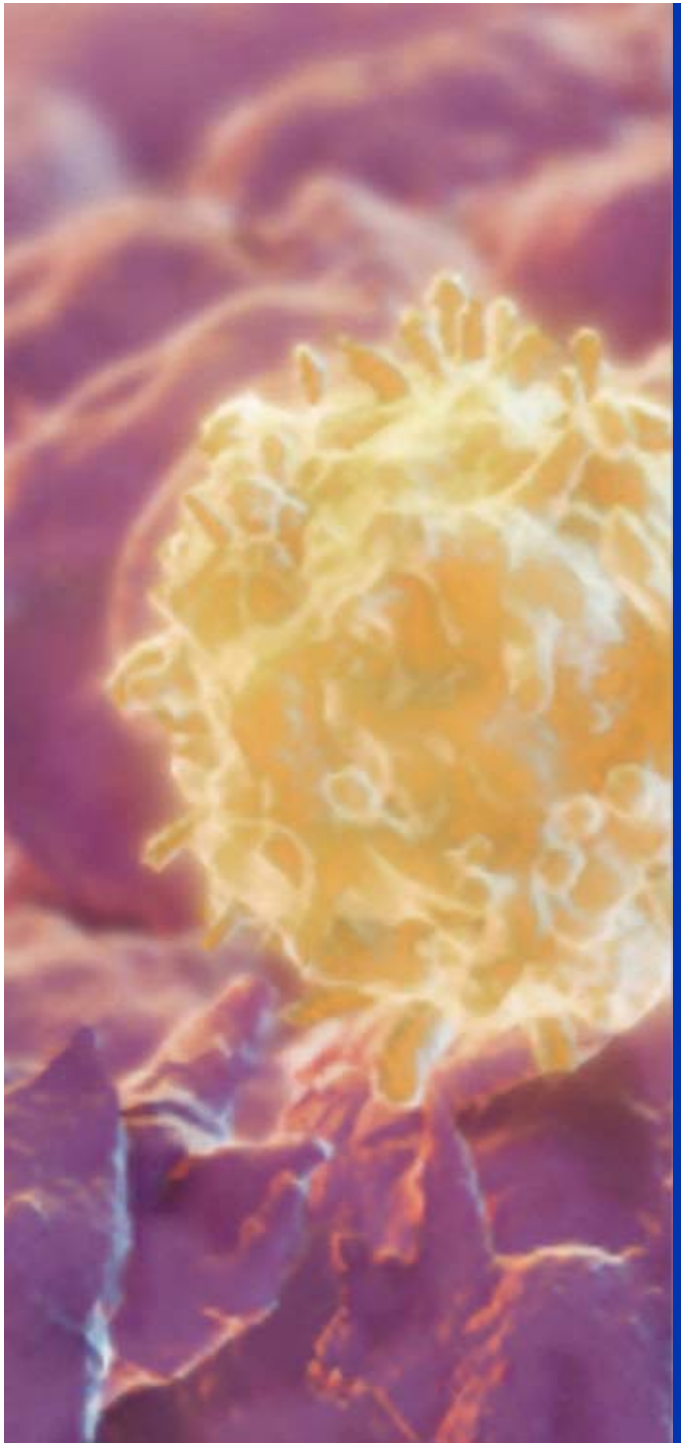

A Phase II Study of Tremelimumab (CP-675,206), an Anti-CTLA4 Monoclonal Antibody, in Patients With Refractory Metastatic Colorectal Cancer

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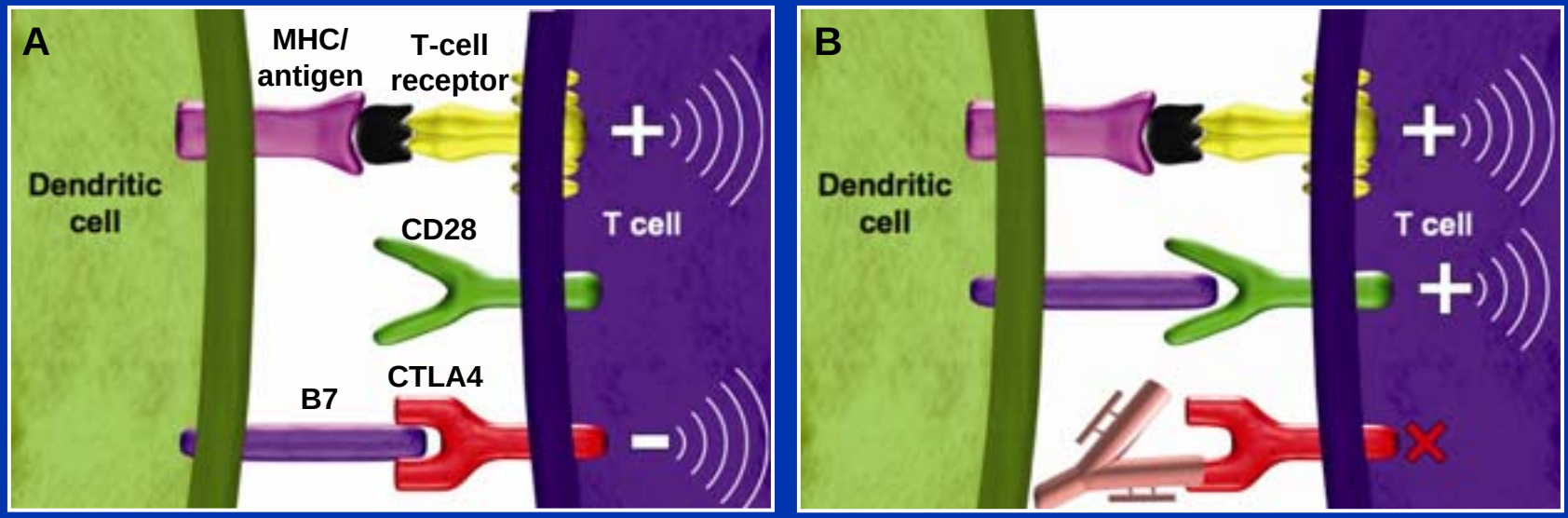
Introduction



A. Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) is a negative regulator of T-cell activation
B. CTLA4 blockade prolongs T-cell activation and proliferation in response to tumor antigens

Leach DR, et al. *Science*. 1996;271:1734-1736.

Introduction

- CTLA4 blockade may stimulate a more robust antitumor response by sustaining activation and proliferation of T lymphocytes and may overcome immune suppression mediated by regulatory T cells (Treg)
  - In a rat model of colon carcinoma, tumor growth was associated with increased numbers of Treg[1]
  - In addition, antitumor immune responses induced by CTLA4 blockade were correlated with a reduction in Treg[2]
  - In a murine model, anti-CTLA4 monoclonal antibody (mAb) induced rejection of colon carcinoma cells and protected against subsequent challenge with colon carcinoma[3]
  - CTLA4 blockade significantly prolonged survival (P = .011) in a murine model of colorectal cancer[4]

1. Ghiringhelli F, et al. *Eur J Immunol*. 2004;34:336-344.
2. Reuben JM, et al. *Cancer*. 2006;106:2437-2444.
3. Leach DR, et al. *Science*. 1996;271:1734-1736.
4. Lute KD, et al. *Blood*. 2005;106:3127-3133.

Tremelimumab

- Tremelimumab is a fully human IgG2 mAb targeting CTLA4 with high affinity (IC_{50} = 0.46 nM; $t_{1/2}$ = 22 d) with preclinical activity in colorectal xenograft models
- Clinical activity in 1 colorectal cancer patient in Phase I single agent tremelimumab trial (single 3 mg/kg dose)
  - ↓ CEA, improved KPS, objective ↓ hepatic lesion and lymph node; effects lasted 2 to 3 months
- Safety and efficacy of 15 mg/kg Q90D schedule established in a Phase II melanoma trial

IC = Inhibitory concentration; $t_{1/2}$ = Half-life; CEA = Carcinoembryonic antigen; KPS = Karnofsky performance status.

Phase II Study in CRC: Single agent tremelimumab

- Primary endpoint: best response by RECIST criteria
  - Powered for response rate (RR) ≥ 15%
    - 5 responses out of 47 patients needed to reject the null hypothesis (RR ≤ 3%) using a 1-sided binomial test at 5% level of significance
- Secondary endpoints: safety, PFS, duration of response, and OS
  - Correlative: to identify potential relationships between polymorphisms in CTLA4, Fc_{gamma} receptor IIa, or IgG2a genes with safety and/or immune response

RECIST = Response Evaluation Criteria in Solid Tumors.

Entry Criteria

- Inclusion criteria
  - Adult patients with measurable, metastatic colorectal adenocarcinoma and
    - ECOG performance status of 0 or 1
    - Adequate bone marrow, hepatic, and renal function
    - Disease progression subsequent to treatment with standard therapies
- Exclusion criteria
  - Patients were excluded if they had
    - Received prior anti-CTLA4 therapy
    - Known brain metastases
    - History of chronic inflammatory or autoimmune disease
    - Received a dose of immunosuppressive medications within 4 weeks of enrollment

Treatment Plan

- Patients received intravenous tremelimumab 15 mg/kg Q90D
  - Patients could receive up to 4 doses
  - No dose reductions were permitted
  - No pretreatments were routinely administered before infusion
- Tumor assessments were performed at baseline, 3 months after treatment, and every 6 weeks thereafter

Patient Characteristics (N = 47)

Demographics

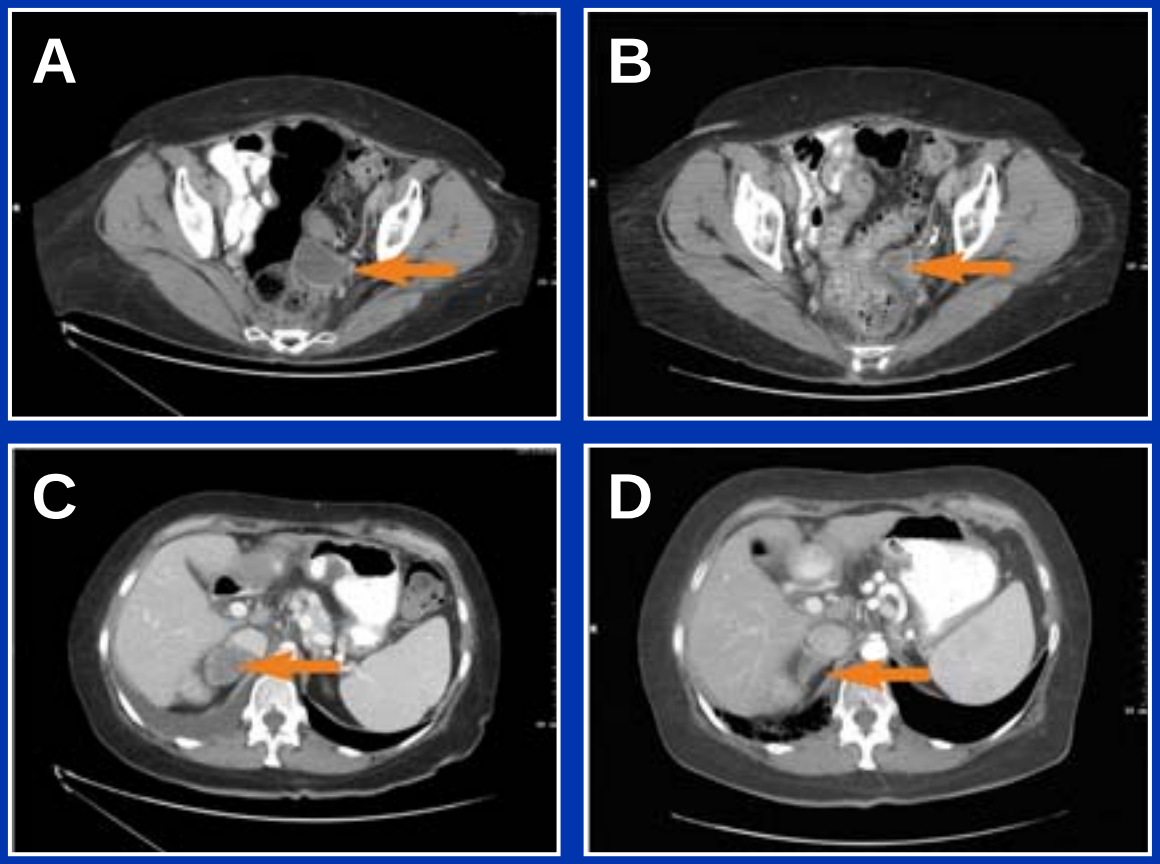
Median age, yr (range)	61 (40 - 79)
Male, n (%)	28 (60)
ECOG performance status, n (%)	
0	30 (64)
1	17 (36)
Median prior regimens, n (range)	5 (3 - 10)
Previous therapies, n (%)	
Fluoropyrimidine	47 (100)
Irinotecan	46 (98)
Oxaliplatin	46 (98)
Cetuximab	43 (91)
Bevacizumab	41 (87)

ECOG = Eastern Cooperative Oncology Group.

Efficacy Analysis

- **Response rate 2%** (95% CI: 0 - 11%; 1 of 47 patients)
  - 46 of 47 patients discontinued due to disease progression, disease-related death, or serious adverse events before reaching the planned second dose
  - One patient experienced a **partial response** at the end of the second dose cycle and had stable left pelvic mass and substantial regression in an adrenal mass
    - Patient was previously treated with all standard agents for metastatic colorectal adenocarcinoma
    - Patient has subsequently received several additional doses
    - Patient remains alive to date
  - The null hypothesis (H_0: RR ≤ 3%) was not rejected

Patient With a Partial Response



Panels A and B are computed tomography (CT) scans of pelvic masses. Panel A is baseline; panel B is after third dose (longest tumor diameter decreased from 4.3 cm to 2.3 cm). Panels C and D are adrenal masses. Panel C is baseline; panel D is after third dose (longest tumor diameter decreased from 4.2 cm to 2.5 cm).

We would like to thank Dr. Stephen B. Beck for providing his experience in the selection and analysis of the CT scans.

Safety Analysis

- Diarrhea was the most frequently reported adverse event (21% Grade 1/2; 11% Grade 3)
- Immune Related Adverse Events
  - Grade 3 diarrhea (n = 1), which appeared “ulcerative colitis-like” and was responsive to steroids – patient was withdrawn from the study
  - Grade 4 autoimmune thrombocytopenia (n = 1) was responsive to platelet transfusions and steroids and resolved within 32 days
  - Grade 1 uveitis (n = 1) resolved in 48 hours with steroid eye drops
- There were no tremelimumab-related hypersensitivity reactions during infusion

Treatment-Related Adverse Events Occurring in ≥ 2 Patients (N = 47)

Adverse event, n (%)	Grade 1	Grade 2	Grade 3
Diarrhea	9 (19)	3 (6)	5 (11)
Fatigue	4 (9)	2 (4)	2 (4)
Nausea	4 (9)	2 (4)	0
Pyrexia	6 (13)	0	0
Vomiting	2 (4)	3 (6)	0
Colitis	2 (4)	0	1 (2)
Constipation	1 (2)	2 (4)	0
Rash	4 (9)	0	0
Rash pruritic	1 (2)	2 (4)	0
Pruritus	3 (6)	0	0
Abdominal pain	2 (4)	1 (2)	0
Hypoalbuminaemia	1 (2)	1 (2)	0
Hypokalaemia	1 (2)	1 (2)	0

Represents all adverse events as of October 3, 2007.

Duration of Most Common Treatment-Related Adverse Events ≥ Grade 2

Adverse event	Median time to onset, days (range)	Median time to resolution, days (range)
Diarrhea/colitis	26 (4 - 63)	4 (0 - 63)
Fatigue	29 (10 - 91)	148 (14 - 210+)

Number of days reflects the median for all events.

- The majority of cases of diarrhea/colitis resolved within 1 week

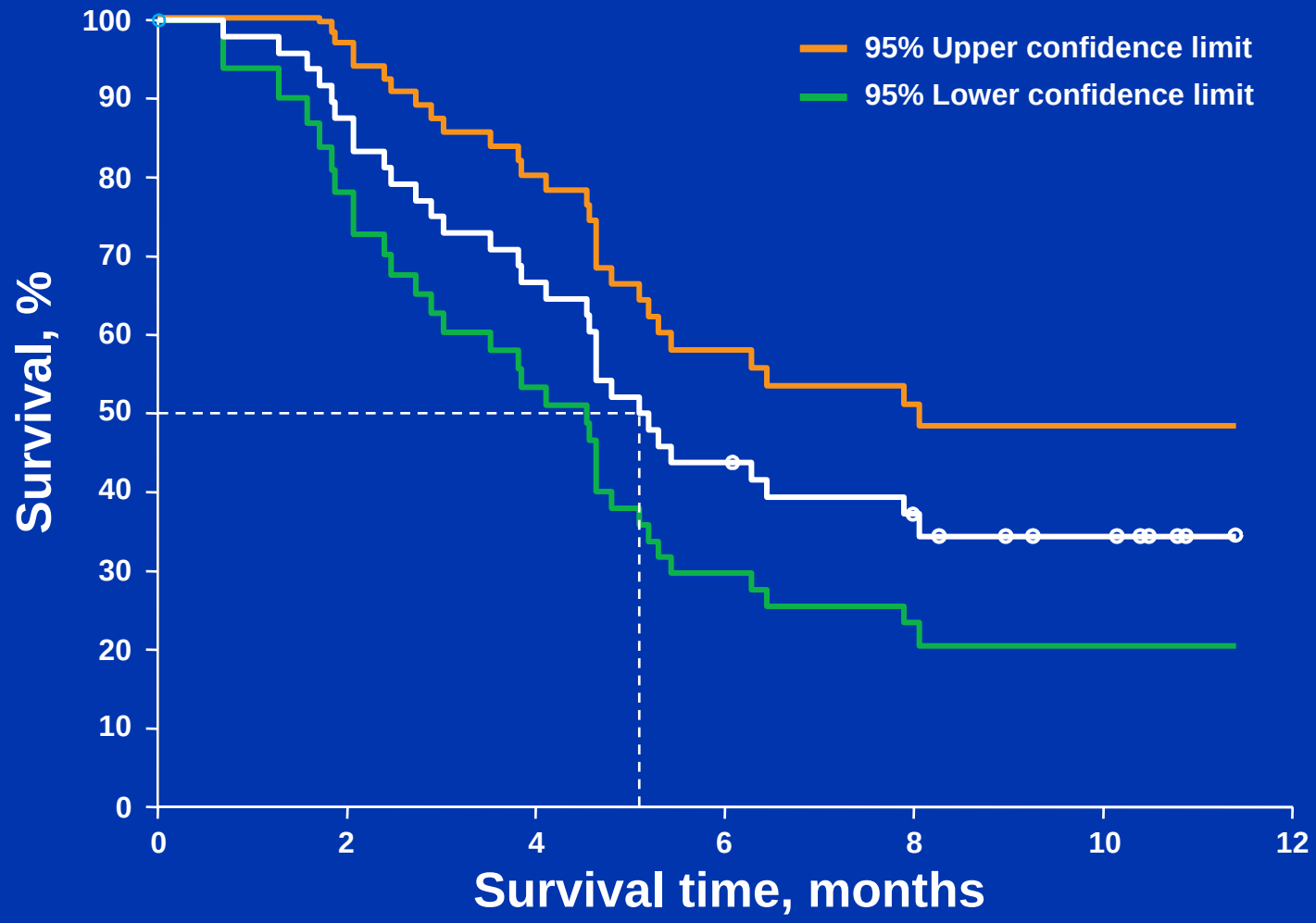
Antidiarrheal Management of Subset of Patients Requiring Medication (n = 15)

Treatment	Patients, n (%)
Loperamide	9 (53)
Systemic steroids	4 (24)
Diphenoxylate and atropine	1 (6)
Infliximab	1 (6)

Survival

- Median survival was 5.1 months (95% CI: 4.5, 8.1 months)
  - Estimated survival rate at 6-months is 43%
  - However, given that 30 patients (64%) had ECOG performance status of 0 at initiation of this advanced refractory disease trial, the implications of this finding are unclear

Kaplan-Meier Plot of Overall Survival



Conclusions

- In a study of patients with colorectal cancer (ECOG 0 to 1) who have exhausted standard therapy options treated with tremelimumab, the null hypothesis was not rejected (H_0: RR ≤ 3%)
- Toxicity profile was as expected for this class of agents and was manageable, with diarrhea and fatigue as the most common events
- Based on its mechanism of action and manageable toxicity, incorporation of tremelimumab into combination regimens in colorectal cancer may be explored