival.

Conclusions

- Darbepoetin significantly reduces the proportion of patients requiring RBC transfusion over the entire course of the treatment as well as the total number of RBC units transfused ($p<0.001$).
- Darbepoetin increases hematopoietic response
- Darbepoetin significantly improves self-reported fatigue as measured by the FACT-Fatigue scales compared with placebo and transfusions.
- No antibodies were detected and patients appear to tolerate the therapy well.

Critique

- Strengths
  - Double-blind, placebo controlled study design.
- Limitations
  - Comparison was not done directly between patients on platinum chemotherapy and those not on chemotherapy.

Acquisition Costs

Drug/ Vial Size	FSS Price Per Vial/ Package Size
EPOGEN MAY ONLY BE MARKETED FOR DIALYSIS TREATMENTS	
EPOGEN 2,000units/ml SDV	**$14.13 per vial/package size 10 vials**
EPOGEN 3,000units/ml SDV	**$21.14 per vial/package size 10 vials**
EPOGEN 4,000units/ml SDV	**$28.11 per vial/package size 10 vials**
EPOGEN 10,000units/ml SDV	**$70.06 per vial/package size 10 vials**
EPOGEN 10,000units/ml MDV –2 ml	**$140.67 per vial/package size 10 vials**
EPOGEN 20,000units/ml MDV	$149.85 per vial /package size 10 vials
PROCRIT MAY ONLY BE MARKETED FOR CRI & ONCOLOGY TREATMENTS	
PROCRIT 2,000units/ml SDV	$14.28 per vial/ package size 25 vials
PROCRIT 2,000units/ml SDV	$14.75 per vial/ package size 6 vials
PROCRIT 3,000units/ml SDV	$21.82 per vial/ package size 25 vials
PROCRIT 3,000units/ml SDV	$22.38 per vial/ package size 6 vials
PROCRIT 4,000units/ml SDV	$29.05 per vial/ package size 25 vials
PROCRIT 4,000units/ml SDV	$29.98 per vial/ package size 6 vials
PROCRIT 10,000units/ml SDV	$71.05 per vial/ package size 25 vials
PROCRIT 10,000units/ml SDV	$73.62 per vial/ package size 6 vials
PROCRIT 10,000units/ml MDV 2 ml	$143.97 per vial/ package size 6 vials
PROCRIT 20,000units/ml MDV 1 ml	**$144.93 per vial/ package size 6 vials**
PROCRIT 40,000units/ml MDV 1 ml	**$286.52 per vial/ package size 4 vials**
ARANESP DOES NOT HAVE BINDING LEGAL ISSUES FOR TREATMENT USE	
ARANESP 25 mcg/ml SDV	$69.31 per vial/ package size 4 vials
ARANESP 40 mcg/ml SDV	$114.34 per vial/ package size 4 vials
ARANESP 60 mcg/ml SDV	$151.22 per vial/ package size 4 vials
ARANESP 100 mcg/ml SDV	$279.18 per vial/ package size 4 vials
ARANESP 200 mcg/ml SDV	$571.67 per vial/ package size 1 vials

*Amerisource Pricing from 2/11/02

Cost of Initiation Therapy

No dosage adjustments are recommended in the first 4 weeks of therapy, below are dosing schedules for initiation phase.

Predialysis Patients[14:] (published)

Drug	Weekly Dose	Cost/Week/70kg Patient ($)	Cost/4 wks/Patient ($)
Darbepoetin	0.45 µg/kg/ week	$114.34 (40 mcg vial)	$457.36
Erythropoetin alpha (Procrit)	100 U/kg/week	$56.22 (2 vials of 4000 units biw with 1000 unit waste)	$224 .88

Dialysis Patients[28] (unpublished)

Drug	Median Maintenance Dose	Cost/Week/ 70 kg Patient	Cost/4 wks/Patient ($)
Darbepoetin	0.45 µg/kg/ week	$114.34 (31.5 µg use 40 µg vial with 8.5 units of waste)	$ 457.36
Erythropoetin alpha (Epogen)	150 units/kg/week	$76.09 (3500 units dosed tiw with 20,000 unit MDV in clinic)	$304.36

Maintenance Costs

-Dosing to maintain equally efficacious response to hemoglobin in each subset population as measured in clinical trials.

Predialysis Patients[14;] (published)

Drug	Median Maintenance Dose	Cost/Wk/ 70 kg Patient	Cost/Year/Patient ($)
Darbepoetin	0.34 µg/kg/ week	$69.31 (25 µg vial)	$3,604.12
Erythropoetin alpha (Procrit)	56.9 U/kg/week	$28.26 (2 vials of 2000units for biw)	$1,469.52

Dialysis Patients[27](unpublished)

Drug	Median Maintenance Dose	Cost/Week/ 70 kg Patient	Cost/Year/Patient ($)
Darbepoetin	0.56 µg/kg/ week	$114.34 (40 µg vial)	$5945.68
Erythropoetin alpha (Epogen)	156 units/kg/week	$79.13 (3640 units dosed tiw with 20,000 unit MDV in clinic)	$4114.85

Cancer Patients receiving Chemotherapy[22] (unpublished)

Drug	Maintenance Dose	Cost/Week/70 kg Patient	Cost/12 wks therapy/Patient ($)
Darbepoetin	3-9 mcg/kg/ q 2 week	$ 320.49/week for 210mcg (200+25 mcg vials with 15 mcg waste) – $ 914.68/ week for 630mcg (2 vials 200 mcg + 40 mcg vial with 10 mcg waste)	$3845.88 –10976.16 per treatment coarse of 12 weeks
Erythropoetin alpha (Procrit)	40,000 units/week	$313.69/ week with 25% refractory patients using 60,000units/week	3764.28 per treatment coarse of 12 weeks

Conclusions:

Efficacy

In chronic renal insufficiency and cancer patients, efficacy can be measured by several means. Some factors to be considered include the time to achieve a hemoglobin response, need for transfusions, ability to maintain target hemoglobin. The average time to respond was 7 weeks. This accounts for the time it takes for the erythropoeisis process. On this account, both Darbepoetin and rHuEPO were able to increase the patient's hemoglobin levels within the said time period. The increase in dosing interval with the prolonged half-life of Darbepoetin did not affect any of the markers for efficacy. It did not delay or accelerate the response time for patients. An extended half-life also resulted in similar ability to maintain hemoglobin doses with similar efficacy. The need for transfusions were decreased in both groups as well as the need for iron.

In oncology patients, measures of effectiveness included the above as well as additional parameters like a patient's health-related quality of life and ECOG status performance. Once again, the studies show that both medications are equally effective in improving the patient's well-being, decrease need for transfusions and still maintain to keep the patient's anemia under control.

Safety

There are several safety issues that must be taken into consideration with Darbepoetin's ability to treat anemia. The clinician must always take into consideration the rate of increase in hemoglobin, predisposing factors that may increase the risk of the patient for side effects (e.g. an uncontrolled hypertension patient) and other factors that could possibly affect a patient's response to Darbepoetin. These factors include hypoferremia, infections, and other therapies the patients might be receiving. In addition to this, the duration of administering Darbepoetin is also something to consider. Most of the studies reviewed above had an average duration of 12 to 24 weeks. The side effect profile of Darbepoetin compared with Erythropoetin appears similar in patients with chronic renal insufficiency. Differences in hypertension incidence were observed in the CRI population, however relevance of this finding is questionable given the unequal characteristics of baseline blood pressures as reported in patient demographics.

Cost Analysis

The costs between Darbepoetin and rHuEPO varies with the given dose and patient population. Darbepoetin may be given at a lesser frequency. This may mean clinic visits potentially could decrease for those patients that can not self-administer agent, and may need home health nurse or clinic nurse to administer. However, whether the increase in convenience from both patients and providers justifies the large price difference is debatable.

Formulary Recommendations:

Darbepoetin should remain non-formulary for compassionate use only. Presently there is little information available with most of the safety and efficacy data demonstrating minimal differences between Darbepoetin and rHuEPO. Additional comparison studies are needed to make a clear conclusion across the various subsets of populations that utilize erythropoeitin supplementation therapy. The main difference lies in cost. Whether the luxury of a weekly dosing justifies the increase in cost is still questionable.

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