Colorectal cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths in the U.S. [1]. Almost a third of patients already have metastatic disease at diagnosis, and half the patients diagnosed and resected with early-stage disease subsequently develop metastases [2]. Nearly all patients with metastatic cancer die of their disease.

For many decades, the only effective first-line treatment for metastatic colorectal cancer remained fluorouracil (FU). Subsequently, coadministration of FU with leucovorin (LV) increased response rates and time to progression, but only marginally improved overall survival [3, 4]. Various attempts were made to optimize this regimen using different doses and schedules, but although these modifications revealed interesting differences in their side-effect profiles, they failed to deliver noticeably improved clinical benefit. Similarly, capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.roche.us), an oral FU prodrug, while more convenient and with a more acceptable side-effect profile, has not increased survival over that achieved with i.v. regimens [5, 6].

As oncology entered the 21st Century, however, the deadlock that had characterized metastatic colorectal cancer for so many years began to shift. Combinations of newer agents with FU in the first-line setting for this hitherto intractable disease have improved survival. The first of these recent arrivals was the topoisomerase-I inhibitor, irinotecan (Camptosar®; Pfizer Pharmaceuticals Inc., New York, NY, http://www.pfizer.com). When added to bolus or infusional FU, irinotecan results in a greater overall survival rate and a longer time to progression than FU/LV alone [7, 8]. However, this agent has significant toxicities, which can occasionally be severe, particularly when given with bolus FU.

The second agent to show a survival benefit when added to FU in the first-line setting was oxaliplatin (Eloxatin®; Sanofi-Synthélabo Inc., New York, NY, http://www.sanofi-synthelabo.us), a third-generation platinum compound. In the first such trial, results were encouraging, although the improvement in overall survival was not statistically higher than with FU/LV; however, it should be noted that crossover may have obscured a small impact on overall survival [9]. More recently, a bigger phase III study of oxaliplatin combined with a bolus/infusional FU regimen (FOLFOX4) produced a superior response rate, time to progression, and overall survival compared with the bolus irinotecan/FU/LV (IFL) regimen [10]. Based on these data, FOLFOX4 was approved in the U.S. for the first-line treatment of colorectal cancer. However, oxaliplatin also carries a significant toxicity profile—one of these toxicities (namely neuropathy) is cumulative and often necessitates treatment interruption after 6 months.

The year 2004 also saw the approval of two new biologic agents for colorectal cancer—bevacizumab (Avastin®;
gene.com) and cetuximab (Erbitux®; ImClone Systems
both agents are monoclonal antibodies directed against
specific cancer-related targets, they differ significantly. Most
importantly, bevacizumab targets tumor angiogenesis by
specifically binding to vascular endothelial growth factor
(VEGF), and thus blocking VEGF signaling in endothelial
cells, and is approved for use in the first-line setting when
combined with any i.v. FU regimen. Such combinations
include regimens based on bolus irinotecan (e.g., IFL),
infusional irinotecan (e.g., FOLFIRI), infusional oxaliplatin
(e.g., FOLFOX), and bolus FU/LV without either irinotecan
or oxaliplatin.

So could adding a biologic agent to these chemothera-
peutic regimens be the key to longer survival for patients
with metastatic colorectal cancer? Results from early trials
are encouraging. In a pivotal 923-patient study evaluating
the addition of bevacizumab to IFL, bevacizumab conferred
superior survival, time to progression, and response rates
that were both clinically and statistically significant [11].
Overall survival for patients treated with IFL/bevacizumab
was 20.3 months—almost double the survival with FU/LV
alone only 5 years ago [3]. Notably, this result was
achieved with a chemotherapy regimen no longer consid-
ered the standard of care and in the relative absence of
effective second-line therapy. For those patients who pro-
gressed and did receive oxaliplatin-based chemotherapy,
the median survival time was even better, at approximately
25 months [11]. Interestingly, this suggests that second-line
therapies have an impact on overall survival. Indeed, a
recent study showed that median overall survival correlates
significantly with the percentage of patients receiving
FU/LV, irinotecan, and oxaliplatin over their disease
course. This suggests that all these agents should be made
available to all patients with metastatic colorectal cancer.

Importantly, a combined analysis of studies assessing
the addition of bevacizumab to FU/LV chemotherapy with-
out irinotecan has also shown advantages in both overall
and progression-free survival times compared with FU or
IFL chemotherapies [12]. Thus, bevacizumab plus FU/LV
benchmarks well in its activity compared with irinotecan
plus FU/LV—but with a much more manageable side-
effect profile. With few, if any, overlapping toxicities with
traditional chemotherapies, the primary side effect of beva-
cizumab is hypertension [11]. This is easily managed,
requiring the addition or adjustment of oral antihyperten-
sives in only 11% of patients. A warning was issued recently
to physicians by the manufacturer and the U.S. Food
and Drug Administration regarding an estimated overall
risk rate of up to 5% for serious arterial thrombotic events
associated with the use of bevacizumab, although this
information is included in the drug’s packaging. While
many experts recognize the benefits of the use of beva-
cizumab in colorectal cancer patients, as with any medica-
tion, the risk-benefit ratio must be carefully considered on
an individual patient basis.

While bevacizumab can be safely combined with FOL-
FOX4 [13], efficacy data with this combination are not yet
available. Data from the Eastern Cooperative Oncology
Group have recently been reported and showed an improved
survival for patients in the FOLFOX+bevacizumab arm
compared to FOLFOX alone [14]. Trials are also under way
to evaluate bevacizumab in the adjuvant setting.

Cetuximab, a monoclonal antibody directed against the
human epidermal growth factor receptor (HER-1/EGFR),
was approved in 2004 based on its activity in combination
with irinotecan in the second- and third-line treatment of
patients who had recently progressed on irinotecan or an
irinotecan-containing regimen. Although cetuximab also
showed some single-agent activity in this setting, a combi-
nation of irinotecan plus cetuximab resulted in a higher
response rate (22.9% versus 10.8%) and a longer time to
progression (4.1 versus 1.5 months) compared with cetux-
imab alone. Although no survival benefit was observed, this
finding must be interpreted with caution as this was a phase
II trial and insufficiently powered to determine survival
impact [15]. Clinical trials are now being done to study
cetuximab in the first- and second-line settings for patients
who have not received prior irinotecan. The primary toxic-
ity of cetuximab is an acneiform rash, which is common
and may correlate with antitumor activity [16].

Compared with only a short time ago when the only
treatment option was FU/LV, there are now five additional
agents approved for use in metastatic colorectal cancer. Each
has completed a pivotal registration study to demonstrate

Figure 1. New first-line combinations have significantly prolonged
survival in patients with metastatic colorectal cancer. Notably,
bevacizumab has improved the efficacy of the IFL regimen, and it
benchmarks well against irinotecan when used with FU/LV.
activity and clinical value. To try to further improve the clinical usefulness of these agents, trials evaluating alternative combinations and sequences are now in progress [17]. We hope that ongoing trials will help us understand further how agents should be used to achieve maximum clinical benefit.

In the last 5 years, we have seen the addition of several new treatments for a disease that was once considered untreatable, and survival has nearly doubled in that time; there are now five additional agents approved for use in metastatic colorectal cancer, with median survivals now approaching 2 years (Fig. 1). These recent advances should give us—and our patients—justifiable hope that further advances are not only possible, but also likely. However, the static overall mortality rate reminds us that there is still much progress to be made in the treatment of this disease.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

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**REFERENCES**


