TRC-0301:
Bevacizumab (Avastin®) plus 5-FU/Leucovorin (FU/LV) for advanced colorectal cancer (CRC) that has progressed after standard chemotherapies

Helen Chen, Margaret Mooney, Matt Boron, Don Vena, Kimberly Mosby, Louise Grochow, James Zwiebel, Cheryl Grandinetti, Richard Kaplan, The TRC Participating Investigators

Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; The EMMES Corporation, Rockville, MD

NATIONAL® CANCER INSTITUTE

CTEP

Cancer Therapy Evaluation Program

TRC-0301 NCI-Sponsored Study

Background

- **Treatment Referral Center (TRC) was established by NCI in 1991 to handle inquiries for the availability of investigational agents from physicians seeking treatment options for their patients. The network includes NCI-designated Comprehensive Cancer Centers, as well as other cancer institutions selected to provide geographic coverage nationwide.**

- **At the 2003 ASCO Annual Meeting, results of the pivotal Phase III trial of bevacizumab ± IFL(irinotecan/5-FU/LV) became available -- In the 1st-line (untreated) setting of metastatic colorectal cancer (CRC), the addition of bevacizumab to IFL significantly prolonged the overall survival over IFL alone (15.6 vs 20.3 months).**

- **The activity of bevacizumab in CRC patients previously treated with chemotherapy is unknown – The combination of bevacizumab + FOLFOX4 in the 2nd-line setting (after prior irinotecan) is being evaluated in the Intergroup Phase III trial (ECOG 3200) and the results are pending.**

Chen et al, ASCO 2004 (Abstract #3515)

Background (2)

- **In response to the inquiry from patients and physicians for access to bevacizumab pending FDA approval, the Cancer Therapy Evaluation Program (CTEP) at NCI worked with Genentech, patient advocates and the FDA, and developed this TRC protocol (TRC-0301) for patients with advanced CRC in the 3rd line setting, where no standard treatment options were available.**

- **Because no data were available supporting the benefit of bevacizumab in this setting, TRC-0301 was initiated with the following goals:**

  - **To evaluate the safety safety and activity of bevacizumab plus 5-FU/LV in advanced CRC previously treated with irinotecan- and oxaliplatin- based chemotherapy**
  - **To provide a rapid and widely available access to bevacizumab in the setting of a clinical trial for patients without other treatment options.**

Chen et al, ASCO 2004 (Abstract #3515)

Objectives

- **Assess the Response Rate (RR) to bevacizumab plus 5-FU/LV in patients with advanced CRC who have disease progression after irinotecan- AND oxaliplatin based chemotherapy.**
- **Assess the safety profile of bevacizumab plus 5-FU/LV in the 3rd line setting.**
- **Document the Progression Free Survival (PFS) and Overall Survival (OS) in 3rd line patients treated with this regimen.**

TRC-0301 NCI-Sponsored Study

Study Design

This is a single arm, multi-center clinical trial with 2 stages:

- **First stage: Planned accrual - 100 evaluable patients (Response-Assessment Cohort) for the assessment of RR**

  - will distinguish a RR of ≥ 10% vs < 2%, with α and β levels both at 0.05.

  [response-evaluable patients = patients who are eligible, with measurable disease, and have received at least one dose of study therapy]

- **Second stage: If 5 responses were observed in the first 100 patients, this second stage would open for additional patient enrollment until bevacizumab was commercially available.**

Patient Monitoring and Follow-up

- **Tumor assessment every 8 weeks (1 cycle) based on RECIST criteria;**
- **AE reporting reporting (based on CTCAE v3.0) through two mechanisms:**
  - **Expedited: through AdEERS, for unexpected, or serious AEs requiring hospitalization**
  - **On off-study forms: for all G3-5 AEs**
- **All patients followed for two years**

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

Main Eligibility Criteria

- PS 0-2
- Locally advanced or metastatic colorectal cancer
- Tumor progression after (or inability to tolerate) irinotecan-based AND oxaliplatin-based chemotherapy
- Adequate organ functions: ANC $\geq$ 1500/uL, Platelet$\geq$100,000 uL, Transaminase <5 x ULN, PT INR $\leq$ 1.5, PTT $\leq$ ULN
- No major surgery within 28 days of the study therapy
- No thromboembolic conditions requiring full-dose anticoagulation

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

Treatment and monitoring Plan

One of the following regimens based on treating physicians' choice

Regimen A:	**Roswell Park 5-FU/LV + bevacizumab**
	Bevacizumab 5 mg/kg q2w *plus* (5-FU 500 mg/m^2 + LV 500 mg/m^2) qw x 6 *(starting dose of 5-FU 400 mg/m^2 or 320 mg/m^2 permitted based on prior tolerability)*
Regimen B:	**de Gramont 5-FU/LV + bevacizumab**
	Bevacizumab 5 mg/kg q2w *plus* (LV 400 mg/m^2 Day 1 and 2, 5-FU 400 mg/m^2 bolus followed by 600 mg/m^{2}over 22 hrs Day 1 and Day 2) q2w. *(starting dose of 5-FU 320/500 mg/m^2 or 240/400 mg/m^2 permitted based on prior tolerability)*

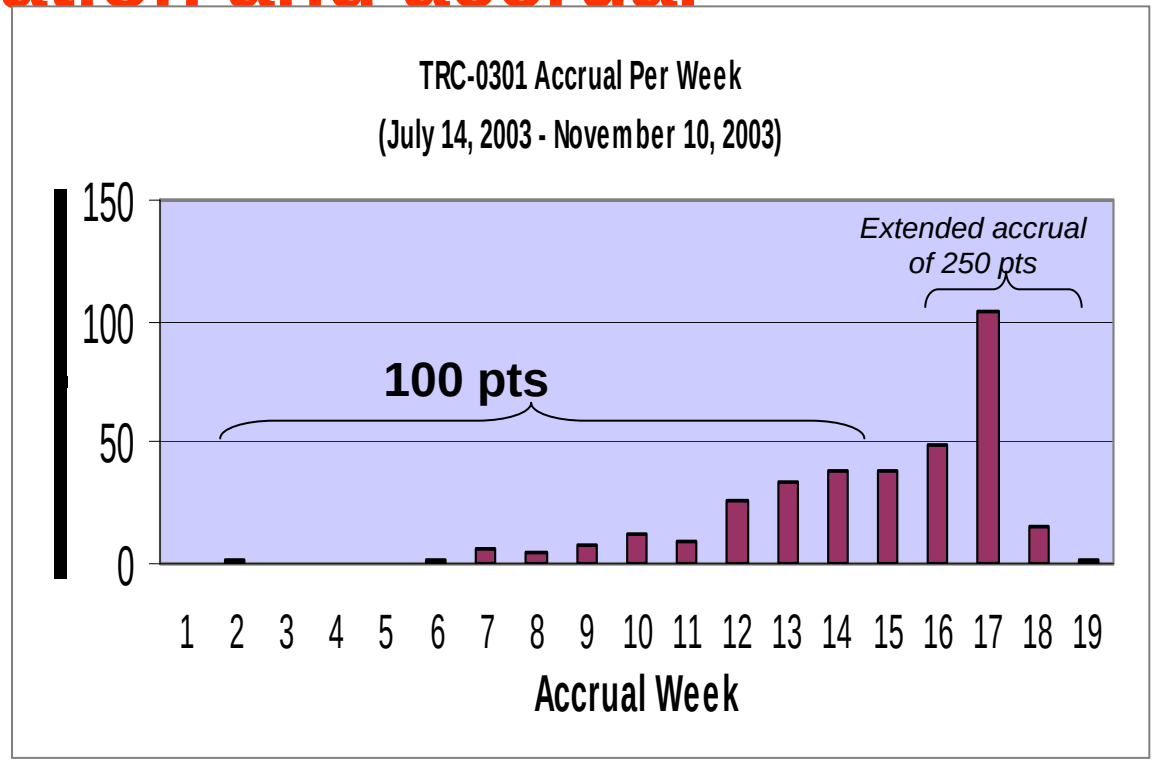
➢**1 cycle = 8 weeks. Treatment continues until tumor progression or unacceptable toxicity**

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

Study implementation and accrual*

- The TRC-0301concept was initiated in May 2003, protocol approved by CTEP in June 2003. 36 sites obtained IRB approval by October 2003.
- Between 7/14/2003 and 10/07/2003, **100 response evaluable patients were accrued.**
- On February 26, 2004, bevacizumab was approved by the FDA for first line use with 5-FU based chemotherapy. TRC-0301 permanently closed to accrual

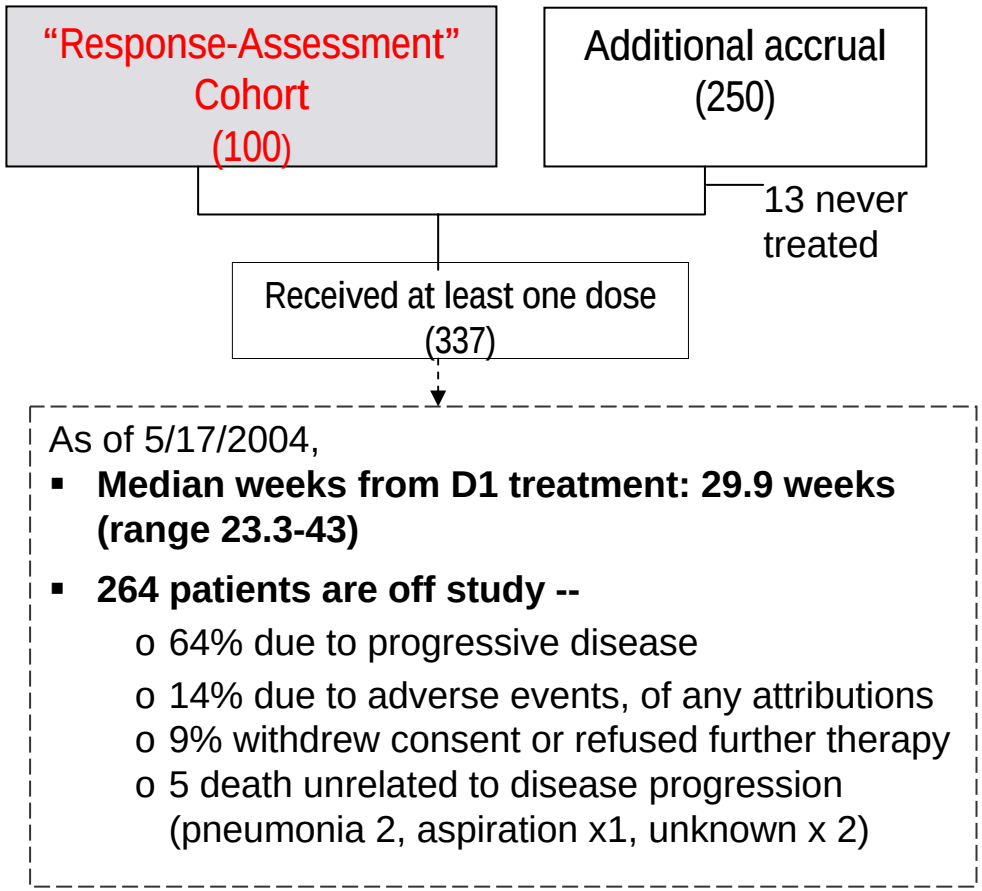


* Upon recommendation by patient advocacy groups, enrollment was extended for 2 weeks to accommodate patients who were being screened. As a result, 250 additional patients were included in the first stage. The protocol was closed to accrual pending response data from the first 100 patients.

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

Results



Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

PATIENT CHARACTERISTICS

	Initial Response Assessment Cohort (n=100)	*All Treated Patients (n=337)*
Age, median (range)	61 (30-92)	*61 (26-92) yrs*
ECOG PS		
0-1	95%	*93%*
2	5%	*7%*
Gender		
Male	52%	*56%*
Female	48%	*45%*
Prior Treatment		
Radiation	29%	*34%*
Irinotecan AND oxaliplatin	100%	*100%*
- Off Irinotecan due to PD	85%	*88%*
- Off Oxaliplatin due to PD	86%	*87%*
Disease Site		
Primary site/tumor bed	17%	*19%*
Lung	69%	*65%*
Liver	82%	*78%*
Other Abdominal	41%	*41%*
Measurable disease	100%	*93%*
Choice of 5-FU Regimen		
Roswell Park	73%*	*73%***
De Gramont	27%*	*27%***

*77% initiated therapy at standard dose of 5-FU

**86% initiated therapy at standard dose

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study

Selected Adverse Events (all attributions)

	Grade 3	Grade 4	Grade 5
	(treated patients with off-study forms) (N=264)		
Hematologic			
ANC	Not collected	1.2%	-
Febrile neutropenia	0.8%	-	-
Non-Hematologic			
Fatigue	10%	0.4%	-
Diarrhea	9%	-	-
ALT/AST/bilirubin	3.6%	1.1%	-
Dyspnea/Respiratory	4.7%	0.4%	0.4%*
Infection	4.4%	0.4%	0.4%**
Cardiovascular			
Hypertension	4%	-	-
Cardiac arrhythmia	0.8%	-	-
LV dysfunction	-	0.4%	-
Cerebral Vascular Event	-	0.4%	-
Cardiac ischemia/infacrction	0.4%		-
Thrombosis/embolism	4.7%	0.8%	-
Hemorrhage			
-CNS	0.4%	-	-
-GI	3.5%	-	-
-GI (varices)	0.4%	0.4%	-
- nose	0.4%	-	-
- other	0.8%	0.4%	-
Other			
Perforation (GI)	-	-	-
Fistula	-	-	-
Proteinuria	0.4%	-	-
Ischemic bowel	0.4%	0.4%	-

*One patient developed grade 5 respiratory complication likely due to rapid progression of lung metastasis.

** One patient died from complications of pneumonia and sepsis.

- 50% of patients had at least one G3-5 Adverse Events, of all attributions
- 13% of patients were removed from study therapy due to adverse events

Chen et al, ASCO 2004 (Abstract #3515)

Responses

	"Response Assessment" Cohort (n=100) (%)	*Additional Treated Pts (n=213)*
Reported by Participating Sites	**4 (4%)** ***(95% CI: 1.1-9.9%)***	*4 (confirmatory scans pending in 6 more patients)*
Confirmed by NCI Independent Review	**1 (1%)[1]** ***(95% CI: 0-5.5%)***	*Response review incomplete*

1. **Among the 3 patients whose PRs were not confirmed, all had stable disease**

Progression-Free Survival (PFS) and Overall Survival (OS)

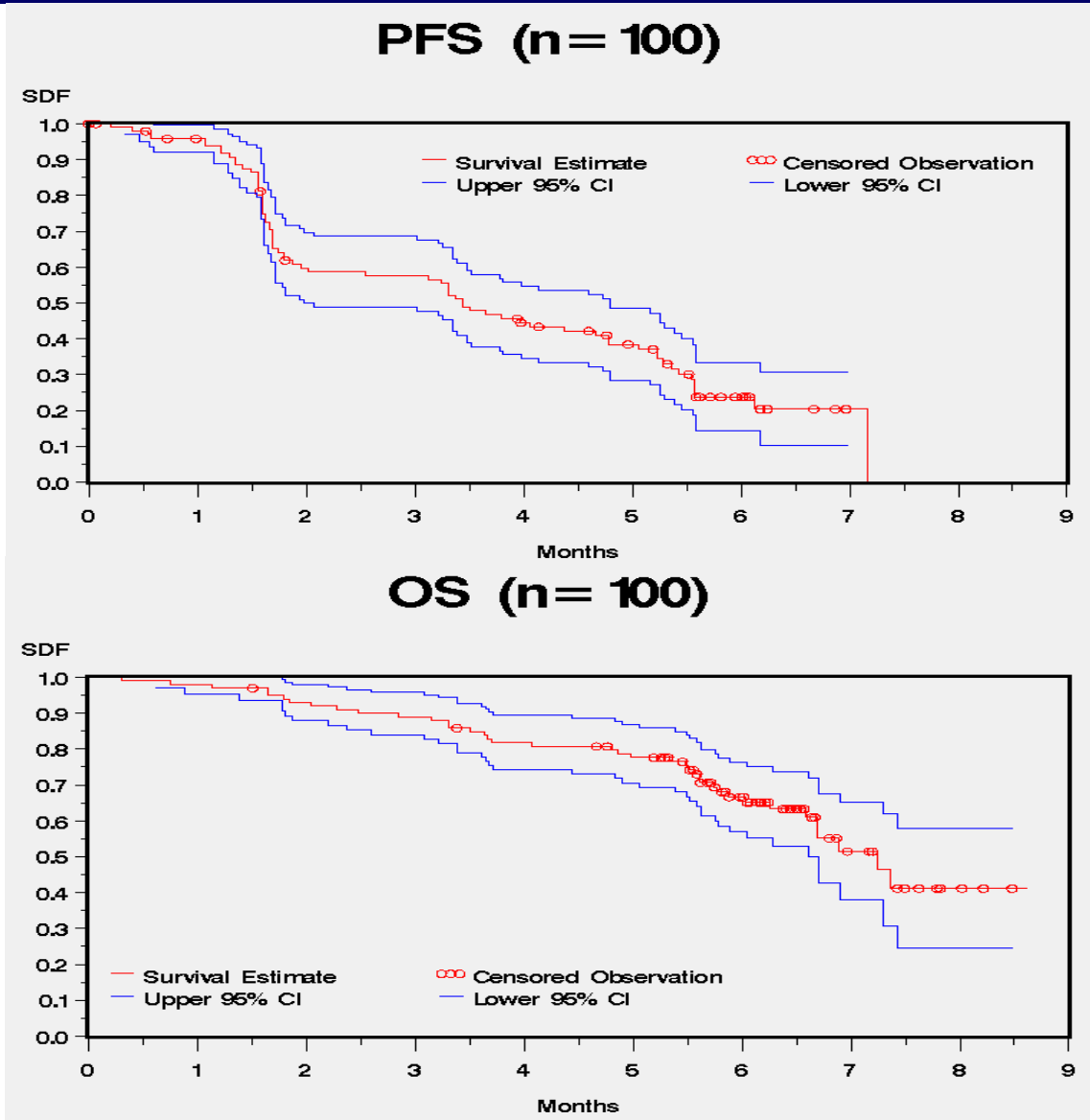
"Response Assessment" cohort (n=100)

- **Median weeks from D1 treatment: *33 weeks (range 31-38.7)***
- **90 patients are off**
  - 59 (66%) due to PD
  - 10 (11%) due to toxicity/complications
  - 9 (10%) withdrew consent
  - 4 (4%) death not due to PD
  - 7 (8%) other/ unknown

	Response Assessment cohort (N=100)	*All treated patients (N=337)*
Median TTP	**3.5 months (15.1 weeks)** *(95% CI: 2.0-4.8 months)*	*3.7 months (16 wks)*
Median survival (OS)	**Data premature**	*Data premature*

Chen et al, ASCO 2004 (Abstract #3515)

TRC-0301 NCI-Sponsored Study



Chen et al, ASCO 2004 (Abstract #3515)

Conclusions

- **The combination of bevacizumab and 5-FU/LV has very low response rate in patients with advanced or metastatic colorectal cancers that have progressed after irinotecan- and oxaliplatin-based chemotherapy.**

- **The safety profile of bevacizumab plus 5-FU/LV is similar to that reported in other trials using similar regimens. Grade 3 or 4 hemorrhage occurred in 4.3% of all patients treated on this protocol (7% based on patients who are off study), including 3% with bleeding in the GI tract; other expected adverse events such as hypertension and thrombosis were also observed.**

- **In the third line setting, bevacizumab should only be used in additional clinical trials with other agents.**

Acknowledgements

- **Genentech: this trial was conducted under the Cooperative Research And Development Agreement (CRADA) between NCI and Genentech, Inc**
- **Patient advocacy groups**
- **The US FDA**
- **All TRC-0301 participating investigators and research nurses**

TRC-0301 NCI-Sponsored Study

Participating Sites	State	Site Principle Investigator
USC/Norris Comprehensive Cancer Center	CA	Heinz-Josef Lenz, M.D.
Jonsson Comprehensive Cancer Center, UCLA	CA	William Isacoff, M.D. Mark Pegram, M.D.
University of Colorado Cancer Center	CO	S. Gail Eckhardt, M.D.
Yale Cancer Center	CT	Jill Lacy, M.D.
Lombardi Cancer Research Center	DC	Jimmy D. Hwang
Atlanta Regional CCOP	GA	Thomas E. Seay, M.D.
Holden Comprehensive Cancer Center	IA	Daniel J. Berg, M.D.
Robert H. Lurie Cancer Center	IL	Al B. Benson, M.D.
Cardinal Bernardin Cancer Center	IL	Kenneth C. Micetich, M.D.
Wichita CCOP	KS	Shaker Dahkil, M.D.
Eastern Main Medical Center	ME	Thomas H. Openshaw, M.D.
Montana Cancer Consortium CCOP	MI	Patrick Cobb, M.D.
St. Joseph's Mercy Hospital	MI	Philip J. Stella, M.D.
Northwest Metro-Minnesota CCOP	MN	Patrick Flynn, MN
Duluth CCOP	MN	Robert J. Dalton, M.D.
University of Mississippi	MS	J. Tate Thigpen, M.D.
Wake Forest Comprehensive Cancer Center	NC	Coty Ho, M.D.
Duke Comprehensive Cancer Center	NC	Herbert I. Hurwitz, M.D.
Merit Care Hospital CCOP	ND	Preston D. Steen, M.D.
Norris Cotton Cancer Center	NH	Gregory H. Ripple, M.D.
Southern Nevada Cancer Res Fdn CCOP	NV	John Ellerton, M.D.
Roswell Park Cancer Institute	NY	Marwan Fakih, M.D.
New York Hospital – Cornell Medical Center	NY	Scott Wadler, M.D.
Ireland Cancer Center	OH	Smitha Krishnamurthi, M.D.
University of Oklahoma	OK	Howard Ozer, M.D.
University of Pennsylvania Cancer Center	PA	Daniel D. Haller, M.D.
Kimmel Cancer Center – Thomas Jefferson University	PA	Edith P. Mitchell, M.D.
Sioux Community Cancer Consortium CCO	SD	Loren K. Tschetter, M.D.
Massey Cancer Center	VA	James E. Shaw, M.D.
Vermont Cancer Center	VT	Marc S. Greenblatt, M.D.
Virginia Mason Research Center	WA	Andrew D. Jacobs, M.D.
Fred Hutchinson Cancer Research Center	WA	Sujata Rao, M.D.

Chen et al, ASCO 2004 (Abstract #3515)