



Low Dose Capecitabine as Maintenance Therapy in Colorectal Cancer with  
Irresectable Metastasis

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## List of abbreviations

5-FU:	5 fluorouracil
AAPC:	attenuated adenomatous polyposis coli
ACF:	aberrant crypt foci
ADL:	average daily living
AFAP:	attenuated familial adenomatous polyposis
AJCC:	American Joint Committee on Cancer
APC:	adenomatous polyposis coli
BEV:	bevacizumab
bFGF:	basic fibroblast growth factor
BSA:	body surface area
CAP:	College of American Pathologists
CEA:	carcinoembryonic antigen
CEPs:	circulating endothelial progenitor cells
CFI:	chemotherapy free interval
CI:	confidence interval
CIMP:	CpG island hypermethylation phenotype

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CK1 $\alpha$ :	Casein kinase 1 $\alpha$
CRC:	Colorectal cancer
CT scan:	computed tomography scan
CT:	chemotherapy
CTCAE:	Common Terminology Criteria for Adverse Events
DCC gene:	deleted in colorectal cancer gene
DCC:	duration of disease control
DKK1:	Dickkopf-1
DSH:	disheveled (protein)
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
ECs:	microvascular endothelial cells
ECM:	extracellular matrix
EGFR:	Epidermal growth factor receptor
EMT:	epithelial-mesenchymal transition
ERUS:	Endorectal ultrasound
FAP:	Familial adenomatous polyposis

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FZD:	Frizzled
GI:	gastrointestinal
GSK3 $\beta$ :	glycogen synthase kinase 3 $\beta$
H:	hours
HFS:	hand-foot syndrome
HNPCC:	Hereditary nonpolyposis colorectal cancer
HR:	hazard ratio
HS:	highly significant
IQR:	interquartile range
IVF:	intravenous fluids
LNs:	lymph nodes
LOH:	loss of heterozygosity
LV:	lecuvorin
M:	distant metastases
MAPK:	mitogen activated protein kinase
mCRC:	metastatic colorectal cancer
MCV:	mean corpuscular volume
Mets:	metastases

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MMP:	membrane-type 1
MMPs:	matrix metalloproteinases
MMR:	mismatch repair
MRI:	magnetic resonance imaging
MSI:	microsatellite instability
MSI-H:	high-frequency microsatellite instability
MSI-L:	low-frequency microsatellite instability
MSS:	microsatellite stable
MT:	microtubule
MTD:	maximum tolerated dose
N:	number
N:	regional lymph node
NS:	non-significant
ORR:	overall response rate
OS:	overall survival
PDGF:	platelet-derived growth factor
PDGFRs:	platelet-derived growth factor receptors
PET:	positron emission tomography

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PFS:	progression free survival
PIP <sub>3</sub> :	phosphatidyl-inositol-3-phosphate
PlGF:	placental growth factor
PPE:	palmar-plantar erythrodysesthesia
PO:	per os
PS:	performance status
PTEN:	phosphatase and tensin homolog
Pts:	patients
QOL:	quality of life
S:	significant
SD:	mean standard deviation
SD:	stable disease
SEER: Results	Surveillance, Epidemiology, and End
SFRP:	secreted-frizzled-related-protein
Std:	standard
T:	tumor
TCF:	T-cell factor family

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TGF $\beta$ :	transforming growth factor $\beta$
TKI:	tyrosine kinase inhibitor
TP:	thymidine phosphorylase
TPN:	total parenteral nutrition
TSP-1:	thrombospondin- 1
TTP:	time to progression
UC:	ulcerative colitis
UICC:	Union Internationale Contre le Cancer
ULN:	upper limit of normal
VDAs:	vascular disrupting agents
VEGF:	vascular endothelial growth factor
VEGFR:	vascular endothelial growth factor receptor
WIF1:	WNT inhibitory factor-1
WT:	wild type

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# Introduction

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States, where an estimated number of 108,070 new cases of colon cancer and approximately 40,780 cases of rectal cancer would occur, and 49,960 people would die from colon and rectal cancer in year 2008 (*Jemal et al, 2008*).

The NCI in Egypt estimated colorectal cancer to be the 5<sup>th</sup> common incident cancer in both males and females, accounted for 4.2% of incident cases in males and for 3.8% in females (*Elattar, 2005*).

Impressive gains in response rates, progression-free survival, overall survival, and -sometimes- potential cure were achieved in the past decade in the field of metastatic colorectal cancer treatment as a result of evolution of new chemotherapeutic agents (*Goldberg et al, 2007*).

Addition of agents like oxaliplatin (*De Gramont et al, 2000*) and irinotecan (*Saltz et al, 2000*) to the standard 5-FU/leucovorin has improved efficacy over 5-FU/leucovorin alone. Targeted therapies as bevacizumab, cetuximab and panitumumab introduction have shown to increase response rates, progression-free survival, and -in the case of bevacizumab- overall survival, particularly when used in combination with cytotoxic chemotherapy (*Tabernero et al, 2007*). Capecitabine has proved to be an acceptable alternative for 5-FU, adding more treatment options (*Cassidy et al, 2008*).

However, the abundance of the treatment options, despite offering prolonged survival to patients if they have access to these options, it also comes with specific

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challenges, the most important of which is that the most effective sequence of agents, the best combination regimens, and the optimum duration of therapy remain not well defined (*Grothey, 2007*).

The desire for less toxic regimens, and decreasing the need for hospitalization, with keeping the advantage of prolonging overall survival have changed current treatment approaches to an individualized therapeutic strategy, examples include the stop-and-go approaches with maintenance therapy phases, chemotherapy-free intervals, and reduced dosing less toxic maintenance regimens (*Wu et al, 2008*).

Maintenance therapy or sometimes referred to as “metronomic” dosing is the chronic administration of an agent at relatively low, nontoxic doses on a frequent schedule of administration with no prolonged drug-free breaks (*Kerbel and Kamen, 2004*).

Some metronomic regimens can have surprisingly potent antitumor effects compared with respective maximum tolerated dose regimens, despite being less toxic (*Bertolini et al, 2003*), in addition to their anti-angiogenic activities attained by targeting proliferating endothelial cells in tumor blood vessels (*Ooyama et al, 2008*).

Several trials are being performed to evaluate the efficacy, safety, and quality of life through the use of maintenance therapy in advanced colorectal cancer. This includes irinotecan (*Loupakis et al, 2006*), chronically administered infusion 5-FU (*Marshall et al, 2007*), and oral fluoropyrimidine (*Scalamogna et al, 2007*).