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June 13, 2007

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Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Mailstop: C1-12-28
7500 Security Boulevard
Baltimore, MD 21244

[Submitted Electronically]

Re: Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions (CAG-000383N)

Dear Dr. Phurrough:

Genentech, Inc. ("Genentech") appreciates the opportunity to submit the following comments in response to The Centers for Medicare & Medicaid Services ("CMS") proposed national coverage decision memorandum for the use of erythropoiesis stimulating agents ("ESAs") in cancer and related neoplastic conditions ("Proposed NCD").

As you are aware, Genentech is a leading biotechnology company focused on discovering, developing, manufacturing, and commercializing biotherapeutics that address serious unmet medical needs. Genentech has discovered and introduced over a dozen significant therapies for serious and life-threatening diseases affecting the lives of Medicare patients, including cancer, heart disease, pulmonary disease, rheumatoid arthritis, and age-related macular degeneration. Medicare policy relating to both coverage and reimbursement of products like ESAs directly impacts patient access to the life-saving therapies we develop and is, therefore, of significant interest to Genentech.

While Genentech supports CMS' ongoing efforts to promote the collection of evidence for use by physicians in making treatment decisions, we are concerned that the draft policy, as currently written, does not accomplish this goal. In fact, the Proposed NCD may inappropriately limit Medicare beneficiary access to and physician choice of proven and medically appropriate therapies used to treat life-threatening conditions like cancer. We are particularly concerned that the Proposed NCD wrongly prohibits Medicare coverage for ESAs

used in patients with treatment regimens including anti-angiogenic drugs like bevacizumab (Avastin®), as this proposal is neither grounded in nor supported by scientific or clinical evidence.

The following comments provide evidence, based on existing data, that ESAs do not have a deleterious effect on cancer by causing tumor growth and counteracting the clinical effect of an anti-angiogenesis drug like Avastin. We also provide data from Phase III clinical trials that illustrate ESA use does not increase the risk of adverse events like arterial or venous thromboembolic events and hypertension when using anti-angiogenesis drugs like Avastin. Genentech is concerned that the Proposed NCD, if finalized in its current form, could seriously harm Medicare beneficiaries and limit the treatment options available to beneficiaries with cancer. As written, the Proposed NCD could improperly cause physicians not to prescribe Avastin, a product with proven survival benefits, either because physicians incorrectly infer that there is a safety risk associated with ESAs when used with Avastin, or because physicians may be forced to choose between prescribing a therapy like Avastin or prescribing ESAs that they determine are necessary to treat a patient's anemia. Based on these concerns, we request CMS to remove any restrictions of ESA use with Avastin in its final coverage policy.

I. Overall Policy Comments on Proposed NCD

Below, we provide overall comments on the policy implications of the Proposed NCD.

Inappropriate Restriction of Anti-Cancer Chemotherapeutic Regimen

As part of statutory authority to cover only products and services for which it deems "reasonable and necessary" for Medicare beneficiaries,[1] CMS also is required to cover drugs or biologicals used in an anti-cancer chemotherapeutic regimen for a medically accepted indication that has been approved by the FDA, is supported by one of the recognized compendia, or is determined by a Medicare contractor to be supported in the peer-reviewed medical literature.[2] Although the Proposed NCD does not place any direct coverage restrictions on anti-angiogenesis products like Avastin, we are concerned that restricting use of ESAs when used with Avastin is, by default, inappropriately restricting coverage of an anti-cancer regimen.

While CMS has a legitimate role in determining whether products are "reasonable and necessary" and therefore a covered benefit for Medicare beneficiaries, we are concerned that the Proposed NCD, while intended to limit coverage of ESAs due to safety concerns, also will unintentionally limit patient access to other, proven anti-cancer therapies. Although Genentech also appreciates the need for CMS to be a judicious steward of Medicare funds, we do not believe that significantly restricting use of ESAs with proven safe and efficacious anti-cancer treatments is an appropriate and effective use of CMS' authority, nor is in the best interest of Medicare beneficiaries.

[1] Social Security Act (SSA) 1862(a)(1)(A).
[2] SSA 1861(t)(2).

Proposed NCD Not Evidence-Based

In concert with the multitude of other provider, patient, and industry stakeholders who have provided comments to CMS on the Proposed NCD, Genentech also believes that CMS inappropriately restricts use of ESAs and other named anti-cancer therapies because the Proposed NCD relies on pre-clinical, theoretical data that are in conflict with the standard of care for cancer patients currently practiced in the United States. CMS' reliance on data from off-label, experimental, and investigational uses to determine a non-coverage decision for life-saving therapies like Avastin sends a conflicting message to the stakeholder community regarding the robustness of evidence-based medicine for which CMS claims to base its coverage decisions. CMS' explicit demand for use of proven evidence, not theoretical assumptions, to make coverage decisions appears to be ignored in the Proposed NCD.

Instead of relying on scientifically rigorous data to base its decision, CMS specifically cites the *lack* of data as the basis for its Proposed NCD. Although restricting coverage of FDA-approved indications for a Medicare Part B drug due solely to the absence of clinical data has not been previously imposed by CMS, the current adoption of such a policy is unrealistic and unsustainable, particularly with respect to Medicare beneficiaries with cancer. It seems extreme for CMS to expect all products administered to Medicare beneficiaries be tested against endless combinations of other products in order to rule out the possibility of a potential adverse event or deleterious effect. Although CMS may consider it within its realm of authority to make such coverage decisions, denying beneficiaries' access to therapies proven safe and efficacious by the FDA for their labeled indication because of a theoretical safety concern is clearly not in the best interest of Medicare beneficiaries.

CMS Inappropriately Assuming Role of FDA

Genentech also is concerned that CMS is circumventing the role of the FDA in the Proposed NCD. Specifically, it is not CMS' role to make scientific judgments about the appropriate use of products prior to FDA decisions on the same issue, even if under the guise of CMS' "reasonable and necessary" authority. Congress has vested the FDA with the responsibility of evaluating the safety and efficacy of drugs and biologics, not CMS. As such, CMS should wait to make decisions regarding Medicare coverage for a product until the FDA has completed its safety review of the product in question. By CMS making decisions regarding the safety and efficacy of various products already approved by the FDA, it is prematurely limiting the ability for patients to access products already approved by the regulatory agency responsible for making such decisions, and is, in essence, dictating the treatment decisions of physicians.

Interfering with Doctor/Patient Relationship

By prohibiting/restricting coverage for ESAs in the Proposed NCD, CMS is improperly inserting itself into physicians' clinical decision-making and interfering with the physician/patient relationship by substituting its judgment for that of the practicing physician. The Proposed NCD appears to be based largely on an incorrect assumption that physician decisions currently are not evidence-based and thus, require intervention by CMS. Such proscriptive

medicine ignores patient-specific needs and differences, like co-morbidities and quality of life factors, present at the time a treatment decision is made.

In order to ensure the highest quality of care is provided to Medicare beneficiaries, physicians must be allowed to determine the most medically appropriate course of treatment for each patient, based on their review of the evidence available, each patient's unique characteristics, and patient preferences. Broad practice guidelines developed at the national level by CMS cannot and will not be sufficiently nuanced to reflect important patient differences. In situations for which CMS feels it necessary to created national coverage policies that dictate physician behavior, it should ensure such policies are made on the basis of proven scientific evidence, not theoretical assumptions. Rather than focus on ways to control physician decision-making, particularly for oncology patients, Genentech encourages CMS to focus on ways to ensure physicians have access to the most recent and evidence-based information available in order to inform their decision-making.

Lack of Clarity Regarding Proposed Non-Coverage for Anti-Angiogenesis Drugs

Genentech is concerned that by denying coverage of ESAs with Avastin, the Proposed NCD could have the unintended effect of also denying or restricting the use of Avastin, a therapy proven to increase survival of Medicare beneficiaries with first or second-line metastatic colon cancer and first-line metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with intravenous chemotherapy regimens.[3] Avastin itself is not known to cause anemia; however, it is administered in combination with chemotherapeutic regimens that frequently are associated with myelosuppression and anemia, the latter often treated with an ESA.

While we recommend that CMS remove its proposed restriction relating to coverage of ESAs when used with anti-angiogenic agents altogether, we further object to CMS' singling out bevacizumab (Avastin) as the only anti-angiogenic drug listed in the Proposed NCD. We note that a multitude of products claim anti-angiogenic properties, yet the Proposed NCD mentions only Avastin. By doing so, some physicians have unfortunately interpreted this to mean that CMS has specific evidence suggesting a safety problem related to Avastin, which does not exist, and that the Proposed NCD may restrict coverage for Avastin, which also is not the case. Given the treatment benefit Avastin provides to Medicare beneficiaries with colorectal and non-small cell lung cancer, any confusion over its use or coverage could have the unintended and negative effect of denying Medicare beneficiary access to this important therapeutic.

The FDA approved Avastin (bevacizumab) in February 2004 in combination with intravenous 5-fluorouracil-based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon or rectum. In 2006, the FDA approved Avastin for second-line treatment of metastatic colorectal cancer, and later that same year, for use in combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC). Per its FDA-approved package insert (PI), the recommended dose of Avastin for metastatic colorectal cancer is

5mg/kg every 14 days when used in combination with bolus-irinotecan, 5-fluorouracil bolus and leucovorin (IFL) and 10mg/kg every 14 days when used in combination with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX4). The recommended dose of Avastin for NSCLC is 15mg/kg, as an IV infusion, once every 3 weeks with carboplatin and paclitaxel[4]. After the first six cycles of treatment with chemotherapy for NSCLC, Avastin is typically given alone.

In the Proposed NCD, CMS proposes to non-cover ESA treatment in patients with "treatment regimens including anti-angiogenic drugs such as bevacizumab;" however, it is unclear from the proposed NCD what is meant by a "treatment regimen;" specifically, when a treatment regimen for an individual patient starts and stops with respect to coverage under the Proposed NCD. This lack of clarity likely will confuse providers and patients when attempting to abide by the parameters of the policy. For example, if a patient diagnosed with first-line metastatic colon cancer is prescribed a chemotherapeutic regimen of 5-FU at the time of diagnosis and after one week of chemotherapy becomes anemic and receives an ESA, then receives Avastin three weeks later, would the patient's first three weeks of chemotherapy treatment be non-covered since Avastin was added to the patient's treatment regimen at a later date? Requiring long-term treatment decisions for oncology patients to be made pre-maturely without regard to assessing a patient's tolerance for each treatment could have significant negative and unintended effects on the quality of care provided to Medicare beneficiaries.

II. Comments on Clinical Aspects of Proposed NCD

In addition to the general policy concerns cited above, we also are troubled by CMS' statements in the Proposed NCD that conclude ESA use is not reasonable and necessary for patients undergoing treatment in an oncology setting with regimens including anti-angiogenic drugs such as bevacizumab[5]. As the company that discovered, developed, and now markets Avastin (bevacizumab) in the United States, we strongly disagree with CMS' review of the literature cited in the Proposed NCD and provide data below to illustrate ESA treatment in patients with anti-angiogenic treatments regimens, specifically Avastin, should continue to be considered reasonable and necessary for Medicare beneficiaries.

Minimal Role of Erythropoietin in Tumor Biology

Of the many laboratories around the world that have been studying normal and abnormal (cancer-associated) angiogenesis over the past 30 years, few have recognized erythropoietin (EPO) and erythropoietin receptors (EPO-R) as biologically and clinically relevant factors in the regulation of angiogenesis. Although non-hematopoietic roles of EPO and EPO-R exist, none of these roles are essential for cell development. Conversely, numerous reviews of other important biologic regulators of angiogenesis, particularly vascular endothelial growth factor

[4] *Ibid*.

(VEGF), have been published in the peer-reviewed literature[6]. Additionally, no scientific basis exists to suggest that ESAs negate the therapeutic utility of anti-angiogenic agents.[7]

Even as a theoretical construct, the papers cited in the Proposed NCD do not indicate a clinical relevant relationship between EPO/EPO-R and angiogenesis, including a deleterious effect like tumor growth as the result of an ESA. In fact, the work by Hardee et al[8] provides evidence, based on human tumor models, that the EPO/EPO-R pathway has no direct effect on angiogenesis. Moreover, the papers by Ribatti and colleagues are merely descriptive reports that involve an extremely small numbers of patients (20 patients with neuroblastoma and 50 patients with liver cancer)[9]. Descriptive reports of pre-clinical data that purport an association between EPO/EPO-R expression and microvessel density (a surrogate for angiogenesis) and higher histologic grade and clinical stage are not sufficient, on their own, to claim a scientific or clinical relationship between EPO/EPO-R and angiogenesis.

If one sought to study the potential for an independent contribution of EPO/EPO-R to angiogenesis, it would need to be explored by conducting a multivariate analysis with other, well documented and proven mediators of angiogenesis [such as VEGF and basic fibroblast growth factor (bFGF)]. If such an analysis did in fact confirm an independent association of EPO/EPO-R and microvessel density, scientific rigor would next require more direct evidence of a relationship EPO/EPO-R and angiogenesis. As mentioned above, Hardee and colleagues provide the evidence that directly *contradicts* the hypothesis set forth by Ribatti et al. Hence, for CMS to base a decision to non-cover ESAs in all Medicare beneficiaries with anti-angiogenesis treatments on the unconvincing level of evidence proposed by Ribatti et al is not defensible.

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[6] Gerber HP, Ferrara N. The role of VEGF in normal and neoplastic hematopoiesis. J Mol Med. 1003 Jan;81(1:20-31. Epub 2002, Dec 14. Kowanetz M, Ferrara N. VEGF signaling pathways: therapeutic perspective. *Clin Cancer Res*. 2006 Sep 1;12(17):5018-22. Ferrara N. VEGF as a therapeutic target in cancer. *Oncology*. 2005;69 Suppl 3:11-6. Epub 2005 Nov 21. Willett CG, Kozin SV, Duda DG, di Tomaso E, Kozak KR, Boucher Y, Jain RK. Combined vascular endothelial growth factor-targeted therapy and radiotherapy for rectal cancer: theory and clinical practice. *Semin Oncol*. 2006 Oct;33(5 Suppl 10): S35-40. Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science*. 2006 May 26; 312(5777):1171-5.

[7] Tam BY, Wei K, Rudge JS, Hoffman J, Holash J, Park SK, Yuan J, Hefner C, Chartier C, Lee JS, Jiang S, Niyak NR, Kuypers FA, Ma L, Sundram U, Wu G, Garcia JA, Schrier SL, Maher JJ, Johnson RS, Yancopoulos GD, Mulligan RC, Kuo CJ. Title. *Nature Medicine*. 2006; Jul;12(7):793-800. Epub 2006 Jun 25. Kuo, CJ. VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. *Proceedings of the National Academy of Sciences*. 1998;4605.

[8] Hardee M, Kirkpatrick J, Shan S, Snyder S, Vujaskovic Z, Rabanni Z, Dewhirst M, Blackwell K. Human recombinant erythropoietin (rEpo) has no effect on tumor growth or angiogenesis. *Br J Cancer*. 2005;93:1350-5.

[9] Ribatti D. A potential role of erythropoietin in angiogenesis associated with myelodysplastic syndromes. *Leukemia*. 2002;16:1890. Ribatti D, Marzullo A, Nico B, Crivellato E, Ria R, Vacca A. Erythropoietin as an angiogenic factor in gastric carcinoma. *Histopathology*. 2003;42:246–50. Ribatti D, Poliani P, Longo V, Mangieri D, Nico B, Vacca A. Erythropoietin/erythropoietin receptor system is involved in angiogenesis in human neuroblastoma. *Histopathology*. 2007;50:636-41. Ribatti D, Marzullo A, Gentilli A, Longo V, Nico B, Vacca A, Dammacco F. Erythropoietin/erythropoietin-receptor system is involved in angiogenesis in human hepatocellular carcinoma. *Histopathology*. 2007;50:591-6.

Analysis of Existing Clinical Data on Avastin and ESAs

Genentech and our collaborators at Roche and the National Cancer Institute (NCI) have reported the results of 10 large randomized and controlled clinical trials of Avastin in the oncology setting including colon, lung, breast, renal, and pancreatic cancers. Several of these trials formed the basis of FDA approval for our marketing applications for Avastin and all of these trials were conducted during a time that ESAs were approved by the FDA for both chemotherapy-associated anemia and for the anemia of cancer[10]. Nine of these 10 trials studied Avastin in combination with chemotherapy and one studied Avastin in combination with interferon. In addition, all 10 clinical trials were conducted under protocols which specified that hematopoeitc growth factors—both ESAs and myeloid growth factors—could be used at the investigators' discretion under generally accepted clinical guidelines, including guidelines published by the American Society of Clinical Oncology (ASCO) and The National Comprehensive Cancer Network (NCCN)[11].

The use of ESAs was captured in 6 of these 10 trials as outlined in Table One below. Three of the trials (AVF2107, AVF2192, and AVF2119) were conducted primarily in the United States (US) and three (NO16966, AVAIL, and AVOREN) were conducted primarily or exclusively outside the US. Specifically, these 6 trials, involving more than 4,400 patients, routinely captured ESA use on Case Report Forms (CRFs) under a category entitled "Concomitant Medications," for which the use of all pharmacologic agents (other that the specified treatment outlined in the protocol) is captured for each patient[12].

Table One: Avastin Clinical Trials for Which Data Are Available on Use of ESAs

Avastin Trial	Type of Cancer	Trial Sponsor	Number of Patients Enrolled
AVF2107	Colorectal	Genentech	788
AVF2192	Colorectal	Genentech	204
NO16966	Colorectal	Roche	1,400
AVF2119	Breast	Genentech	444
AVAIL	Lung	Roche	986
AVOREN	Renal	Roche	641
		Total Patients	**4,463**

Genentech performed a comprehensive analysis of the data available from these 6 trials in order to better understand the possible impact of ESAs with Avastin and provide CMS with the data it requested to support use of ESAs with anti-angiogenic therapies like Avastin for Medicare beneficiaries. Specifically, we explored the relationship between ESA use and clinical benefit from Avastin by calculating the hazard ratio for both progression-free survival (PFS) and overall survival (OS), using the log-rank test, in two separate groups of patients—

[10] Avastin Package Insert. Available at www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf.

[11] _____.

[12] The remaining four trials were conducted under an Investigational New Drug (IND) application held by the NCI, which does not routinely utilize CRFs for concomitant medications and therefore ESA use in these four trials was not collected.

ESA users and ESA non-users. We also assessed the rates of three targeted adverse events [arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), and hypertension] in these two patient groups.

In the analysis, "ESA users" were identified by a concomitant medications database query for the following terms: epoetin alfa, epoetin beta, epoetin not otherwise specified (NOS), and darbepoetin alfa. Any use of any of these agents for any duration was considered sufficient to place a patient in the "ESA user" group. Conversely, "ESA non-users" are defined as those patients who have no recorded use of these epoetin-related agents. The results of our analyses are described below.

Concurrent Use of ESAs in Avastin Clinical Trials

The ESA use in both the control and Avastin groups of these six trials varies by trial, likely due to differences in the underlying chemotherapy regimens. In this analysis, there was a statistically lower rate of ESA use in patients treated with Avastin compared to the control group. This observation occurred despite the significantly longer time on Avastin treatment, including chemotherapy, noted in five of the six trials. (Table Two below).

Table Two: Concurrent Use of ESAs in Avastin Clinical Trials

Avastin Trial	Control Group (%)	Avastin Group (%)
AVF2107	36.1	33.4
AVF2192	27.9	34.0
NO16966	6.3	6.3
AVF2119	17.7	12.7
AVAIL	14.4	10.8
AVOREN	3.6	2.4
Overall*	**15.2**	**13.1**

*p=0.04

Use of ESAs in Avastin Trials by Prognostic Factors

As expected, ESA use was not a random event in these trials. We explored the rate of ESA use in three important prognostic subgroups that were uniformly available in these trials;,

1) Patients less than 65 years of age versus patients 65 years of age or older;
2) Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 versus 1 or greater[13]; and
3) The baseline serum albumin levels in all patients.

As shown in Table Three, ESA use was consistently higher in patients with adverse prognostic factors. These data are important when interpreting the data contained in Table Five below.

Table Three: Percent ESA Use by Prognastic Factors Including Age, Performance Status, and Albumin Levels

	Age		Performance Status		Albumin (mg/dl) Non-ESA	
	<65	**>65**	**0**	**≥1**	**ESA User**	**Non ESA User**
AVF2107	31.5	38.0	28.0	41.3	3.8	3.6
AVF2192	19.5	32.7	28.8	30.7	3.6	3.3
NO16966	5.5	7.8	6.2	6.7	14.1*	22.7*
AVF2119	13.7	20.8	10.3	18.7	3.9	3.7
AVAIL	12.6	8.6	11.5	11.4	4.0	4.0
AVOREN	3.4	2.1	2.7	4.2	--	**--**

*Percent below the lower limit of the lab normal.
Note: Albumin levels were not collected for AVOREN.

Treatment Effect of Avastin with ESA Use

Table Four displays the relative treatment effect of Avastin in five of these six clinical trials. (Given the very low rate of ESA use in AVOREN, data from this trial was not included in our outcome analyses.) Four of these five trials were “positive,” meaning they achieved their pre-specified primary efficacy endpoint of progression-free survival (PFS) or overall survival (OS). The sole exception was trial AVF2119, which did not achieve its primary endpoint; however, the potential of an efficacy interaction was also investigated in this trial.

The treatment affect achieved with the addition of Avastin to chemotherapy in these trials was similar, looking at either PFS or OS endpoints. The point estimates of effect were similar in ESA users versus non-ESA users, with broadly overlapping confidence intervals around those estimates. The data suggest no indication of a lessened treatment effect with Avastin when used in combination with ESAs.

Table Four: Hazard Ratios for Progression-Free Survival (PFS) and Overall Survival (OS) of Patients in Avastin Clinical Trials Based on ESA Use Versus Non-ESA Use*

Avastin Trial	PFS				OS			
	ESA User		Non-ESA User		ESA User		Non-ESA User	
AVF2107	0.49 (0.37-0.66)		0.61 (0.49-0.77)		0.73 (0.53-1.00)		0.64 (0.50-0.83)	
AVF2192	0.72 (0.38-1.37)		0.40 (0.26-0.63)		0.58 (0.32-1.06)		0.91 (0.61-1.35)	
NO16966	0.66 (0.41-1.05)		0.84 (0.74-0.95)		0.75 (0.45-1.25)		0.90 (0.78-1.03)	
AVF2119	0.93 (0.47-1.82)		0.92 (0.71-1.19)		1.29 (0.62-2.68)		1.05 (0.76-1.46)	
AVAIL**	1.27 (0.75-2.2)	0.76 (0.45-1.28)	0.69 (0.56-0.84)	0.81 (0.66-0.99)	--	--	--	--

*Hazard ratios for control versus Avastin.
**First hazard ratio listed is for 7.5mg/kg dose group, second hazard ratio listed is for 15mg/kg dose group.
Note: Overall survival data is not available for the AVAIL trial due to insufficient death events at thistime.

Table Five displays the absolute treatment effect of patients in the control group compared to the Avastin group (i.e., those who received chemotherapy alone versus the Avastin group who received chemotherapy with Avastin). The data suggest that ESA use *may* be associated with an inferior outcome, regardless of Avastin use; however because ESA use is associated with other negative prognostic features (as shown in Table 3), we cannot conclude, without further multivariate analyses, whether this inferior outcome is a direct result of ESA use or whether ESA use is simply a surrogate for a patient group with inferior outcomes due largely to other prognostic reasons. In the absence of data to indicate a direct correlation, CMS should refrain from implementing a policy that could unintentionally and negatively limit Medicare beneficiary access to Avastin, particularly when the overall positive treatment effect of Avastin in these patients is clear.

Table Five: Median Number of Months of PFS and OS for Patients in Avastin Clinical Trials Based on ESA Use versus Non-ESA Use

Avastin Trial	PFS (months)				OS (months)			
	Control		Avastin		Control		Avastin	
	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User
AVF2107	5.7	7.0	9.2	10.7	13.4	16.1	16.2	22.8
AVF2192	5.6	5.5	7.2	9.8	9.4	15.5	17.6	15.7
NO16966	6.7	8.1	9.4	9.4	15.2	20.1	20.9	21.5
AVF2119	5.2	4.1	4.6	4.9	14.5	17.8	10.8	15.1
AVAIL*	6.5	6.0	6.1/7.2	6.7/6.4	--	--	--	--

*First value listed is for 7.5mg/kg dose group, second value listed is for 15mg/kg dose group.

Note :Overall survival data is not available for the AVAIL tria l due to insufficient death events at this time.

Safety of Avastin with ESA Use

Tables Six through Eight display the rates of three targeted safety signals: arterial thromboembolic events (ATEs),venous thromboembolic events (VTEs), and hypertension.

Table Six :Arterial Thromboembolic Events (ATEs) for Patients in Avastin Clinical Trials Based on ESA Use versus Non-ESA Use

Avastin Trial	All Patients				Patients ≥ 65 Years Old			
	Control		Avastin		Control		Avastin	
	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User
AVF2107)	3 (2.1%)	2 (0.8%)	6 (4.6%)	7 (2.7%)	2 (3.6%)	0 (0%)	3 (6.4 %)	4 (5.1%)
AVF2192	4 (13.8%)	1 (1.3%)	2 (5.9%)	7 (10.6%)	3 (12.0%)	1 (1.8%)	2 (6.7%)	6 (11.1%)
NO16966	1 (2.3%)	6 (0.9%)	0 (0%)	13 (2%)	0 (0%)	2 (0.9%)	0 (0%)	9 (4.2%)
AVF2119	0 (0%)	1 (0.6%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)
AVAIL	2 (4.3%)	13 (4.6%)	1 (1.4%)	17 (2.9%)	1 (8.3%)	5 (5.4%)	0 (0%)	3 (1.8%)
AVOREN	0 (0%)	1 (0.3%)	0 (0%)	4 (1.2%)	0 (0%)	0 (0%)	0 (0%)	3 (2.5%)
Combined Total	10 (3.2%)	24 (1.4%)	9 (2.8%)	49 (2.3%)	6 (5.1%)	8 (1.4%)	5 (4.1%)	26 (4.0%)

Table Seven: Venous Thromboembolic Events (VTEs) for Patien t s in Avastin Clinical Trials Based on ESA Use versus Non-ESA Use

Avastin Trial	All Patients				Patients ≥ 65 Years Old			
	Control		Avastin		Avastin		Control	
	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User	ESA User	Non-ESA User
AVF2107	27 (18.9%)	27 (18.9%)	23 (17.6%)	23 (17.6%)	37 (14.2%)	12 (21.4%)	11 (13.6%)	11 (23.4%)
AVF2192	7 (24.1%)	7 (9.3%)	4 (11.8%)	4 (11.8%)	6 (24.0%)	5 (9.1%)	4 (13.3%)	4 (13.3%)
NO16966	5 (11.6%)	29 (4.6%)	8 (17.8%)	48 (7.4%)	2 (12.5%)	9 (4.0%)	5 (22.7%)	23 (10.8%)
AVF2119	1 (2.6%)	6 (3.4%)	6 (3.4%)	10 (5.0%)	0 (0%)	1 (4.2%)	2 (40.0%)	0 (0%)
AVAIL	5 (10.6%)	16 (5.7%)	3 (4.2%)	43 (7.3%)	2 (16.7%)	6 (6.5%)	2 (14.3%)	12 (7.2%)
AVOREN	0 (0%)	2 (0.7%)	0 (0%)	6 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Combined Total	45 (14.5%)	88 (5.1%)	44 (13.8%)	148 (7.1%)	22 (18.8%)	32 (5.4%)	24 (19.8%)	50 (7.7%)

Table Eight: Hypertension* Observed in Patients in Avastin Clinical Trials Based on ESA Use versus Non-ESA Use

Avastin Trial	All Patients			
	Control		Avastin	
	ESA User	Non-ESA User	ESA User	Non-ESA User
AVF2107	4 (2.8%)	6 (2.4%)	20 (15.3%)	29 (11.1%)
AVF2192	0 (0%)	2 (2.7%)	3 (8.8%)	12 (18.2%)
NO16966	1 (2.3%)	7 (1.1%)	2 (4.4%)	26 (4.0%)
AVF2119	0 (0%)	1 (0.6%)	6 (20.7%)	40 (20.0%)
AVAIL	0 (0%)	6 (2.1%)	3 (4.2%)	47 (8.0%)
AVOREN	1 (9.1%)	1 (0.3%)	0 (0%)	13 (4.0%)
Combined Total	6 (1.9%)	23 (1.3%)	34 (10.7%)	167 (8.0%)

*Hypertension as defined by the National Cancer Institute Common Toxicity Criteria (CI-CTC) grade ≥3.

Based on these data, no additive or synergistic effect appears to occur in the three targeted adverse events outlined above for patients receiving ESAs and Avastin. Although the rate of VTEs appears to be higher in the ESA user group, this increase is independent of Avastin use.

Clarification Needed on Scientific Terminology

Genentech is concerned that CMS has not thoroughly defined some of the scientific terminology used in the Proposed NCD, which likely will cause inconsistent interpretations and confusion about how to implement the policy once finalized. In particular, it is not clear how CMS is defining anti-angiogenic drugs for purposes of the Proposed NCD. Besides Avastin, other FDA-approved anti-cancer therapies have mechanisms of action that include an anti-angiogenic effect, including small molecule oral VEGFR kinase inhibitors. Many classes of classical cytotoxic chemotherapy agents also have demonstrated anti-angiogenic effects in pre-clinical models.

Moreover, it is Genentech's understanding that when CMS refers to "patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor,"[14] it means only antibodies directed against the human epidermal growth factor receptor (HER1)/EGF receptor. Although HER2, HER3, and HER4 also are members of the family of EGF receptors, we do not think CMS intended for products targeted against these receptors to be within the scope of the Proposed NCD. As a result, we have not addressed the impact of such products in our comments.

If our interpretation of the above language is not in agreement with CMS' intent, we request CMS provide more clarity and time for public comment before finalizing the policy specific to EGF receptors other than HER1.

III. Comments on Additional Data Collection Efforts

In the Proposed NCD, CMS solicits public comment on whether Medicare coverage for ESAs should "only occur within appropriately designed clinical research studies where informed consent and safety monitoring can be assured."[15] Presumably, CMS is requesting comments on whether applying the principle of Coverage with Evidence Development (CED) is appropriate to gain an even better understanding of the clinical interaction between ESAs and anti-angiogenesis therapies like Avastin.

While Genentech continues to support CMS' efforts to collect data that would further inform treatment decisions for patients, including information on the use of ESAs in Medicare beneficiaries, we are confident such data collection efforts can be accomplished through existing patient registries that already are collecting related data. As such, we are opposed to CMS compelling manufacturers to conduct more costly large-scale data collection efforts to study CMS' perceived theoretical assumptions about ESAs and anti-angiogenesis. Such efforts are not a productive use of resources that otherwise would be used to develop therapies for unmet medical need.

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[15] *Ibid*.

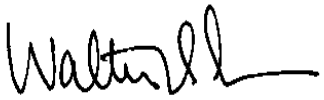
IV. Conclusion

In summary, the data analyses Genentech performed in response to the Proposed NCD illustrate that in randomized, controlled clinical trials over 4,400 patients—600 of whom were treated with ESAs in addition to Avastin—do not suggest a negative interaction between ESA and Avastin use, either with respect to safety or efficacy. We therefore believe that these data are sufficient to remove the restriction included in the Proposed NCD for coverage of ESAs when used in combination with Avastin.

In making its final determination, we urge CMS to reconsider the restrictions outlined in the Proposed NCD, and the negative impact these restrictions are expected to have on the care provided to Medicare beneficiaries. We also request that CMS fulfill its commitment to implement policy changes that are evidence-based and not based merely on theoretical assumptions.

Thank you for the opportunity to provide comments on the draft policy. Please contact Dr. Robert Mass at (650) 225-7223 or via e-mail at mass.robert@gene.com for any clinical questions regarding the above data analyses. Please contact Heidi Wagner at (202) 296-7272 or wagner.heidi@gene.com should you have any general follow-up questions regarding our comments.

Sincerely,



Walter Moore
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