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510(k) SUMMARY

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

The assigned 510(k) number is **K071729**

NOV 2 0 2007

807.92 (a)(1): Name: Veridex, LLC
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807.92 (a)(2): Device Name – trade name and common name, and classification

Trade name: CellSearch™ Circulating Tumor Cell Kit

Common name: CellSearch™ Circulating Tumor Cell Kit

Classification: Immunomagnetic Circulating Cancer Cell Selection and Enumeration System, Class II, 21 CFR 866.6020, Product Code NQI, Immunology Devices- 82

807.92 (a)(3): Identification of the legally marketed predicate device
CellSearch™ Circulating Tumor Cell Kit, K062013

807.92 (a)(4): Device Description
The CellSearch™ Circulating Tumor Cell Kit contains a ferrofluid-based capture reagent and immunofluorescent reagents. The ferrofluid reagent consists of nanoparticles with a magnetic core surrounded by a polymeric layer coated with antibodies targeting the EpCAM antigen for capturing CTC. After immunomagnetic capture and enrichment, fluorescent reagents are added for identification and enumeration of CTC. The fluorescent reagents include the following: anti-CK-Phycoerythrin (PE) specific for the intracellular protein cytokeratin (characteristic of epithelial cells), DAPI which stains the cell nucleus, and anti-CD45-Allophycocyanin (APC) specific for leukocytes.

The reagent/sample mixture is dispensed by the CellTracks® AutoPrep® System into a cartridge that is inserted into a MagNest® cell presentation device. The strong magnetic field of the MagNest® device attracts the magnetically labeled epithelial cells to the surface of the cartridge. The CellTracks® Analyzer II or CellSpotter® Analyzer automatically scans the entire surface of the cartridge, acquires images and displays any event to the user where CK-PE and DAPI fluorescence are co-located. Images are presented to the user in a gallery format for final classification. An event is classified as a tumor cell when its morphological features are consistent with that of a tumor cell and it exhibits the phenotype EpCAM+, CK+, DAPI+ and CD45-.

807.92 (a)(5): Intended use

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 or metastatic colorectal cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast or metastatic colorectal cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring breast and colorectal cancer. Evaluation of CTC at any time during the course of disease allows assessment of patient prognosis and is predictive of progression free survival and overall survival.

807.92 (a)(6): Technological Similarities and Differences to Predicate

There have been no material changes to the CellSearch™ Circulating Tumor Cell Kit; this 510(k) is being submitted for an expanded indications for use.

807.92 (b)(1): Brief Description of Non-clinical data

Recovery

Blood samples from a single healthy donor were pooled and five of six 7.5 mL aliquots were spiked with approximately 1300, 325, 81, 20, and 5 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 $Y=0.93x + 3.87$ with an $R^2=0.999$ ($R=0.999$). 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.

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 initial sample in the dilution series (i.e. the first tube) 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, and an $R^2 = 0.990$ ($R = 0.995$). Therefore, once the percent recovery (cell loss) was factored out of the CTC values of each of the initial samples, the analysis of the data demonstrated that the detection of CTC was linear over the reportable range of 0 to 1238 tumor cells.

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.

Reproducibility:

a. **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[2]. 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%

b. System Reproducibility with Patient Samples

Metastatic Breast Cancer (MBC)

A total of 163 duplicate blood samples were collected from 47 metastatic breast cancer patients over the course of the clinical study. These samples were processed at multiple sites to determine the reproducibility of CTC measurements. The regression equation for the comparison of these 163 duplicate samples was $Y=0.98x + 0.67$, $R^2=0.99$. **Figure 1** shows a scatter plot of the duplicate CTC results in blood from MBC patients plotted on a logarithmic scale, with the threshold of 5 CTC indicated by the dashed lines.

Figure 1. Reproducibility of CTC Counts in Duplicate MBC Samples (n=163) with Average of <5 or ≥5 CTC per 7.5 mL of blood.

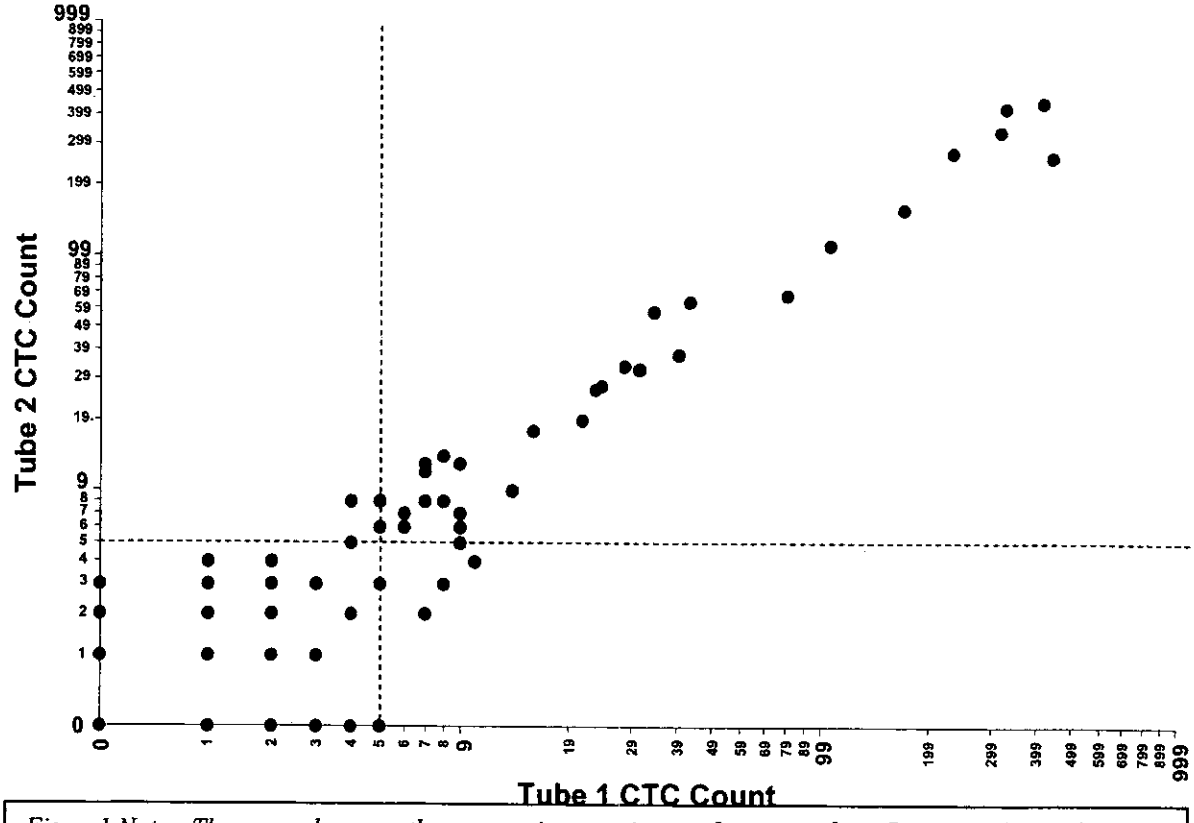


Figure1 Note: There may be more than one point superimposed over another. For example, on this plot, there are 50 instances (31%) where both tubes had 0 CTC, 18 instances (11%) where Tube 1 had 0 CTC and Tube 2 had 1 CTC, and another 18 instances (11%) where Tube 1 had 1 CTC and Tube 2 had 0 CTC.

Metastatic Colorectal Cancer (MCRC)

A total 1,627 duplicate blood samples were collected from 430 MCRC patients over the course of the clinical study. These samples were processed at multiple sites to determine the reproducibility of CTC measurements. The regression equation for the comparison of these 1,627 duplicate samples was $Y=0.98x + 0.18$, $R^2=0.96$. **Figure 2** shows a scatter plot of the duplicate CTC results in blood from MCRC patients plotted on a logarithmic scale, with the threshold of 3 CTC indicated by the dashed lines.

Figure 2. Reproducibility of CTC Counts in Duplicate MCRC Samples (n=1627) with Average of <3 or ≥3 CTC per 7.5 mL of blood.

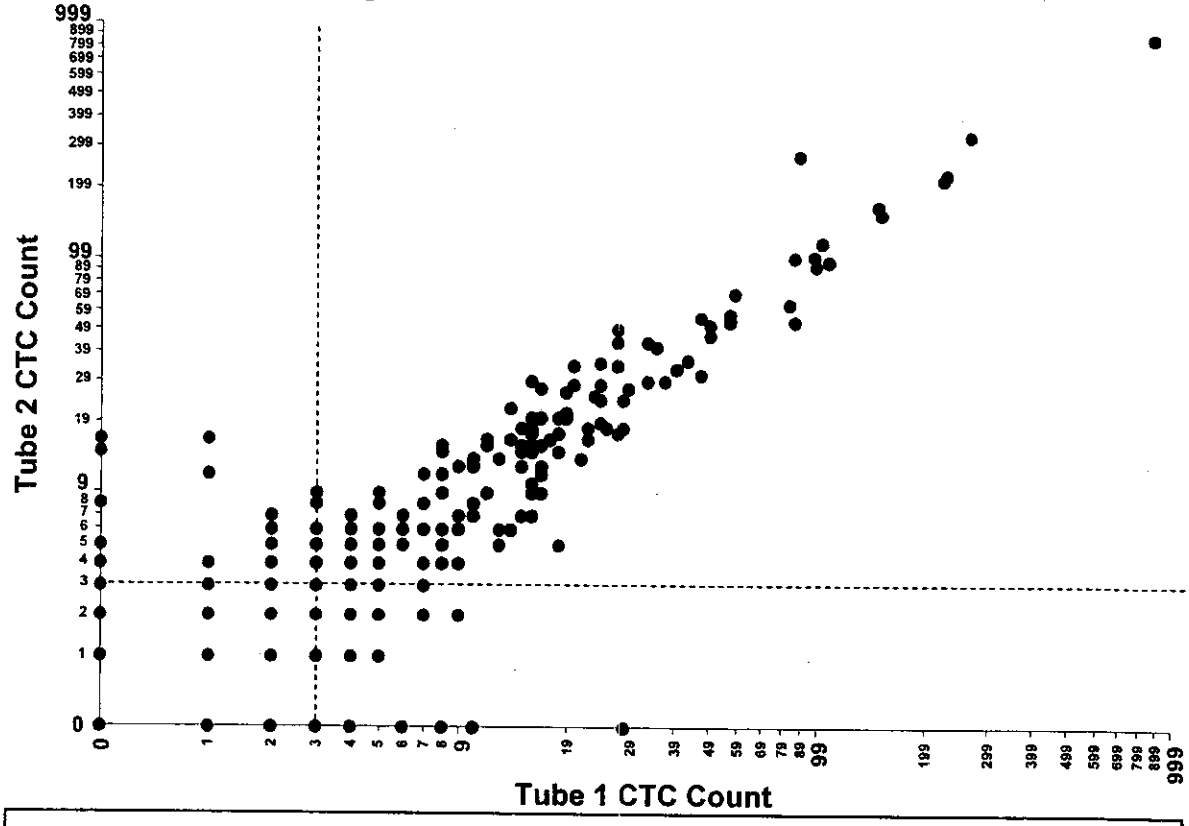


Figure 2 Note: There may be more than one point superimposed over another. For example, on this plot, there are 975 instances (60%) where both tubes had 0 CTC, 116 instances (7%) where Tube 1 had 0 CTC and Tube 2 had 1 CTC, and another 109 instances (7%) where Tube 1 had 1 CTC and Tube 2 had 0 CTC.

1 Metastatic Colorectal Cancer (MCRC) Patients

A multi-center prospective, clinical trial was conducted to determine whether the number of CTC predicted disease progression and survival. Metastatic colorectal cancer patients with measurable (N=430) disease starting a new line of therapy were enrolled. Clinical data were analyzed on an intent-to-treat basis. Patient demographic information is presented in **Table 3.**

Baseline CTC count was determined prior to initiation of a new line of therapy. Follow-up CTC counts were determined after the initiation of therapy at approximately 3 to 4 week intervals. 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 follow-up analyses, PFS was measured from the time of the follow-up blood draw to diagnosis of progression or death, and OS was measured from the time of the follow-up blood draw to the time of death.

Table 3: MCRC Patient Demographics

Category	Description of Categories	N=430 Patients
Age at Baseline (in years)	**Mean ± Std. Deviation (Median)**	63.0 ±12.6 (64)
Years to Metastasis	**Mean ± Std. Deviation (Median)**	0.9 ±1.4 (0.1)
		Number of Subjects (% of total)
Gender	**Female**	192 (45%)
	Male	238 (55%)
Race	**White**	305 (71%)
	Black	44 (10%)
	Other	12 (3%)
	Unknown	69 (16%)
Baseline ECOG Score	**0**	196 (46%)
	1	187 (43%)
	2	31 (7%)
	Unknown	16 (4%)
Tumor Type at Primary Diagnosis	**Colon**	292 (68%)
	Rectal	71 (17%)
	Colorectal	66 (15%)
	Unknown	1 (0%)
Stage at Primary Diagnosis	**1**	12 (3%)
	2	45 (11%)
	3	118 (27%)
	4	232 (54%)
	Unknown	23 (5%)
Liver Metastasis	**No**	117 (27%)
	Yes	313 (73%)
Line of Therapy	**1st Line**	309 (72%)
	2nd Line	95 (22%)
	3rd Line	26 (6%)
Type of Therapy	**Bevacizumab**	243 (56%)
	Irinotecan	103 (24%)
	Oxaliplatin	253 (59%)
	Unknown	25 (6%)

1.1 CTC frequencies

Of the total number of 430 MCRC patients, 9 had a baseline blood draw and no follow-up blood draws. Of these 9 patients, four died before a follow-up blood draw could be obtained, two were taken off their therapy due to treatment related toxicity, one patient had surgery to remove their measurable disease, one patient refused further treatment, and one patient refused any further blood draws. Of the remaining patients, 362, 342, 321, and 211 had follow-up blood draws 1-2 weeks, 3-5 weeks, 6-12 weeks, and 13-20 weeks after the initiation of therapy, respectively. The difference in the number of patients evaluable for PFS and OS at each time point is due to the progression of some patients prior to the blood draw, while the difference in the number of patients at each time point is due to the number of patients with blood draws and evaluable CTC results.

Table 4 shows the numbers of patients at each time point excluded from the PFS, OS, or PFS & OS analyses and the reasons for their exclusion.

Table 4: Exclusions from Progression Free and Overall Survival Analyses

Blood Draw Timing	Reasons for Exclusion of MCRC Patients from Analyses:						Total # of MCRC Patients Evaluable:	
	PFS & OS				PFS Only	OS Only		
	Blood Not Drawn	Blood Drawn 1-7 days after administration of therapy	No Follow-up Beyond Date of Blood Draw	Non-Evaluable CTC Results	Blood drawn after date of disease progression	No Follow-up Beyond Date of Blood Draw	PFS	OS
Baseline	1	11	0	5	0	0	413	413
1-2 Weeks	68	0	0	5	1	0	356	357
3-5 Weeks	88	0	1	8	4	0	329	333
6-12 Weeks	109	0	4	7	26	0	284	310
13-20 Weeks	219	0	9	8	14	1	180	193

The CTC results obtained from the follow-up blood draws at 1-2 weeks, 3-5 weeks, 6-12 weeks, and 13-20 weeks after the initiation of therapy were classified as being favorable (<3 CTC) or unfavorable (≥3 CTC). If more than one CTC result was obtained within any of the designated follow-up timepoints, the CTC result from the blood draw furthest from the baseline blood draw was used.

Table 6 summarizes the total number of MCRC patients and percentage of patients with unfavorable CTC in the clinical trial that differs from the numbers and percentages of patients for Progression Free Survival shown in **Table 5**.

1.2 Progression Free Survival (PFS) Analysis of MCRC Patients

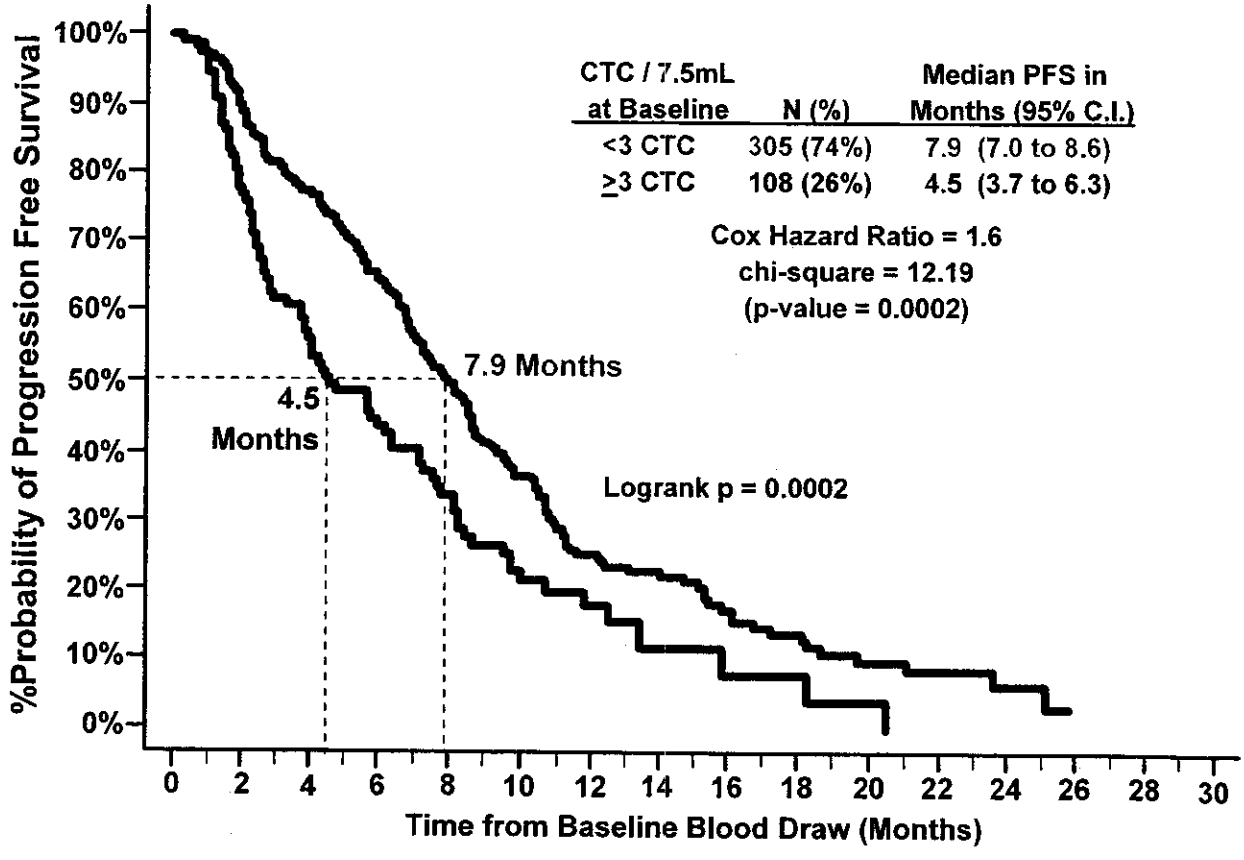
PFS Using Baseline CTC Results

413 of the 430 MCRC patients had a baseline CTC result available. For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- The Favorable group (N=305), represented in **green**, consisted of patients with <3 CTC.
- The Unfavorable group (N=108), represented in **red**, consisted of patients with ≥3 CTC.

Median PFS was significantly longer in the Favorable group compared to the Unfavorable group (7.9 vs 4.5 months, respectively). These results are illustrated in **Figure 3** or **Table 5**.

Figure 3: PFS of MCRC Patients with < 3 or ≥ 3 CTC at Baseline (N=413).



PFS Using Follow-up CTC Results

For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at each of the various follow-up blood draws. Both patient groups at each of the different follow-up blood draw times after initiation of therapy for PFS are illustrated in **Figure 4**. PFS times were calculated from the time of each blood draw, and any patient showing evidence of progression prior to a particular blood draw was excluded from the analysis of that and all subsequent follow-up blood draws. **Figure** 4 illustrates the ability of CTC in MCRC patients

with <3 and ≥3 CTC 1-2 weeks, 3-5 weeks, 6-12 weeks, and 13-20 weeks after the initiation of therapy to predict PFS.

- The Favorable group, represented in olive green, **blue**, **purple**, and cyan, consisted of patients with <3 CTC,
- The Unfavorable group, represented in **brown**, **black**, **grey**, and [illegible], consisted of patients with ≥3 CTC.

Figure 4: PFS of MCRC Patients with < 3 or ≥ 3 CTC at different times of Follow-Up

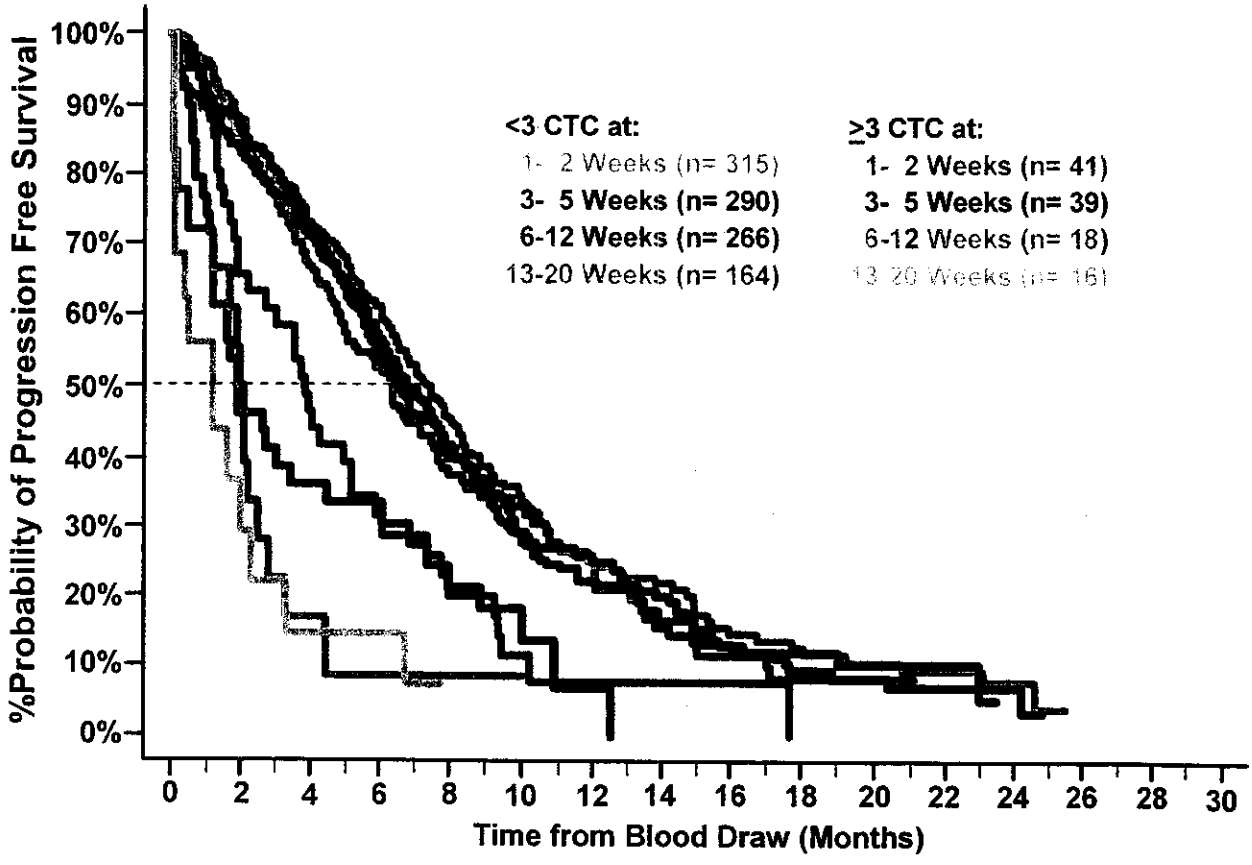


Table 5 summarizes the results of the PFS analysis using the CTC levels and a threshold of ≥3 CTC/7.5mL at each of the different blood draw time points.

Table 5: Progression Free Survival (PFS) for MCRC patients with <3 or ≥ 3 CTC at different time points

1	2	3	4	5	6
Sampling Time After Tx Initiation	**N**	**≥3 CTC**	**Median PFS in Months (95% CI)**		**Log-rank p-value**
			<3 CTC	**≥3 CTC**	
Baseline	413	108 (26%)	7.9 (7.0 - 8.6)	4.5 (3.7 - 6.3)	0.0002
1-2 Weeks	356	41 (12%)	7.3 (6.5 - 8.1)	3.8 (1.9 - 5.1)	<0.0001
3-5 Weeks	329	39 (12%)	6.8 (6.1 - 7.6)	1.9 (1.2 - 4.4)	<0.0001
6-12 Weeks	284	18 (6%)	6.5 (5.8 - 7.7)	2.0 (0.5 - 2.5)	<0.0001
13-20 Weeks	180	16 (9%)	6.3 (4.9 - 7.4)	1.2 (0.1 - 2.3)	<0.0001

As illustrated in **Figure 4** and **Table 5**, **MCRC** patients with elevated CTC (≥3 CTC/7.5mL whole blood) at any of the time points had a much higher likelihood of rapid progression than did those with <3 CTC. **Table 5** column 4 shows the median PFS times for those patients with <3 CTC ranged from 6.3 to 7.9 months and were substantially longer than the median PFS times for those patients with ≥3 CTC, which ranged from 1.2 to 4.5 months (column 5).

Reduction or Increase in CTC Predicts Improved or Decreased PFS

Elapsed PFS times were calculated from the baseline blood draw. For Kaplan-Meier analysis (**Figure 5**), MCRC patients were segmented into four groups based upon their CTC counts at baseline, 1-2 weeks, 3-5 weeks, 6-12 weeks, and 13-20 weeks:

- Group 1 (**green** curve), 303 (70%) patients with <3 CTC at all time points. Seven (2%) of these patients only had a baseline blood draw while eight (3%) had a single blood draw between their first and last blood draw that had ≥3 CTC;
- Group 2 (**blue** curve), 74 (17%) patients with ≥3 CTC prior to the initiation of therapy but who had decreased to <3 CTC at the time of their last blood draw;
- Group 3 (orange curve), 29 (7%) patients with <3 CTC at an early draw (baseline, 1-2 weeks, and/or 3-5 weeks) but who increased to ≥3 CTC at the time of their last blood draw;
- Group 4 (**red** curve), 24 (6%) patients with ≥3 CTC at all time points. Three (13%) of these patients had only a baseline blood draw, one (4%) had only a 3-5 week blood draw, and one (4%) had a single blood draw between their first and last blood draw that had <3 CTC.

Figure 5: A Reduction in CTC Below 3 After the Initiation of Therapy Predicts Longer PFS in MCRC Patients

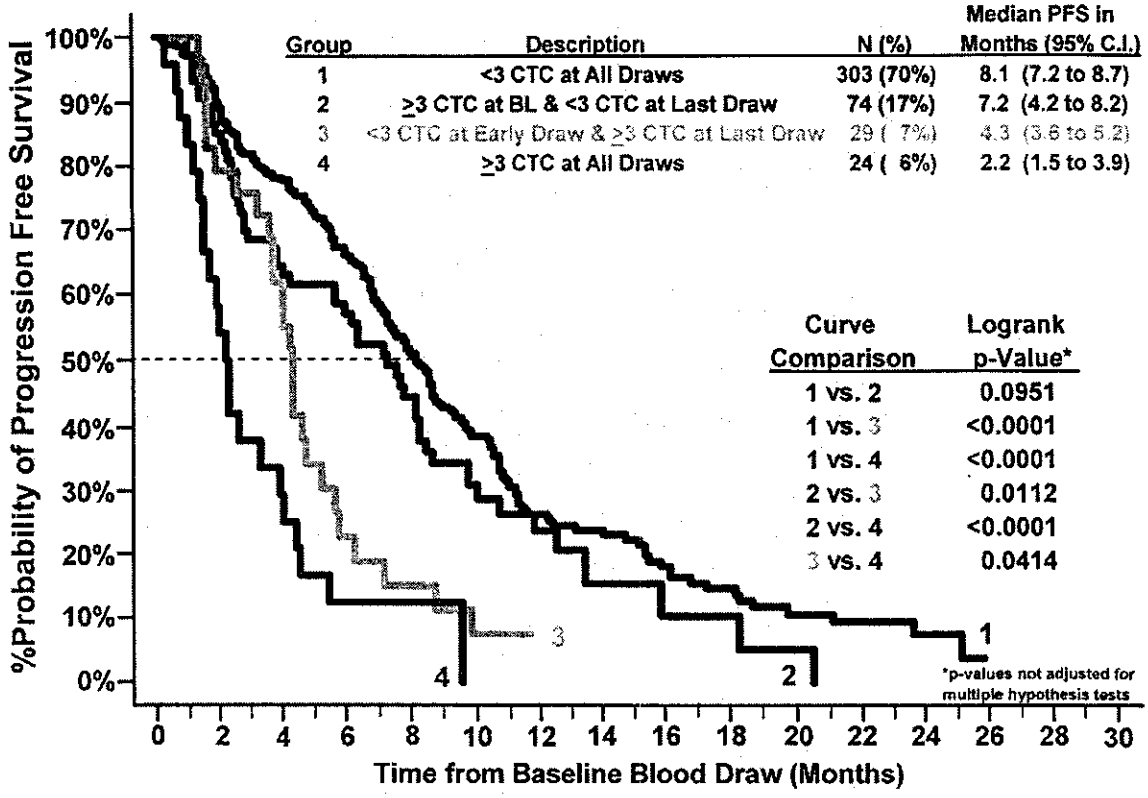


Figure 5 shows that MCRC patients with ≥3 CTC at all time points (**Group 4**) had the shortest median PFS, which was significantly different compared to the median PFS of Group 3, **Group 2** and **Group 1**. The difference in the median PFS between those patients who showed a CTC reduction after the initiation of therapy (**Group 2**) was significantly longer compared to those patients who showed a CTC increase (Group 3).

1.3 Overall Survival (OS) Analysis of MCRC Patients

OS Analysis Using Baseline CTC Results

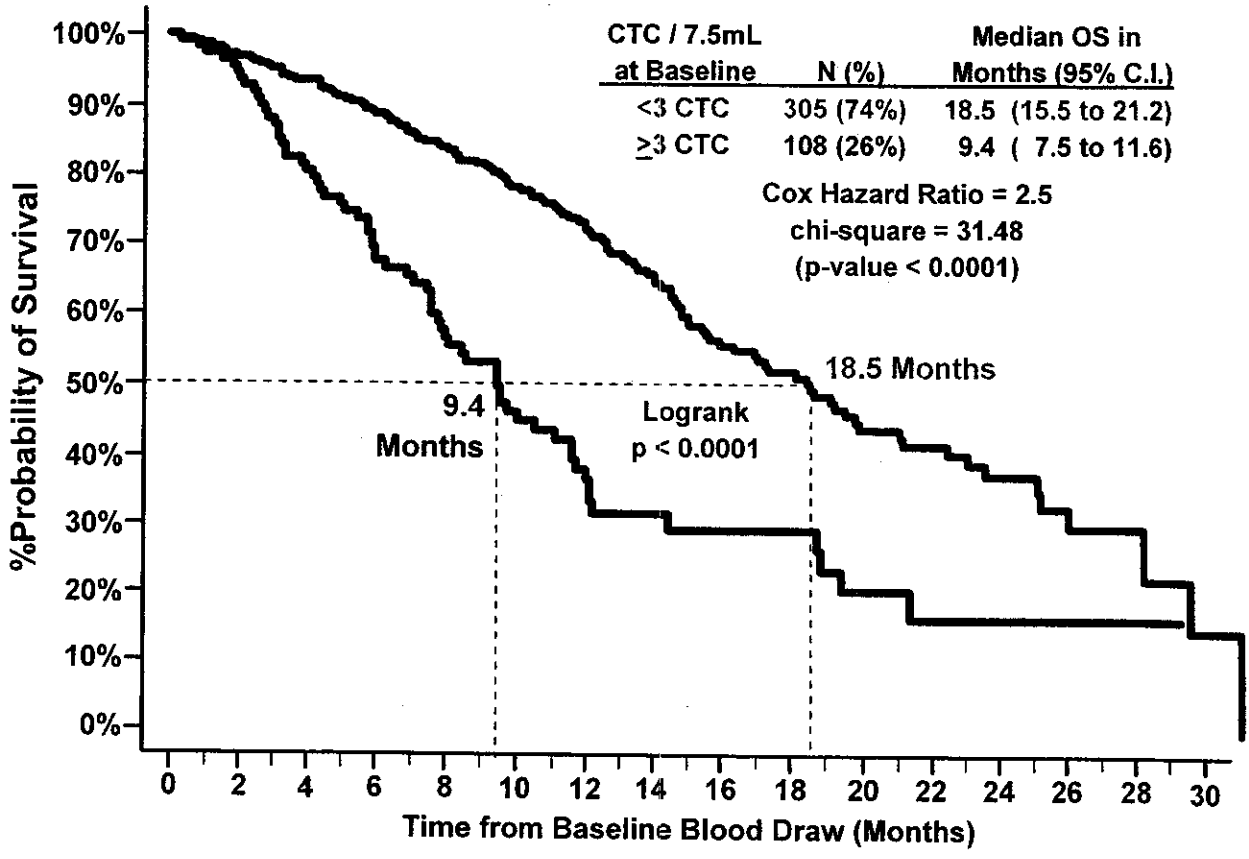
Death occurred in 202 (47%) of the 430 MCRC patients, with a mean follow-up time for the 228 (53%) patients still alive of 12.6 ± 6.5 months (median = 11.0, range = 0.8 – 30.0). At the time of these analyses, 124 (41%) of 305 patients from Favorable group (<3 CTC at baseline) compared to 68 (63%) of 108 from Unfavorable group (≥3 CTC at baseline) had died.

For Kaplan-Meier analysis, patients were segmented into two groups based upon their CTC count at baseline:

- The Favorable group (N=305), represented in **green**, consisted of patients with <3 CTC.
- The Unfavorable group (N=108), represented in **red**, consisted of patients with ≥3 CTC.

Median OS was significantly longer in the Favorable group compared to the Unfavorable group (18.5 vs. 9.4 months, respectively). These results are illustrated in **Figure 6**.

Figure 6: OS of MCRC Patients with < 3 or ≥ 3 CTC at Baseline (N=413).



OS Using Follow-up CTC Results

The Kaplan-Meier analyses of both MCRC patient groups at each of the different follow-up blood draw times after initiation of therapy are illustrated in **Figure 7**. This figure illustrates the ability of CTC in patients with <3 and ≥3 CTC 1-2 weeks, 3-5 weeks, 6-12 weeks and 13-20 weeks after the initiation of therapy to predict time to death in 421 patients with metastatic colorectal cancer. OS times were calculated from the time of each blood draw.

- The Favorable group, represented in olive green, **blue**, **purple**, and cyan, consisted of patients with <3 CTC,
- The Unfavorable group, represented in **brown**, **black**, grey, and orange, consisted of patients with ≥3 CTC.

Figure 7: OS of MCRC Patients with < 3 or ≥ 3 CTC at different times of Follow-Up.

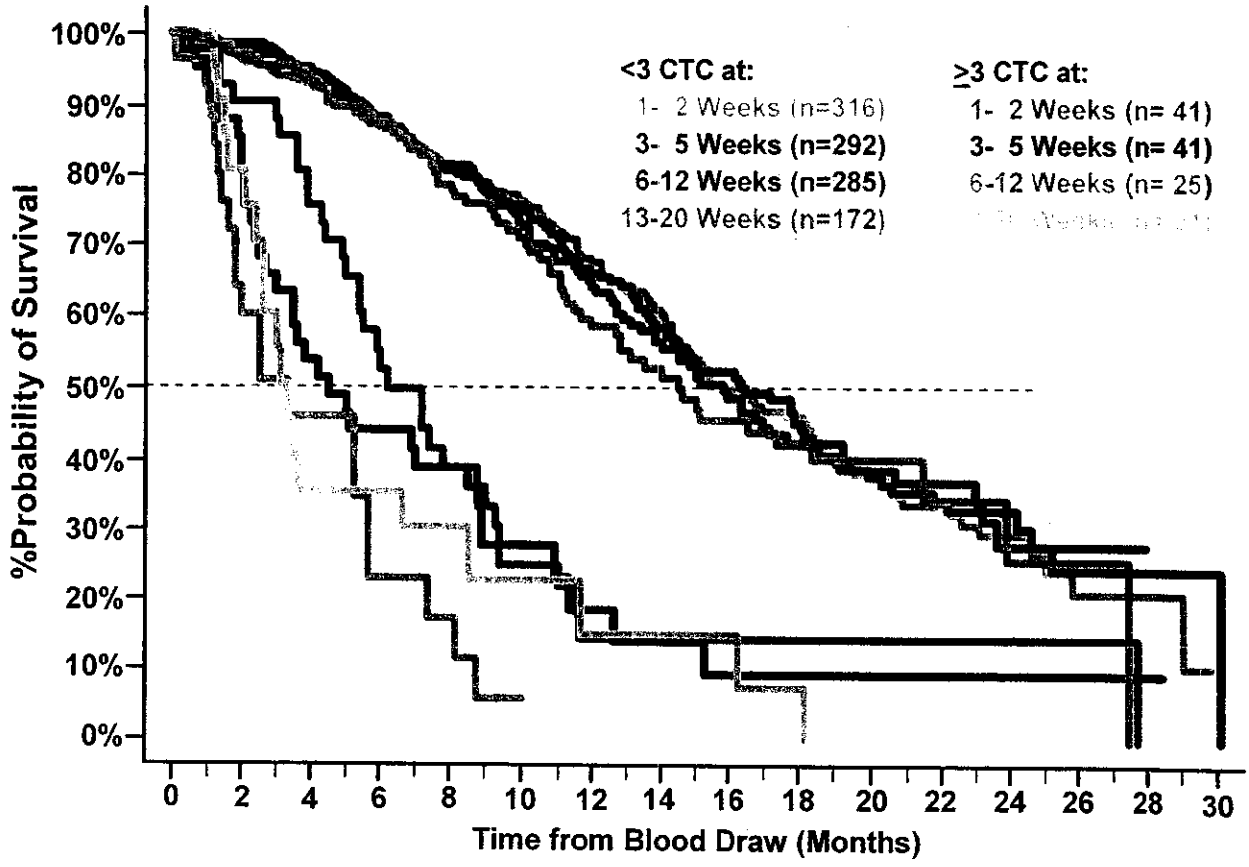


Table 6 summarizes the results of the OS analysis using the CTC levels and a threshold of ≥3 CTC/7.5mL at each of the different blood draw time points.

Table 6: Overall Survival (OS) for MCRC patients with <3 or ≥ 3 CTC at different time points

1	2	3	4	5	6
Sampling Time After Tx Initiation	**N**	**≥3 CTC**	**Median OS in Months (95% CI)**		**Log-rank p-value**
			<3 CTC	**≥3 CTC**	
Baseline	413	108 (26%)	18.5 (15.5 - 21.2)	9.4 (7.5 - 11.6)	<0.0001
1-2 Weeks	357	41 (11%)	15.7 (14.3 - 18.4)	6.1 (4.9 - 8.9)	<0.0001
3-5 Weeks	333	41 (12%)	16.4 (14.1 - 18.3)	4.4 (2.6 - 8.7)	<0.0001
6-12 Weeks	310	25 (8%)	15.8 (13.8 - 19.2)	3.3 (1.8 - 5.6)	<0.0001
13-20 Weeks	193	21 (11%)	14.6 (12.0 - 21.5)	3.3 (2.4 - 8.5)	<0.0001

As illustrated in **Figure 7** and **Table 6** in columns 4 & 5, MCRC patients with ≥3 CTC at any of the time points had a much higher likelihood of dying sooner than did those with <3 CTC. The median OS times for those patients with <3 CTC ranged from 14.6 to 18.5 months and were substantially longer than the median OS times for those patients with ≥3 CTC, which ranged from 3.3 to 9.4 months.

Reduction or Increase in CTC Predicts Improved or Decreased OS

Elapsed OS times were calculated from the baseline blood draw. For Kaplan-Meier analysis (**Figure 8**), MCRC patients were segmented into four groups based on their CTC counts at baseline, 1-2 weeks, 3-5 weeks, 6-12 weeks, and 13-20 weeks:

- Group 1 (**green** curve), 303 (70%) patients with <3 CTC at all time points. Seven (2%) of these patients only had a baseline blood draw while eight (3%) had a single blood draw between their first and last blood draw that had ≥3 CTC;
- Group 2 (**blue** curve), 74 (17%) patients with ≥3 CTC prior to the initiation of therapy but who had decreased to <3 CTC at the time of their last blood draw;
- Group 3 (orange curve), 29 (7%) patients with <3 CTC at an early draw (baseline, 1-2 weeks, and/or 3-5 weeks) but who increased to ≥3 CTC at the time of their last blood draw;
- Group 4 (**red** curve), 24 (6%) patients with ≥3 CTC at all draw time points. Three (13%) of these patients had only a baseline blood draw, one (4%) had only a 3-5 week blood draw, and one (4%) had a single blood draw between their first and last blood draw that had <3 CTC.

Figure 8: A Reduction in CTC Below 3 After the Initiation of Therapy Predicts Longer OS whereas an Increase in CTC Count to 3 or above Predicts Shorter OS in MCRC Patients

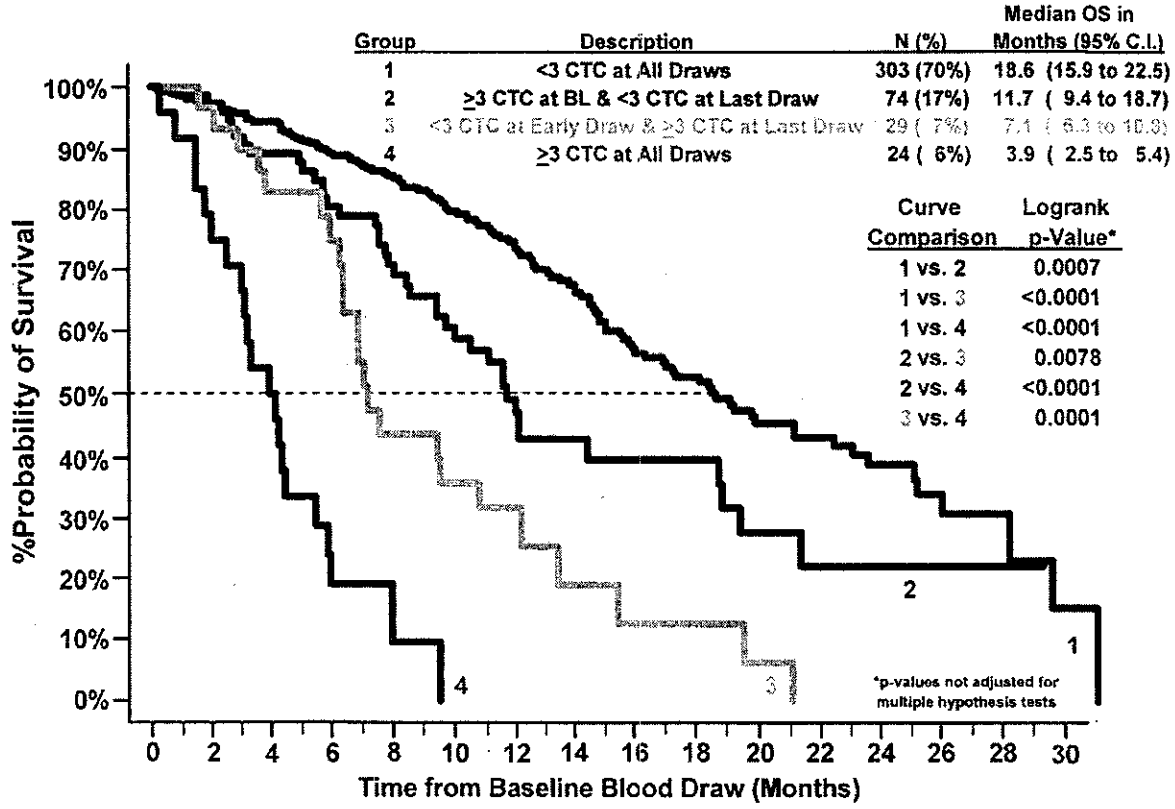


Figure 8 shows that MCRC patients who exceed the threshold of 3 CTC at any point after the initiation of therapy had a much higher likelihood of dying sooner. Patients with ≥3 CTC at all time points (**Group 4**) had the shortest median OS, which was significantly different compared to the median OS of Group 3, **Group 2** and **Group 1**. Patients with <3 CTC at all time points (**Group 1**) had the longest median OS, which was significantly different compared to the median OS of **Group 4**, Group 3 and **Group 2**. **Figure 8** also shows that patients who show a decrease in CTC (**Group 2**) have a significantly lower risk of death compared to those patients with an increase in CTC (Group 3).

Univariate Cox Regression Analysis in MCRC Patients

The following parameters were analyzed using Univariate Cox regression analysis to evaluate association with PFS and OS: gender, stage of disease at diagnosis (1-4), time to metastasis (continuous), patient age (≥65 or <65), site of primary disease (colorectal or rectal or colon), ECOG status before initiation of a new line of therapy (0-2), line of therapy (1nd or 2nd or 3rd), presence of liver metastasis (yes or no), type of therapy (bevacizumab, irinotecan, and/or oxaliplatin included or not), baseline CTC counts (≥3 or <3 CTC/7.5mL), and follow-up CTC counts 1-2 weeks, 3-5 weeks, 6-12 weeks and 13-20 weeks after the initiation of therapy (≥3 or <3 CTC/7.5mL). **Table 7** shows the results of this analysis and presents the Cox hazard ratio (HR) and associated p-value (Wald test of Z statistic) as well as the number of patients in each evaluation.

Table 7: Univariate Cox Regression Analysis

Parameter	Categories		# of MCRC Patients	PFS Risk from Baseline		OS Risk from Baseline	
	Positive	Negative		HR	p-value	HR	p-value
Gender	Male (1)	Female (0)	430	1.01	0.944	1.23	0.156
Stage at Primary Diagnosis	4 vs. 3 vs. 2 vs. 1		407	0.98	0.734	1.09	0.330
Time to Metastasis	Time in Years		428	1.00	0.901	0.92	0.121
Age at Baseline Blood Draw	≥65 Years	<65 Years	430	1.65	<0.001	1.82	<0.001
Site of Primary Disease	Colorectal (2) vs. Rectal (1) vs. Colon (0)		429	1.03	0.733	1.02	0.866
Baseline ECOG Status	2 vs. 1 vs. 0		414	1.32	0.002	1.65	<0.001
Line of Therapy	3 vs. 2 vs. 1		430	2.04	<0.001	1.63	<0.001
Liver Mets	Yes	No	430	0.86	0.225	1.23	0.198
Bevacizumab	Yes	No	405	0.54	<0.001	0.62	0.001
Irinotecan	Yes	No	405	1.51	0.001	1.39	0.029
Oxaliplatin	Yes	No	405	0.53	<0.001	0.69	0.008
Baseline CTC Number	≥3	<3	413	1.59	<0.001	2.48	<0.001
1 - 2 Week CTC Number	≥3	<3	357	2.02	<0.001	3.23	<0.001
3 - 5 Week CTC Number	≥3	<3	334	2.19	<0.001	4.23	<0.001
6 - 12 Week CTC Number	≥3	<3	314	4.59	<0.001	10.88	<0.001
13 - 20 Week CTC Number	≥3	<3	203	5.07	<0.001	4.88	<0.001

Multivariate Cox Regression Analysis in MCRC Patients

Multivariate Cox regression analyses were conducted to evaluate the independent predictive power of CTC count by adjusting for the effects of the known important clinical factors that are statistically significant in the univariate analyses. CTC were found to be strong predictors of PFS and OS (**Table 8**).

Table 8: Multivariate Cox Regression Analysis

Variable	N	PFS Risk from Baseline		OS Risk from Baseline	
		Hazard Ratio	p-value	Hazard Ratio	p-value
Baseline CTC (<3 vs. ≥3)	373	1.76	<0.001	2.46	<0.001
Age at Baseline (<65 vs. ≥65)		1.47	0.002	1.84	<0.001
Baseline ECOG Status (0 vs. 1 vs. 2)		1.16	0.107	1.48	0.001
Line of Therapy (1st vs. 2nd vs. 3rd)		1.59	<0.001	1.41	0.009
Bevacizumab (No vs. Yes)		0.65	0.001	0.68	0.021
Irinotecan (No vs. Yes)		0.76	0.156	1.25	0.363
Oxaliplatin (No vs. Yes)		0.57	0.002	1.00	0.984
1 - 2 Week CTC (<3 vs. ≥3)	321	1.76	0.003	2.77	<0.001
Age at Baseline (<65 vs. ≥65)		1.53	0.001	1.85	<0.001
Baseline ECOG Status (0 vs. 1 vs. 2)		1.26	0.025	1.54	0.001
Line of Therapy (1st vs. 2nd vs. 3rd)		1.76	<0.001	1.62	0.001
Bevacizumab (No vs. Yes)		0.66	0.003	0.77	0.156
Irinotecan (No vs. Yes)		0.67	0.066	1.25	0.402
Oxaliplatin (No vs. Yes)		0.53	0.002	0.97	0.904
3 - 5 Week CTC (<3 vs. ≥3)	302	2.35	<0.001	4.54	<0.001
Age at Baseline (<65 vs. ≥65)		1.58	0.001	2.06	<0.001
Baseline ECOG Status (0 vs. 1 vs. 2)		1.16	0.149	1.33	0.032
Line of Therapy (1st vs. 2nd vs. 3rd)		1.74	<0.001	1.65	0.001
Bevacizumab (No vs. Yes)		0.68	0.007	0.86	0.410
Irinotecan (No vs. Yes)		0.58	0.012	0.99	0.966
Oxaliplatin (No vs. Yes)		0.47	<0.001	0.88	0.594
6 - 12 Week CTC (<3 vs. ≥3)	279	3.04	<0.001	9.43	<0.001
Age at Baseline (<65 vs. ≥65)		1.43	0.013	1.73	0.005
Baseline ECOG Status (0 vs. 1 vs. 2)		1.30	0.027	1.53	0.004
Line of Therapy (1st vs. 2nd vs. 3rd)		1.73	<0.001	1.20	0.282
Bevacizumab (No vs. Yes)		0.61	0.001	0.82	0.337
Irinotecan (No vs. Yes)		0.78	0.258	1.47	0.181
Oxaliplatin (No vs. Yes)		0.62	0.020	1.35	0.278
13 - 20 Week CTC (<3 vs. ≥3)	186	4.50	<0.001	4.97	<0.001
Age at Baseline (<65 vs. ≥65)		1.26	0.218	1.55	0.061
Baseline ECOG Status (0 vs. 1 vs. 2)		1.13	0.417	1.13	0.526
Line of Therapy (1st vs. 2nd vs. 3rd)		1.68	0.004	1.12	0.628
Bevacizumab (No vs. Yes)		0.68	0.058	0.89	0.655
Irinotecan (No vs. Yes)		0.73	0.311	1.20	0.636
Oxaliplatin (No vs. Yes)		0.65	0.135	1.31	0.477

1.4 Use of CTC to Monitor Clinical Status of Metastatic Colorectal Cancer

Relationship between survival, CTC, and disease assessment by imaging
Radiological imaging is one of the primary means used to determine disease status and response to therapy in metastatic colorectal cancer patients. To establish the relationship of clinical status as determined by imaging to CTC, CTC measured at two different timepoints and imaging results were compared 1) to the true clinical endpoint overall survival and 2) to each other.

CTC
Previous data has shown that metastatic colorectal cancer patients with ≥3 CTC / 7.5mL of blood at any succeeding follow-up visit after the initiation of therapy had a higher likelihood of progressive disease and decreased overall survival compared to patients with <3 CTC / 7.5mL of blood. The CTC results obtained 3-5 weeks after the initiation of therapy as well as the CTC results obtained within ± one month of the imaging study were classified as Favorable (<3 CTC) and Unfavorable (≥3 CTC). If more than one CTC value was obtained within ± one month of the imaging study, the CTC result obtained closest to the date of the imaging study was used.

Imaging
Each MCRC patient had to have measurable disease, i.e. a minimum of one 2cm lesion up to and including a maximum of 10 such lesions. The method of imaging for each patient was determined by the treating oncologist in keeping with the current standard of care. Either CT or MRI of the chest, abdomen and pelvis were performed with the requirement that all lesions seen at baseline were followed using the same method for all subsequent imaging studies. Image interpretation was performed by a certified radiologist at the participating site using RECIST uni-dimensional criteria to classify each follow-up disease assessment as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).
Each patient was imaged at a minimum of two time points up to 8 different time points. These studies included a baseline image, imaging at subsequent intervals of 2-3 months (6-12 weeks), and a final image study when the patient went off study. Copies of all patients' imaging studies were forwarded to the study coordinator at each clinical site for filing with the patient clinical data.

Out of the total of 430 evaluable MCRC patients enrolled into the study, 28 (7%) did not have a follow-up imaging study performed, 18 (4%) died before a follow-up imaging study could be performed, and 384 (89%) had one or more follow-up imaging studies performed that were assessed using RECIST criteria. At the time of the 1st follow-up in the 384 patients with a follow-up imaging study, 4 (1%) showed a complete response, 117 (31%) showed a partial response, 186 (48%) had stable disease, and 77 (20%) showed progressive disease. For the purposes of these analyses, patients who died before a follow-up imaging study were considered to have progressive disease.

For response to therapy at the first follow-up disease assessment, the Favorable group was defined as those having stable disease (S), partial response (PR) or a complete response (CR) by RECIST criteria (non-progressive disease, NPD) and the Unfavorable group as those with progressive disease or death (PD).

Relationship between survival to imaging and CTC

Separate Kaplan-Meier analyses were performed to compare the overall survival of MCRC patients in the Favorable (<3 CTC) and Unfavorable (≥3 CTC) groups using CTC results at two different time points and the first follow-up imaging study. Using results from the first follow-up imaging studies performed 9.1 ± 2.9 weeks (median = 8.6 weeks) after initiation of therapy (i.e. the baseline blood draw), the median survival of the 307 (76%) patients determined by imaging to have NPD was 19.1 months (95% CI = 17.0 to 23.1) (**Figure 9, Table 9**). For the 95 (24%) patients determined by imaging to have PD, the median survival was 5.8 months (95% CI= 4.4 to 7.7).

A total of 320 MCRC patients had imaging studies performed before and after initiation of therapy or they died prior to a follow-up imaging study being performed and they had CTC assessed 3-5 weeks after initiation of therapy (average = 3.8 ± 0.7 weeks from the time of the baseline blood draw, median = 4.0 weeks). The median survival of 282 (88%) patients with Favorable CTC results (<3 CTC) was 17.3 months (95% CI = 15.0 to 19.5 months) (**Figure 10, Table 9**). The 38 patients (12%) with Unfavorable CTC results (≥3 CTC) had a median survival of 5.4 months (95% CI = 3.6 to 9.4 months).

To determine if CTC assessments performed closer to the time of the imaging resulted in similar survival prospects compared to CTC assessments performed approximately 4 weeks after the initiation of therapy, only those patients with CTC assessments performed within ± one month of the first follow-up imaging study were analyzed (**Figure 11, Table 9**). Three hundred and sixty-four (364) of the 402 patients (91%) had CTC assessments within one month of the first follow-up imaging study, which was performed 9.0 ± 2.9 weeks (median = 8.5 weeks) after the initiation of therapy. The median survival of 335 (92%) patients with Favorable CTC results was 17.2 months (95% CI = 15.0 to 19.2 months). For the 29 (8%) patients with Unfavorable CTC results, the median survival was 5.4 months (95% CI = 3.2 to 7.5 months). These data show that CTC assessments at both time points provide similar results to imaging conducted approximately nine weeks after the initiation of therapy.

Applying multivariate Cox regression analysis to adjust for imaging indicates that both CTC and imaging at 6-12 weeks are independently associated with overall survival but that CTC [adjusted hazard ratio: 7.9 (4.6-13.6)] are a stronger predictor than imaging [adjusted hazard ratio: 3.1 (2.1-4.6)].

Table 9: OS of MCRC Patients with CTC assessment approximately one month after the initiation of therapy and within one month of the radiological assessment

	N	Median Survival & (95% CI) in Months
A. Imaging	402	
Favorable (NPD)	307 (76%)	19.1 (17.0 – 23.1)
Unfavorable (PD)	95 (24%)	5.8 (4.4 – 7.7)
B. 3-5 week CTC	320	
Favorable (< 3 CTC)	282 (88%)	17.3 (15.0 - 19.5)
Unfavorable (≥3 CTC)	38 (12%)	5.4 (3.6 - 9.4)
C. CTC (±1 month of Imaging)	364	
Favorable (< 3 CTC)	335 (92%)	17.2 (15.0 - 19.2)
Unfavorable (≥3 CTC)	29 (8%)	5.4 (3.2 - 7.5)

Figure 9: Correlation of Radiological and CTC Assessment with OS: OS of MCRC Patients with NPD or PD at 1st Follow-Up Imaging Study (N=402)

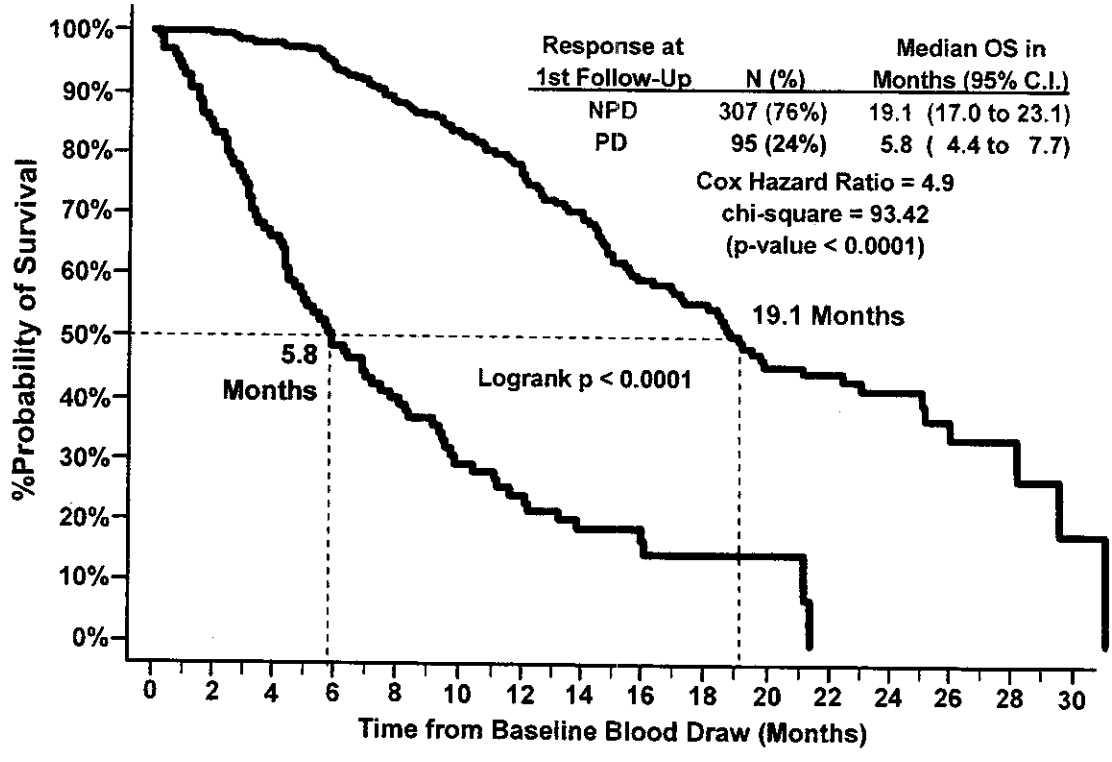


Figure 10: Correlation of Radiological and CTC Assessment with OS: OS of MCRC Patients with <3 or ≥3 CTC at 1st Follow-Up after Initiation of Therapy (N=320)

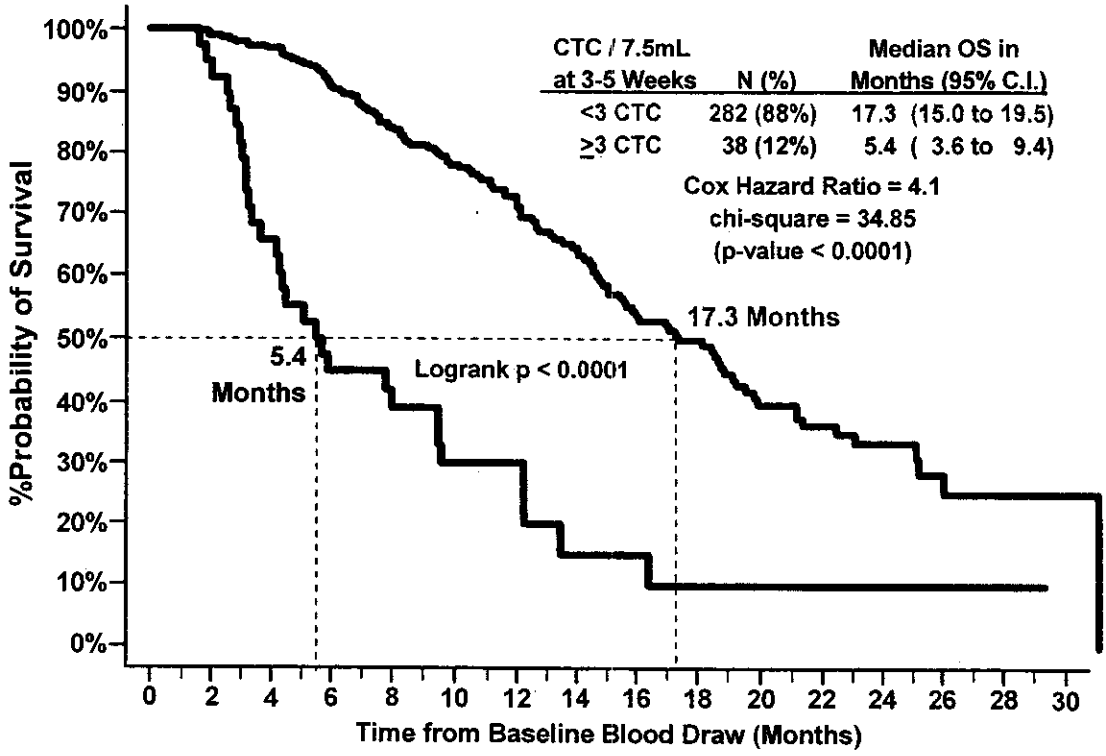
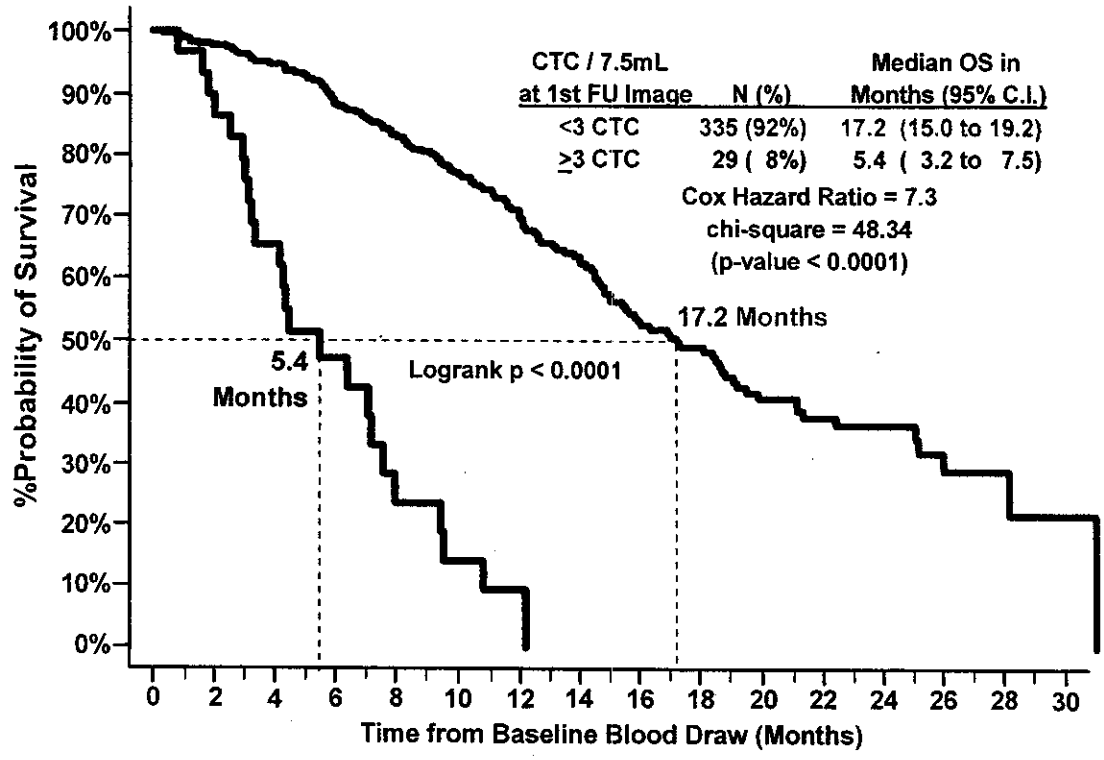


Figure 11: Correlation of Radiological and CTC Assessment with OS: OS of MCRC Patients with <3 or ≥3 CTC within ±1 Month of 1st Follow-Up Imaging Study or Death (N=364)



Concordances between CTC and Radiological Monitoring in MCRC Patients

As noted above, imaging studies are a major component of the current standard of care for determining disease progression and response to treatment in the metastatic colorectal cancer setting. To further support the effectiveness of CTC in making these clinical assessments, two-by-two tabulations of concordant and discordant observations between CTC and radiological imaging were constructed.

For response to therapy, the Favorable group was defined as those having stable disease (S), partial response (PR) or a complete response (CR) by RECIST criteria (non-progressive disease, NPD) and the Unfavorable group as those with progressive disease (PD). Out of the 18 patients who died prior to a follow-up imaging study, 10 had a follow-up blood draw within 30 days of death and these 10 patients were classified as having progressive disease (PD) for the purposes of these comparisons.

The CTC results obtained within ± one month of the imaging study were classified as Favorable (<3 CTC) and Unfavorable (≥3 CTC). If more than one CTC value was obtained within ± one month of the imaging study, the CTC result obtained closest to the date of the imaging study was used. This analysis used all evaluable blood draws from the patients to match up CTC with the imaging studies, not just the ones that were selected for the designated timepoints as described in 1.1 above.

A total of 366 MCRC patients had CTC results within one month of the imaging study or death. The result of this "patient-wise" comparison between CTC and imaging (or death) is shown in **Table 10**.

Table 10: MCRC Patient-Wise Comparison of CTC and Imaging

Response at 1st Follow-Up Imaging Study	CTC within +/- 1 Month of Imaging Study or Death		Total
	<3 CTC/ 7.5mL	≥3 CTC/ 7.5mL	
Non-Progressive Disease	272	13	**285**
Progressive Disease	65	16	**81**
Total	**337**	**29**	**366**

Measurement	Estimate	Lower 95% CI	Upper 95% CI
Positive % Agreement	20%	12%	30%
Negative % Agreement	95%	92%	98%
Positive Predictive Value	55%	36%	74%
Negative Predictive Value	81%	76%	85%
Overall Agreement	79%	74%	83%
Odds Ratio	5.2	2.4	11.2

Of the 384 MCRC patients with one or more follow-up imaging studies, a total of 911 imaging studies that rendered a useable radiological response were performed. A total of 805 of the 911 (88%) imaging studies had CTC results obtained within ± one month of the imaging study. Of the 18 patients who died prior to a follow-up imaging study, 10 had a follow-up blood draw within 30 days of death and these 10 patients were classified as having progressive disease (PD) for the purposes of these comparisons. The result of this "observation-wise" comparison between CTC and imaging (or death) in the 815 observations is shown in **Table 11**.

Table 11: Observation-Wise Comparison of CTC and Imaging

Response at All Follow-Up Imaging Studies	CTC within +/- 1 Month of Imaging Study or Death		Total
	<3 CTC / 7.5mL	≥3 CTC / 7.5mL	
Non-Progressive Disease	597	33	**630**
Progressive Disease	147	38	**185**
Total	**744**	**71**	**815**

Measurement	Estimate	Lower 95% CI	Upper 95% CI
Positive % Agreement	21%	15%	27%
Negative % Agreement	95%	93%	96%
Positive Predictive Value	54%	41%	65%
Negative Predictive Value	80%	77%	83%
Overall Agreement	78%	75%	81%
Odds Ratio	4.7	2.8	7.7

In serial observations, only a minority of the transitions for imaging results between non-progressive disease and progressive disease coincided with a matching transition of CTC counts between <3 and ≥3 CTC / 7.5 mL.

Because the prognostic value of the CTC results at an earlier time-point were equivalent to that of the CTC results at the time of imaging (**Figure 10 & Figure 11**), a patient-wise comparison using results from only the 1st follow-up imaging study, performed approximately 9 weeks after the initiation of therapy, and the CTC results obtained approximately 4 weeks after initiation of therapy was constructed. A total of 320 (80%) of the 402 patients had CTC results 3-5 weeks after the initiation of therapy. The result of this "patient-wise" comparison between CTC at an earlier time point and imaging (or death) is shown in **Table 12**.

Table 12: MCRC Patient-Wise Comparison of CTC and Imaging

Response at 1st Follow-Up Imaging Study	**CTC 3-5 Weeks After Initiation of Therapy**		**Total**
	<3 CTC / 7.5mL	≥3 CTC / 7.5mL	
Non-Progressive Disease	228	18	**246**
Progressive Disease	54	20	**74**
Total	**282**	**38**	**320**

Measurement	**Estimate**	**Lower 95% CI**	**Upper 95% CI**
Positive % Agreement	27%	17%	39%
Negative % Agreement	93%	89%	96%
Positive Predictive Value	53%	36%	69%
Negative Predictive Value	81%	76%	85%
Overall Agreement	78%	73%	82%
Odds Ratio	4.7	2.3	9.5

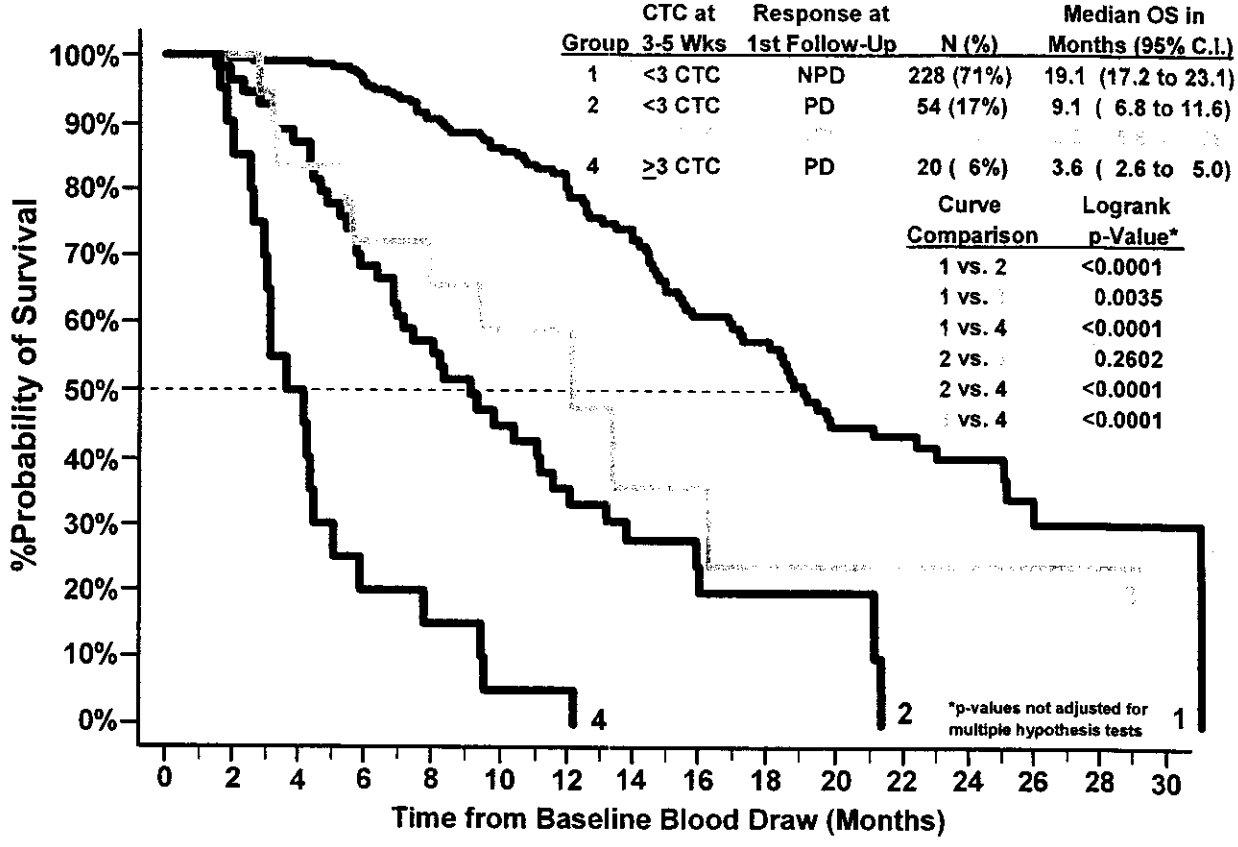
CTC as an Adjunct to Imaging

While the overall agreement between CTC and imaging was good (approximately 78%), there was disagreement in approximately 22% of the MCRC patients. As the information from CTC assessments is intended to be used in conjunction with other diagnostic modalities to make treatment decisions, CTC assessment 3-5 weeks after the initiation of therapy and imaging in the following groups were compared to OS to determine which of the discordant results better reflected the prognosis of the patient:

- Group 1 (**green** curve), 228 (71%) patients with <3 CTC at 3-5 weeks and NPD;
- Group 2 (**blue** curve), 54 (17%) patients with <3 CTC at 3-5 weeks and PD;
- Group 3 (curve), 18 (6%) patients with ≥3 CTC at 3-5 weeks and NPD;
- Group 4 (**red** curve), 20 (6%) patients with ≥3 CTC at 3-5 weeks and PD.

Figure 12 suggests that CTC determination is a strong independent predictor of overall survival. This figure also suggests that the combination of CTC and radiological assessments provides the most accurate assessment of prognosis.

Figure 12: OS of MCRC Patients in Groups 1, 2, and 4 using CTC 3-5 Weeks after Initiation of Therapy (n=320) and the Disease Status Determined at the 1st Follow-Up Imaging Study



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

NOV 2 0 2007

Veridex, LLC
A Johnson and Johnson Company
c/o Ms. Debra J. Rasmussen
Worldwide Executive Director Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Re: k071729
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: Class II
Product Code: NQI
Dated: October 29, 2007
Received: October 30, 2007

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 the Code of Federal Regulations, Title 21, Parts 800 to 898. 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 Part 801); 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) 276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. 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 (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Josephine Bautista

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

Enclosure

INDICATIONS FOR USE

510(K) Number (if known): K071729

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 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 or metastatic colorectal cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast or metastatic colorectal cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring breast and colorectal cancer. Evaluation of CTC at any time during the course of disease allows assessment of patient prognosis and is predictive of progression free survival and overall survival.

The CellSearch system includes: CellSave Preservative Tubes, the CellTracks® AutoPrep® System, the CellTracks® Analyzer II or the CellSpotter® Analyzer, and the CellSearch™ Circulating Tumor Cell Control Kit.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X (Part 21 CFR 801 Subpart D) AND/OR Over –the-Counter Use ___ (21 CFR 801 Subpart C)

Maria M. Chan
Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K071729