510(k) SUMMARY

This summary of 510(k) safety and effectiveness is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K050245

Date Prepared: 03/07/2005

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Identification of the Device:	Trade/Proprietary Name:	CellSearch™ Circulating Tumor Cell Kit
	Common Name:	CellSearch™ Circulating Tumor Cell Kit
	Classification Name:	Immunomagnetic Circulating Cancer Cell Selection and Enumeration System
	Device Classification:	II
	Regulation Number:	21 CFR 866.6020
	Product code:	NQI
	Classification Panel:	Immunology Devices - 82
Special Controls:	No Special controls have been issued for *in vitro* devices under sections 513 and 514.	
Establishment Registration Number:	3004582358	
Predicate Device:	CellSearch™ Epithelial Cell Kit K031588	

Device Description:

Epithelial cells are immunomagnetically labeled by targeting the Epithelial Cell Adhesion Molecule (EpCAM) antigen. Anti-EpCAM monoclonal antibodies conjugated to ferrofluid particles are colloidal and, when mixed with a sample containing the target epithelial cells, bind to the EpCAM antigen associated with the epithelial cells. After immunomagnetic selection of epithelial cells from 7.5 mL of blood. Fluorescent reagents are added at this time to discriminate between the immunomagnetically selected cells. Anti-Cytokeratin – Phycoerythrin (CK-PE) stains the intracellular cytoskeleton cytokeratin proteins expressed in cells of epithelial origin, anti-CD45-Allophycocyan (CD45-APC) stains leukocytes and DAPI stains DNA present in the cell nucleus. A strong magnetic field is applied to the processed reagent/sample mixture that causes the labeled target cells to move to the cartridge surface. The cartridge is then placed on the CellTracks® Analyzer II for data acquisition and analysis. The CellTracks® Analyzer II acquires images of PE, APC and DAPI fluorescence staining of the entire viewing surface.

After data acquisition is completed, the images are analyzed for any event where cytokeratin-PE and DAPI are within a specified space in the cartridge, i.e. indicating the possible presence of a cell with a nucleus that expresses cytokeratin. Images from each fluorescent color as well as a composite image of the cytokeratin staining (green) and the nuclear staining (purple) are presented to the user in a gallery for final cell classification. A cell is classified as a tumor cell when it its EpCAM+ (i.e., it is captured), CK+, DAPI+ and CD45-. A check mark placed by the operator next to the composite images classifies the event as a Circulating Tumor Cell (CTC) and the software tallies all the checked boxes to obtain the CTC count.

Our data demonstrate that metastatic breast cancer patients with 5 or more CTC/per 7.5 mL of blood have a significantly greater probability for shorter progression free and overall survival than patients who have fewer than 5 CTC per 7.5 mL of blood.

Intended Use for the CellSearch Assay:

The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) in whole blood.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast cancer. A CTC count of 5 or more per 7.5mL of blood is predictive of shorter progression free survival and overall survival.

Summary of Technological Characteristics of the CellSearch™ Circulating Tumor Cell Kit:

The CellSearch™ Circulating Tumor Cell Kit has the same technological characteristics (i.e., design, material, chemical composition, energy source) as the CellSearch™ Epithelial Cell Kit. Modifications have been made to the CellSearch™ Epithelial Cell Kit (K031588) to optimize its performance on the CellTracks® AutoPrep System to deliver the same performance as previously established using the CellPrep™ Sample Preparation System. Modifications include:

- Minor formulation and volume changes
- Minor incubation time changes
- Rename product: CellSearch™ Circulating Tumor Cell Kit (Epithelial)

Additionally, the CellSpotter® Analyzer is being modified to replace obsolete parts, place the analyzer inside an enclosure (cosmetic change to make system look more like/compatible to a CellTracks® AutoPrep System), and is being renamed to CellTracks® Analyzer II.
These modifications to the CellSearch™ Circulating Tumor Cell Kit do not raise any new issues of safety and effectiveness and the intended use is identical between the two systems.

Clinical and Non-Clinical Studies:

Non-Clinical Studies
The following non-clinical studies were selected to compare the CellSearch™ Circulating Tumor Cell Kit performance characteristics to the predicate device to show that the two devices are substantially equivalent. After each newly determined performance characteristic, the results are compared to the predicate and followed by the conclusion statement that the CellSearch™ Circulating Tumor Cell Kit meets the performance specification and is thus substantially equivalent.

Recovery
Blood samples from a single healthy donor were pooled and five of six 7.5 mL aliquots were spiked with 5, 20, 81, 325 and 1300 cultured breast cancer cells (SK-Br-3). The sixth tube was unspiked pooled blood and served as a zero point. These samples were processed on the CellTracks® AutoPrep System with the CellSearch™ Circulating Tumor Cell Kit and CTC counts were determined on the CellTracks® Analyzer II. The experiment was repeated for four additional donors. The observed cell counts were plotted against the results of the expected cell count. The results are summarized in **Table 1**.

Table 1. Percent Detection Estimates.

Expected Tumor Cell Count	Mean Observed Tumor Cell Count	Range of Percent Recovery
1300	1215	91 to 95%
325	308	82 to 101%
81	85	80 to 136%
20	22	95 to 140%
5	7	120 to 200%

To determine the overall, or least squares fit, for the comparison of the observed and expected cell counts across all the data, linear regression analysis was performed. The regression equation for these 30 samples was $Y=0.93x + 3.87$, $R^2=0.999$. The results of this study indicate that on average over the tested CTC range the recovery, as derived from regression analysis, is 93%.

Given the linear response of the tumor cell counts, one would expect the slope of the observed versus expected plot to be 1.0. However, the slope was 0.93. This is because the CellTracks® AutoPrep System with CellSearch™ CTC Kit involves the capture and fluorescent labeling of cells followed by their detection and enumeration by the CellTracks® Analyzer II. The loss of cells could therefore be attributed to one of the following possibilities; 1) the recovery of only 93% of the tumor cells spiked into 7.5mL of blood by the CellTracks® AutoPrep System, 2) the detection of only 93% of the tumor cells present in the sample chamber by the CellTracks® Analyzer II or 3) a combination of both of these sources of error.

These results agree well with those obtained for the predicate (K031588) pre-clinical study where a slope of 0.85, intercept of 5.6 and an $r^2 = 0.997$ was observed over a range of 4 to 1142 cells. These data indicate that the recovery of the predicate device was 85%. Thus the new assay's 93% recovery appears to be better than the predicate's.

Linearity/Reportable Range

Another way to examine the previous data is to analyze it as a dilution series to evaluate test linearity. We removed the confounding variable of percent recovery by using the observed value of the original sample divided by the dilution factors to determine the expected values for the dilution series for each patient sample. Regression of all of these numbers of observed tumor cells versus the numbers of expected tumor cells yielded a slope of 1.007, an intercept of 3.0, an $r^2 = 0.99$ and $r = 0.995$. Therefore, once the percent recovery (cell loss) was factored out of the CTC values of each of the original samples, this analysis of the data demonstrated that the detection of CTC was linear over the reportable range of 0 to 1238 tumor cells.

These results demonstrate that the CellSearch™ CTC kit/CellTracks® Analyzer II detected the number of tumor cells expected from the known dilution. They also agree with those obtained previously for the predicate system (K031588) with a slope of 0.99, intercept of 5.7 and $r^2 = 0.99$ over a reportable range of 4 to 1022 CTCs. The linearity and reportable range of the new device is very similar to that of the predicate over a greater range of CTCs.

Limits of Detection

One CTC per 7.5 mL can be detected by the CellTracks® Analyzer II resulting in a limit of detection of 1 CTC in a cartridge. Linear regression shows that on average, 93% of CTC present in a 7.5 mL blood sample are recovered using the CellTracks® AutoPrep System (see **Recovery** section). The loss of approximately 7% of the CTC in the sample is not sufficient to reduce the limit of detection of 1 CTC.

Therefore, a CellSearch™ CTC kit/CellTracks® Analyzer II detection would require that there be at least 1.1 or approximately 1 cell, in the sample chamber prepared from 7.5 mL of whole blood in order to detect at least one cell. This is comparable to the 1.28 cell sensitivity calculation determined for the CellSearch™ Epithelial Cell kit/CellSpotter® Analyzer. This validates that the

CellSearch™ CTC kit/CellTracks® Analyzer II is capable of delivering sensitivity equal to that of the CellSearch™ Epithelial Cell Kit/CellSpotter® Analyzer for whole blood.

Reproducibility

System Reproducibility with CellSearch™ Circulating Tumor Cell Control
Three separate CellSearch™ Circulating Tumor Cell Control samples were prepared and processed each day for over 30 days, per the long run method of NCCLS guideline EP5-A. Each single-use sample bottle contains a low and a high concentration of cells from a fixed cell line that have been pre-stained with two different fluorochromes. Summary statistics for the high and low control cells is presented below.

Table 2. Summary of Precision Analyses

	Low	High
N	99	99
Mean cell count	48	969
Total Precision Standard Deviation (S_T) % CV	18%	5%

The results of the system reproducibility with CellSearch™ Circulating Tumor Cell Controls for the CellSearch™ Circulating Tumor Cell Kit are comparable to the reproducibility results for the predicate, which has a Total % CV of 9.4% for the High Control Cell (Mean 258) and 15.8% for the Low Control Cell (Mean 47). The reproducibility of the CellSearch™ Circulating Tumor Cell Kit meets the performance specification and is substantially equivalent to that of the predicate system.

Comparison Studies:

Comparison of New Device to the Predicate System
To directly demonstrate comparable performance, a study was performed using different cell lines tested at varying concentrations on both the **predicate device**, CellSearch™ Epithelial Cell System (K031588), and the **new device**, CellSearch™ Circulating Tumor Cell System (K050245).

For this comparison, fixed and unstained cells from three different cell lines were spiked into blood from normal donors at three different levels for five days. The three cell lines (SK-Br-3, MCF-7, or PC3-9) were chosen to cover a broad range of EpCAM and Cytokeratin antigen density representing the capture and detection portions of the assay respectively. Three spike levels of each cell line were chosen to cover a range of potential clinical values. Of the three cell lines tested, the PC3-9 cell line has the lowest Cytokeratin antigen density. SK-Br-3 cells demonstrate an uneven bimodal population consisting primarily of moderate level Cytokeratin antigen density cells and a smaller population of higher expressing cells. MCF-7 cells demonstrate the highest level of consistent Cytokeratin expression. The Cytokeratin antigen is the target of the detection reagent for tumor cells in the CellSearch™ Circulating Tumor Cell kits. For MCF-7 cells, the slope of the regression line = 1.03, an intercept of 1.5 and an r^2 = 0.994. For SK-Br-3 cells, the slope of the regression line = 1.01 with an intercept of 2.9 and an r^2 = 0.984. For PC3-9 cells, the slope of the regression line = 1.19 with an intercept of 10.5 and an r^2 = 0.963. The slope of 1.19 for PC3-9 cells may be due to an improved dynamic range of the **new device** resulting in a flattening out of the response curve at higher cell numbers. In other words, the recovery of CTC by the CellSearch™ Circulating Tumor Cell System at high numbers of cells may be somewhat more sensitive than recovery by the predicate, particularly with lower EpCAM antigen density cells as is the case with PC3-9 cells. This difference could also be attributable to increased reliability and/or stability of the CellTracks® AutoPrep Systemas compared to the CellPrep™ Sample Preparation System. Regardless of this potential difference, there appears to be no difference between the CellSearch™ Circulating Tumor Cell System and the predicate at the medical decision level of 5 to 50 CTC.

All of the above new studies with the CellSearch™ Circulating Cell Kit/ AutoPrep/CellTracks® Analyzer II system demonstrate that the detection of tumor cells by the CellSearch™ Circulating Cell Kit/ AutoPrep/CellTracks® Analyzer II system is substantially equivalent to the predicate system. Therefore, the following interpretation of results, interfering substance analysis, and clinical data generated using the predicate system (K035188) is applicable to the new device (K050245).

Interpretation of Results
Results are reported as the number of CTC / 7.5 mL of blood. A CTC count of 5 or more per 7.5 mL of blood is predictive of shorter progression free survival and overall survival.

> **Precaution:** Specimens with more than 5,000 CTC per 7.5 mL of blood were less than 0.03% of those seen in our clinical studies. Sample carryover is of concern when such a high CTC specimen is immediately followed in the CellTracks® AutoPrep System by a specimen yielding a CTC result in the range 5 to 15 CTC per 7.5 mL of blood. In this case, we recommend obtaining a new blood sample from the low CTC patient and

performing a confirmatory CTC analysis. To identify following samples, refer to the CellTracks® AutoPrep User's Guide section on View Data and obtain the detailed batch data, including sample and patient identification for each tube in the batch.

Interfering Substances
SKBr-3 cells spiked into blood samples were exposed to potential interfering substances and compared to untreated controls. Toxic levels (5 times therapeutic index) of the following cancer drugs, over-the-counter drugs, and other exogenous substances were tested: cyclophosphamide, Mitomycin C, Procrit, biotin, 5-fluorouracil, methotrexate, Tamoxifen Citrate, paclitaxel, Arimidex, acetaminophen, acetylsalicylic acid, caffeine, dextromethorphan, Aredia, Human Anti-Mouse Antibody (HAMA) type 1, HAMA type 2, Herceptin, and ibuprofen. No significant differences in SKBr-3 cell numbers were detected, indicating that these substances do not interfere with the CellSearch™ kit.

Samples spiked with toxic levels of doxorubicin resulted in aberrant staining of leukocytes as cytokeratin and CD45 dual positive cells, due to the doxorubicin being a fluorescence compound that is incorporated into nucleated cells. If seen, the staining pattern, of all cells being CD45 positive and cytokeratin positive, is obvious and easily identified by the operator as a known interference staining profile. If blood is drawn outside of the recommended 7 day wash-out period following doxorubicin infusion, this interference is unlikely to be observed in clinical practice, given controlled therapeutic levels and rapid drug clearance.

Potential interference from lipemia was studied by adding Intralipid to samples to a concentration of 2.6%, which is greater than 1000 mg/dl triglyceride. Samples were lysed to simulate total hemolysis. Bilirubin at 7.4 mg/dL, HAMA 1/HAMA 2 and hematocrit from 18-60% were studied. Lipemia, hemolysis, icterus and a broad range of hematocrit values do not interfere with the CellSearch™ assay. HAMA 1 and HAMA 2 also do not interfere, indicating that individuals receiving mouse Ig by parenteral routes can be tested successfully with the CellSearch™ assay.

System Reproducibility with Patient Specimens
A total of 163 duplicate samples were collected from 47 patients over the course of the clinical study. These samples were processed separately on multiple systems at different sites (including different CellPrep™ instruments) to determine the reproducibility of CTC measurements. The regression equation for the comparison of these 163 duplicate samples was $Y=0.98x + 0.67$, $R^2=0.9978$. **Table 3** shows the summary of the data for replicates where the average of the two CTC results was <5 compared to those where the average was ≥5.

Table 3. Reproducibility of CTC Counts in Duplicate Samples (n=163) with an Average of <5 or ≥5 CTC per 7.5 mL of blood

	CTC <5	CTC ≥5
Number of Duplicates	123	40
Mean CTC Count of Duplicates	0.7	210.5
Avg. Duplicate Standard Deviation	0.5	120
Avg. %CV of Duplicates	60.0%	20.0%

Summary of Clinical Trial Results

Expected Values

Healthy volunteers, non-malignant breast disease, non-malignant other disease

Single point CTC analyses were performed on control groups of 145 healthy volunteers, 101 women with non-malignant breast disease, and 99 women with other non-malignant diseases.

Epithelial cells are not expected to be in the peripheral blood. Of the 345 total samples from healthy volunteers and women with non-malignant disease, only one subject had more than 5 CTC/7.5 mL. The results are presented in **Table 4**.

Table 4. Control Subjects

Category	N	Mean # CTC	SD	# Patients with > 5 CTC	Min.*	Max.*
Healthy	145	0.1	0.2	0	0	1
Non-malignant breast disease	101	0.2	1.2	1	0	12
Non-malignant other disease	99	0.1	0.4	0	0	3

*** NCCLS Guideline C28-A2[3]**

Metastatic Breast Cancer Patients

A multi-center prospective, longitudinal clinical trial was conducted. Results were used to determine whether the number of CTC predict disease progression and survival. Patients with measurable disease and who were starting a new line of therapy were enrolled (N=177). Clinical data were analyzed on an intent-to-treat basis.

Table 5. Patient Demographics

Age at Baseline (Median)		58.0 ± 13.4 (58)
Race:	**White**	153 (84%)
	Black	14 (8%)
	Hispanic	7 (4%)
	Unknown	3 (2%)
	ER/PR +	121 (68%)
	ER/PR -	54 (31%)
	Unknown	2 (1%)
	Her-2/neu -	91 (52%)
	Her-2/neu 1+	12 (7%)
	Her-2/neu 2+	18 (10%)
	Her-2/neu 3+	27 (15%)
	Unknown	29 (16%)
Line of Therapy		
	1st	83 (47%)
	2nd	25 (14%)
	≥ 3rd	67 (38%)
	Unk.*	2 (1%)
Type of Therapy		
	Hormone	47 (26%)
	Chemo	87 (49%)
	Immu/C/H	28 (16%)
	H / C	10 (6%)
	No Tx**	4 (2%)
	Unk.*	1 (1%)

*Unk. = Information not available **No Tx. = No treatment information obtained
C or Chemo = Chemotherapy, H or Hormone = Hormone Therapy, I or Immuno = Immunotherapy

Baseline CTC count was determined prior to initiation of a new line of therapy. A first follow-up CTC count was determined after the initiation of therapy. For the baseline analyses, Progression Free Survival (PFS) was measured from the time of the baseline blood draw to the diagnosis of progression by CT scans and/or clinical signs and symptoms, and Overall Survival (OS) was measured from the time of baseline blood draw to the time of death. For the first follow-up analyses, PFS was measured from the time of 1st follow-up blood draw (mean 4.5 ± 2.4 weeks following enrollment) to diagnosis of progression or death, and OS was measured from the time of 1st follow-up blood draw to the time of death.

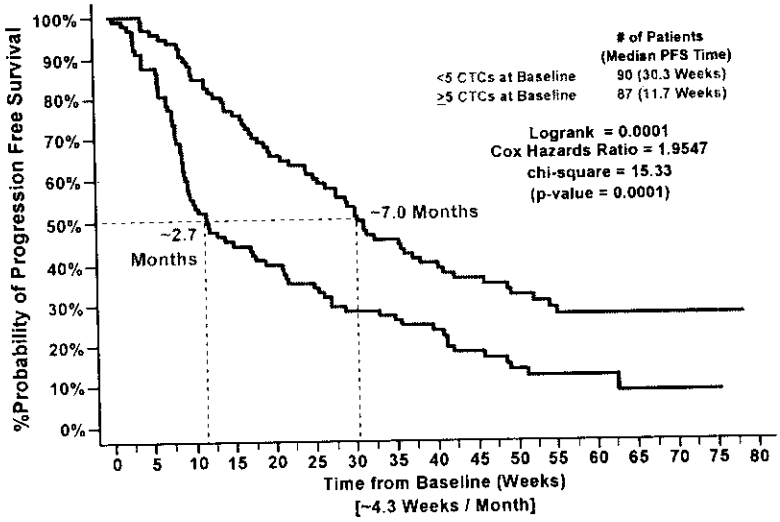
Progression Free Survival (PFS) Analysis
PFS Using Baseline CTC Results

All 177 patients had a baseline CTC test performed. For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- The Favorable group (N=90), represented in **green**, consisted of patients with <5 CTC.
- The Unfavorable group (N=87), represented in **red**, consisted of patients with ≥5 CTC.

Median PFS was 30.3 weeks (~7.0 months) for the Favorable group and 11.7 weeks (~2.7 months) for the Unfavorable group. The difference in PFS between the two groups is highly significant (Log-rank p=0.0001, Cox Hazards Ratio=1.9547, chi-square=15.33, p = 0.0001). These results are illustrated in **Figure 1**.

Figure 1. PFS of Patients with < 5 or ≥ 5 CTC at Baseline (N=177)



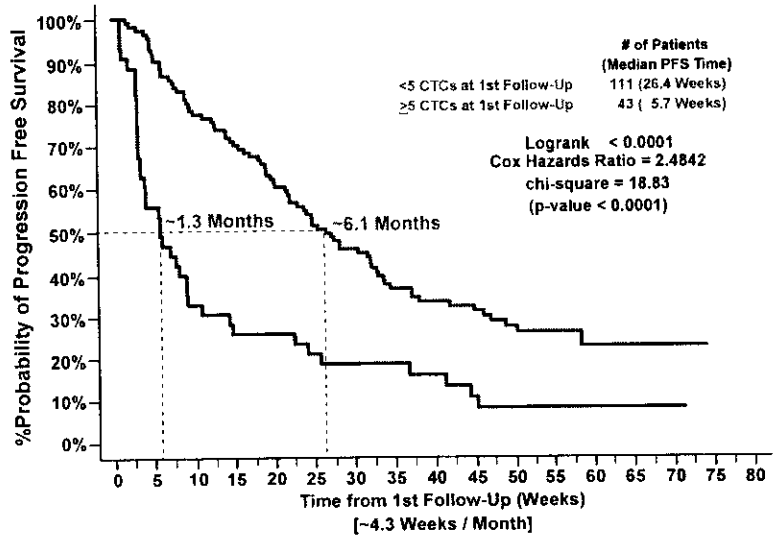
PFS Using 1st Follow-up CTC Results

Of the 177 patients, 23 were not evaluable at first follow-up. Of these 23 patients, ten patients died before a follow-up blood draw could be obtained, nine patients progressed prior to the 1st follow-up blood draw, and four were lost to follow-up. Additionally, the ten patients who died had high to extremely high CTC counts at baseline (CTC counts 9, 11, 15, 24, 111, 126, 301, 1143, 4648 and 23618). For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at 1st follow-up:

- The Favorable group (N=111), represented in **green**, consisted of patients with <5 CTC,
- The Unfavorable group (N=43), represented in **red**, consisted of patients with ≥5 CTC.

Median PFS was 26.4 weeks (~6.1 months) for the Favorable group and 5.7 weeks (~1.3 months) for the Unfavorable group. The difference in PFS between the two groups is highly significant (Log-rank p<0.0001, Cox Hazards Ratio=2.4842, chi-square=18.83, p< 0.0001). These results are illustrated in **Figure 2**.

Figure 2. PFS of Patients with < 5 or ≥ 5 CTC at 1st Follow-Up (N=154)

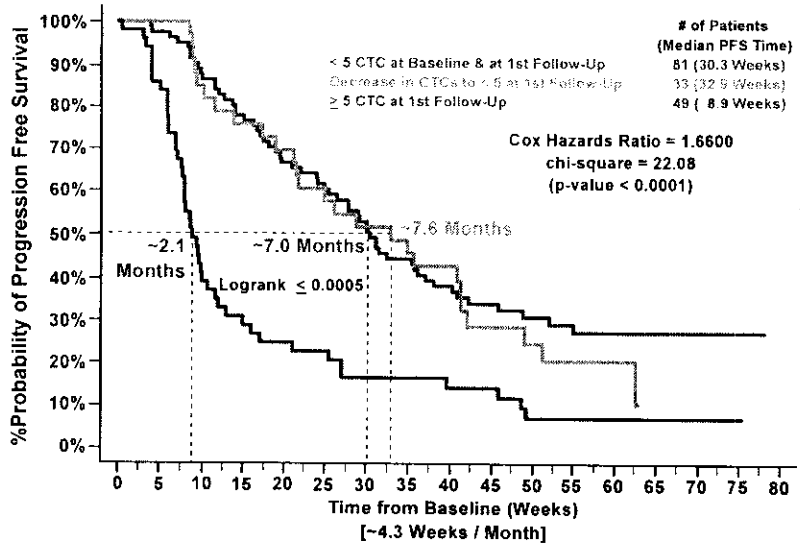


Predictive Value of CTC Reduction on PFS
For Kaplan-Meier analysis, patients were segmented into three groups based on their CTC counts at baseline and 1st follow-up:

- The Favorable group (N=81), represented in **green**, consisted of patients with <5 CTC at both time points,
- Patients with 5 or more CTC at baseline that decreased to below 5 CTC at 1st follow-up are represented in olive green (N=33),
- The Unfavorable group (N=49), represented in **red**, consisted of patients with ≥5 CTCs at 1st follow-up,

Elapsed PFS time was calculated from the baseline blood draw. Three groups were plotted in **Figure 3**. The Favorable group (N=81, **green** line) had a median PFS of 30.3 weeks (~7.0 months) and the patients represented by the olive green line (N=33) had a median PFS of 32.9 weeks (~7.6 months). The Unfavorable group (N=49, **red** line) had a median PFS of 8.9 weeks (~2.1 months). The difference in the PFS of the patients in the Favorable and olive green groups compared to the PFS of the patients in the Unfavorable group is highly significant (Log-rank p≤0.0006, Cox Hazards Ratio=1.6600, chi-square=22.08, p< 0.0001).

Figure 3. A Reduction in CTC Count to Below 5 at the 1st Follow-Up Time Point After the Initiation of Therapy Predicts Improved PFS (N=163)



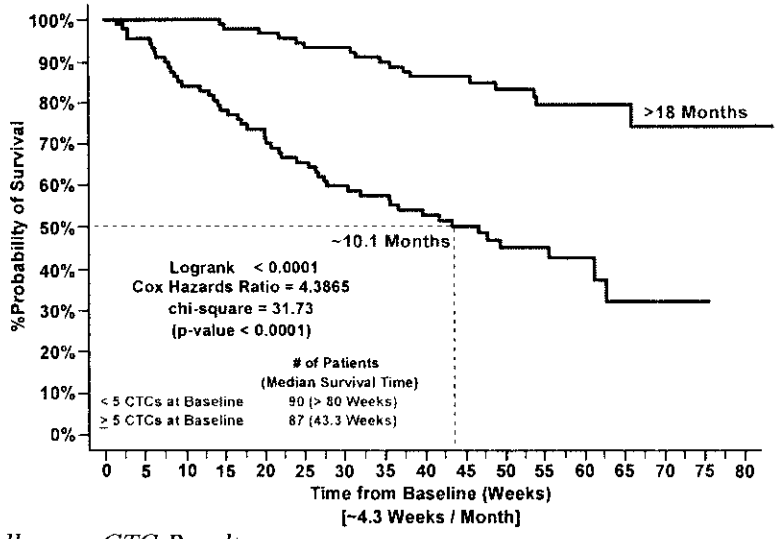
Overall Survival (OS) Analysis
OS Analysis Using Baseline CTC Results

Death occurred in 66 (37%) of the 177 patients during this study. Seventeen (19%) of 90 patients from Favorable group (<5 CTC at baseline) compared to 49 (56%) of 87 from Unfavorable group (≥5 CTC at baseline) died. Median OS was greater than 80 weeks (>18 months) for the Favorable group and 43.3 weeks (~10.1 months) for the Unfavorable group. The OS difference between the two groups is highly significant (Log-rank p<0.0001, Cox Hazards Ratio=4.3865,

chi-square=31.73, p< 0.0001). These results are illustrated in **Figure 4**. For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- The Favorable group (N=90), represented in **green**, consisted of patients with <5 CTC.
- The Unfavorable group (N=87), represented in **red**, consisted of patients with ≥5 CTC.

Figure 4. OS of Patients with < 5 or ≥ 5 CTC at Baseline (N=177)



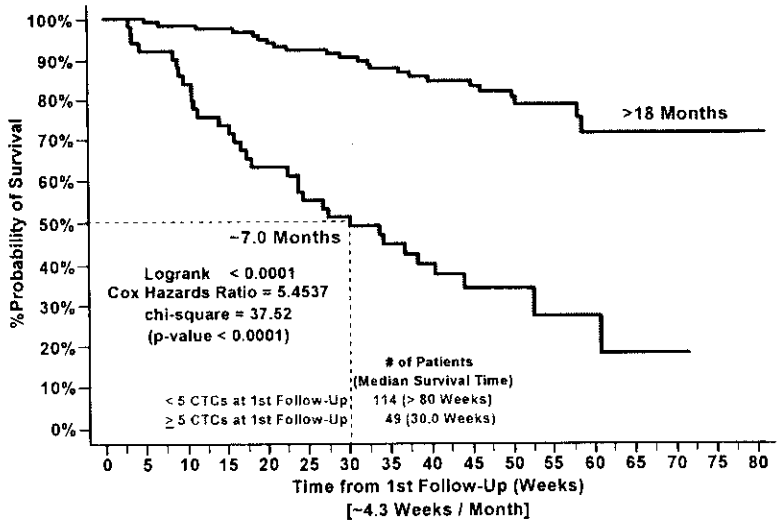
OS Using 1st Follow-up CTC Results

For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at 1st follow-up:

- The Favorable group (N=114), represented in green, consisted of patients with <5 CTC,
- The Unfavorable group (N=49), represented in **red**, consisted of patients with ≥5 CTC.

Of the 163 evaluable patients at first follow-up, 56 (34%) died during this study; 23 of 114 (20%) from the Favorable group, 33 of the 49 (67%) from the Unfavorable group. Patients in the Favorable group had a median survival of greater than 80 weeks (>18 months), while the Unfavorable group had a median OS of 30 weeks (~ 7.0 months). The difference in OS between the two groups is highly significant (Log-rank p<0.0001, Cox Hazards Ratio=5.4537, chi-square=37.52, p< 0.0001). Results are summarized in **Figure 5**.

Figure 5. OS of Patients with < 5 or ≥ 5 CTC at 1st Follow-Up (N=163)



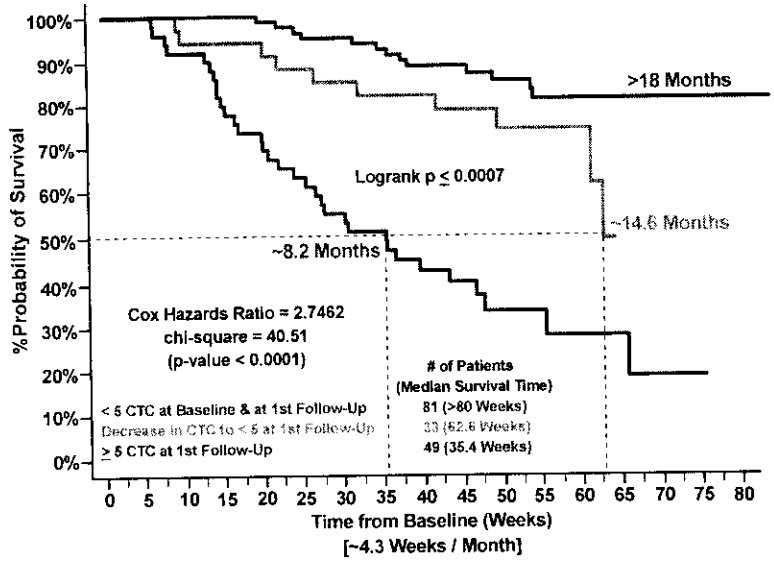
Predictive Value of CTC Reduction on OS

For Kaplan-Meier analysis, patients were segmented into three groups based upon their CTC counts at baseline and 1st follow-up:

- The Favorable group (N=81), represented in **green**, consisted of patients with <5 CTC at both time points,
- Patients with 5 or more CTC at baseline that decreased below 5 CTC at 1st follow-up are represented by the olive green line (N=33),
- The Unfavorable group (N=49), represented in **red**, consisted of patients with ≥5 CTC at 1st follow-up,

Elapsed OS time was calculated from the baseline blood draw. **Figure 6** illustrates that a decrease to <5 CTC after the initiation of therapy significantly impacts OS. The Favorable group (**green** line) had a median OS of >80 weeks (18 months). The patients represented by the olive green line (N=33) had a median OS of 62.6 weeks (~14.6 months). The Unfavorable group (**red** line) had a median OS of 35.4 weeks (~8.2 months). This difference in the OS of the patients in the Favorable and olive green groups compared to the OS of the patients in the Unfavorable group is highly significant (Log-rank p≤0.0007, Cox Hazards Ratio=2.7462, chi-square=40.51, p<0.0001). These data suggest that baseline and 1st follow-up CTC levels are predictive of overall survival.

Figure 6. A Reduction in CTC Count to Below 5 at the 1st Follow-Up Time Point After the Initiation of Therapy Predicts Improved OS (N=163)



Multivariate Cox Regression Analysis

The following parameters were evaluated using multivariate Cox regression analysis, with the SAS PROC PHREG (regression Analysis of Survival Data Based on the Cox Proportional Hazards Model), stepwise selection process to evaluate association with PFS and OS: patient age (continuous), stage of disease at diagnosis (I-IV), time to metastasis (continuous), ECOG status before initiation of a new line of therapy (0-2), ER/PR status (+/-), HER2/neu status (0-3), line of therapy (≥2nd or 1st), type of therapy (chemo/other or hormonal/immuno), baseline CTC count (≥5 or <5 CTC/7.5mL), and 1st follow-up CTC count (≥5 or <5 CTC/7.5mL). A stringency level (p-value) of 0.05 was used to both include and exclude parameters in the multivariate analyses. Results for each parameter that demonstrated a statistically significant correlation to PFS and OS are summarized in **Tables 6** and **7**, respectively. CTC number was the strongest predictor of PFS and OS.

Table 6. Multivariate Cox Analysis: Stepwise Cox Regression for Prediction of PFS

Parameter	Categories		PFS Risk from Baseline			
	Unfavorable	Favorable	HR	p-value	chi^2	# of Patients
Baseline CTC Number	≥5	<5	1.761	0.001	10.58	172
Line of Therapy	≥2nd	1st	1.725	0.002	9.75	
Type of Therapy	Chemo/Other	Hormonal/Immuno	1.611	0.016	5.85	

Parameter	Categories		PFS Risk from Baseline			
	Unfavorable	Favorable	HR	p-value	chi^2	# of Patients
1st Follow-Up CTC Number	≥5	<5	2.516	< 0.001	23.56	162
Line of Therapy	≥2nd	1st	1.579	0.013	6.22	

Table 7. Multivariate Cox Analysis: Stepwise Cox Regression for Prediction of OS

Parameter	Categories		OS Risk from Baseline			
	Unfavorable	Favorable	HR	p-value	chi^2	# of Patients
Baseline CTC Number	≥5	<5	4.261	< 0.001	22.35	170
Line of Therapy	≥2nd	1st	2.384	0.001	10.32	
Type of Therapy	Chemo/Other	Hormonal/Immuno	2.543	0.015	5.90	
ECOG Status	2 vs. 1 vs. 0		1.478	0.024	5.10	
Time to Metastasis	Time in Years		0.922	0.028	4.82	

Parameter	Categories		OS Risk from Baseline			
	Unfavorable	Favorable	HR	p-value	chi^2	# of Patients
1st Follow-Up CTC Number	≥5	<5	6.493	< 0.001	38.34	160
ER/PR Status	Positive	Negative	0.349	0.001	11.19	
Line of Therapy	≥2nd	1st	2.291	0.006	7.67	
ECOG Status	2 vs. 1 vs. 0		1.530	0.025	5.05	

Conclusion:

New performance data demonstrates that the modifications made in the CellSearch™ system did not affect the safety and effectiveness of the test. The newly determined performance characteristics are sufficiently similar (meet specifications) such that the clinical data and interfering substance analysis determined using the predicate device are applicable to the new device and may be included in the new package insert.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAR 15 2005

Ms. Debra J. Rasmussen
World-wide Director of Quality
and Regulatory Affairs
Veridex, LLC
33 Technology Drive
Warren, New Jersey 07059

Re: K050245
Trade/Device Name: CellSearch™ Circulating Tumor Cell Kit
Regulation Number: 21 CFR § 866.6020
Regulation Name: Immunomagnetic Circulating Cancer Cell Selection and Enumeration System
Regulatory Class: II
Product Code: NQI
Dated: January 30, 2005
Received: February 3, 2005

Dear Ms. Rasmussen:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0484. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html

Sincerely yours,

Robert L. Becker, Jr., MD, Ph.D
Director
Division of Immunology and Hematology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K050245

Device Name: **CellSearch™ Circulating Tumor Cell Kit**

Indications for Use:

The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+ and cytokeratin 8 & 18+, and/or cytokeratin 19+) in whole blood in conjunction with the CellTracks® AutoPrep System, the CellSpotter® Analyzer or CellTracks® Analyzer II, and the CellSearch™ Circulating Tumor Cell Control Kit.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast cancer. A CTC count of 5 or more per 7.5 mL of blood generally is predictive of shorter progression free survival and shorter overall survival.

Prescription Use X AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices(OIVD)

Maria M Chan
Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K050245