Feature Article

# Palliative Chemotherapy for Advanced Colorectal Cancer

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## ABSTRACT

*Palliative chemotherapy has been demonstrated to prolong survival in patients with advanced colorectal cancer (CRC). Modulated 5-fluorouracil, the mainstay of treatment for many years, has now been replaced by combination therapy with irinotecan or oxaliplatin as first-line therapy for advanced CRC. Further improvements in treatment outcomes are likely once the optimal combination and sequence of active drugs is determined.*


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## INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer death in Western countries. Over half of all patients will eventually develop advanced/metastatic disease and this is usually fatal, except in a small minority who have resectable liver metastases. The rate of progression of advanced CRC is variable, but the median survival without treatment is only 8 months.[1] Patients with metastatic disease frequently develop a wide variety of physical and psychological symptoms that detract from their quality of life and may precipitate hospital admission.[1,2]

The aims of palliative chemotherapy treatment in this setting are to prolong survival, improve symptom control, and maintain or improve quality of life. These potential benefits must be balanced against the risks of treatment-related morbidity and mortality, factors that may be influenced by the choice of treatment and the oncology team's expertise in selecting patients and managing side effects.[2]

The recent development of a number of new agents with either greater efficacy or a more favorable toxicity profile has resulted in improved outcomes for patients with advanced CRC. This review summarizes the research evidence for the effectiveness of chemotherapy and examines the comparative effectiveness of different chemotherapeutic regimens and routes of administration.

## WHAT IS THE EVIDENCE FOR THE EFFECTIVENESS OF CHEMOTHERAPY?

A systematic review and meta-analysis of 13 randomized controlled trials comparing chemotherapy with supportive care in patients with advanced/metastatic CRC[1] has confirmed that chemotherapy can prolong both time to tumor progression and survival. These trials were published between 1983 and 1998, and primarily included patients receiving first-line fluoropyrimidine-based treatment. Chemotherapy was given either for a set period (usually 6 months) or continuously until disease progression. The trials were heterogeneous in terms of patient populations, interventions, and control groups. Many trials allowed delayed or discretionary use of chemotherapy for patients randomized to the supportive care arm. The pooled results of these trials therefore represent a generalized estimate of the effectiveness of chemotherapy, and they may underestimate differences in survival, disease progression, toxicity, and quality of life.

From the meta-analysis using individual patient data, it was estimated that patients receiving chemotherapy had a significantly reduced risk of progression [hazard ratio (HR) 0.51 (0.40 to 0.64)]. The absolute difference in progression was 25% at 6 months (61% vs 36%) and also at 12 months (41% vs 16%). Median progression-free survival was estimated to be 4 months in the control group and 10 months in the chemotherapy group. Patients receiving chemotherapy also had a significantly reduced risk of dying [HR 0.65 (0.56 to 0.76)]. The absolute difference in survival was 16% at 6 months (79% vs 63%) and also at 12 months (50% vs 34%). The median survival of patients receiving chemotherapy was also prolonged (11.7 months vs 8.0 months). Similar results were obtained when published summary statistics were included from trials that could not supply individual patient data (see Table 1). Based on these results, the number needed to treat with chemotherapy to result in one additional patient alive at both 6 months and 12 months is

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*Combination chemotherapy with modulated 5-fluorouracil (5-FU) plus irinotecan or oxaliplatin is now the standard first-line treatment for advanced colorectal cancer (CRC).*

*Combinations of new agents such as irinotecan and oxaliplatin are showing promising results in randomized trials.*

*Oral 5-FU analogues such as capecitabine may replace infusional 5-FU in future combination chemotherapy regimens for advanced CRC.*

*Palliative chemotherapy for advanced CRC can prolong survival in patients with advanced colorectal cancer without adversely affecting quality of life.*

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8 [95% confidence interval 7 to 9 (6 months) and 6 to 9 (12 months)]. No relationship was found between age and effect of treatment on disease progression or survival. For the oldest patient group in these trials, palliative chemotherapy appeared to be as effective as in younger patients. However, elderly patients were under-represented, as most trials imposed an upper age limit for the recruitment of subjects

The palliative benefits of chemotherapy were less clearly defined, as many of these studies did not adequately assess such important outcomes as improvement in disease-related symptoms, treatment-related morbidity, and quality of life. Nonetheless, the more recent studies suggest that quality of life is not worsened and may even be improved in patients receiving palliative chemotherapy.

## *COMPARISONS OF FIRST-LINE CHEMOTHERAPY FOR ADVANCED CRC*

For 40 years, 5-fluorouracil (5-FU) was the mainstay of treatment for CRC. Much effort has been devoted to exploring ways of enhancing the effectiveness of this agent through different schedules of administration or use of biochemical modulators. A large number of randomized trials have compared different chemotherapy regimens and schedules. In recent years, new drugs with different modes of action have become available, and first-line combination treatment for advanced disease is now possible.

### *5-FU VS Modulated 5-FU*

5-FU requires intracellular activation to exert its cytotoxic effect, which occurs through inhibition of DNA and RNA synthesis. In the presence of the reduced folate, 5,10-methylenetetrahydrofolate ($CH_2FH_4$), the active metabolite 5-fluorodeoxyuridine monophosphate (FdUMP) inhibits thymidylate synthase, the main intracellular target of 5-FU, thereby inhibiting DNA synthesis.[3] 5-FU may also be anabolized to 5-fluorouridine monophosphate (5FUMP) in the presence of a cosubstrate, 5-phosphoribosyl-1-pyrophosphate (PRPP). 5FUMP is subsequently phosphorylated to 5-fluorouridine triphosphate (5FUTP) and incorporated into RNA, inhibiting its synthesis.[3]

The activity of 5-FU may be enhanced by the concurrent administration of leucovorin or methotrexate. Leucovorin is a precursor of $CH_2FH_4$ that increases the intracellular concentration of $CH_2FH_4$, enhancing the antitumor activity of 5-FU against tumors that are relatively deficient in reduced folates.[3] Methotrexate inhibits purine synthesis, leading to intracellular accumulation of PRPP, which leads to an increased formation of FUTP, which is then incorporated into RNA.[3]

The modulation of 5-FU with such agents as leucovorin or methotrexate has been shown to increase response rates in patients with advanced CRC, but survival benefits have been harder to demonstrate. A meta-analysis of nine trials comparing 5-FU plus intravenous leucovorin (5-FU/LV) vs 5-FU alone confirmed that tumor response was more than doubled with 5-FU/LV (23% vs 11%; odds ratio [OR] 0.45; $P$ <.0001), but this did not lead to any improvement in survival (11.5 vs 11.0 months; OR 0.97; $P$=.57).[4] A similar analysis of eight randomized trials of 5-FU plus methotrexate (5-FU/MTX) vs 5-FU alone also demonstrated enhanced response rates with the modulated regimen (19% vs 10%; OR 0.51; $P$ <.0001), and a small but significant improvement in median survival (10.7 vs 9.1 months; OR 0.87; $P$=.024).[5]

Comparisons of different 5-FU/leucovorin schedules (eg, higher-dose vs lower-dose leucovorin) have not demonstrated significant differences in survival, although response rates, toxicity, and effect on quality of life can vary considerably.[6-12] Randomized comparisons of patients treated with 5-FU/leucovorin and 5-FU/methotrexate have shown no differences in response rates or survival.[5,13-16] Similarly, dual modulation of 5-FU using both leucovorin and methotrexate has not yielded superior results to modulation with leucovorin or methotrexate alone, and is associated with increased toxicity.[16]

The addition of α-interferon (αIFN) to 5-FU ± leucovorin does not increase efficacy. A meta-analysis of 17 trials demonstrated no difference in terms of tumor response or survival between patients in the αIFN-containing group and the control group.[17] Although not examined in the meta-analysis, published data from individual studies suggest that addition of αIFN also increases toxicity.[18]

### *Bolus 5-FU vs Infusional 5-FU*

The activity of 5-FU is relatively S-phase dependent and the half-life in serum is short. Thus, prolonged infusion may expose a larger proportion of tumor cells to 5-FU, which is attractive for tumors with a relatively slow

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doubling time such as CRCs. There is good evidence that continuous infusion of 5-FU using a variety of different schedules increases response rates vs bolus administration. A meta-analysis of seven randomized studies of 5-FU administered by continuous infusion vs bolus found that response rates were two-fold higher in the group receiving continuous infusion 5-FU (22% vs 14%; OR 55%; *P*=.0002), and this was associated with a small but statistically significant increase in median survival (12.1 months vs 11.3 months; HR 0.88; *P*=.04).[19] Delivering 5-FU by continuous infusion changes the limiting toxicity from myelosuppression to stomatitis and hand-foot syndrome.[7,19,20] In a study of seven 5-FU-based regimens there was a trend toward increased survival with infusional regimens and more toxicity with bolus 5-FU regimens.[21]

### *Hepatic Infusional Chemotherapy*

The liver is often the first site of metastatic disease in patients with CRC and may be the only site of spread in as many as 30–40% of patients with advanced disease.[22] Chemotherapy administered via a catheter placed in the hepatic artery or portal vein delivers the highest possible concentration of drug to the liver and has been shown to increase response rates. In addition, many fluoropyrimidines are metabolized in the liver, so the systemic drug concentration is much lower than after intravenous chemotherapy, which may reduce systemic toxicity.

A meta-analysis of five trials comparing hepatic artery infusion (HAI) of floxuridine with intravenous floxuridine or 5-FU in patients with unresectable metastatic disease confined to the liver demonstrated that the response rate was nearly three times higher with HAI (41% vs 14%; OR 0.25; *P*<.0001). Despite the improved response rate, no significant survival benefit was demonstrated (median survival 16 months vs 12.2 months; hazard ratio 0.81; *P*=.14), possibly due to the high risk of extrahepatic failure in responding patients in the HAI group.[23]

**TABLE 1. RELATIVE RISK OF DEATH IN PATIENTS RECEIVING PALLIATIVE CHEMOTHERAPY VS THOSE RECEIVING SUPPORTIVE CARE ALONE[1]**

| Time after randomization (months) | Relative risk (95% confidence interval) | Absolute risk reduction |
|---|---|---|
| 6 | 0.67 (0.56–0.79) | 12.5% |
| 12 | 0.80 (0.73–0.88) | 12.9% |
| 18 | 0.88 (0.82–0.95) | 9.2% |
| 24 | 0.92 (0.88–0.97) | 6.4% |

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## *NEW CHEMOTHERAPY AGENTS*

### *Oral 5-FU Analogues*

A number of newer orally active fluoropyrimidines have demonstrated equivalent activity to modulated intravenous 5-FU in randomized trials. Capecitabine, an oral "prodrug," is metabolized to 5-FU in several steps, the final activating enzyme being thymidine phosphorylase, which is found at higher levels in tumor tissues vs normal tissues. This results in selective tumor activation of the drug and minimizes exposure of normal tissues.[24] Two concurrent phase III trials in Europe and North America randomized 602 and 605 patients, respectively, with advanced CRC to receive either capecitabine or 5-FU/LV (Mayo regimen).[25,26] Both studies revealed a significant improvement in response (26.6% vs 17.9% and 23.2% vs 15.5%) in favor of capecitabine. No survival data have been presented as yet. Serious adverse events occurred less frequently in patients treated with capecitabine. The incidence of mucositis and neutropenia were reduced in comparison with the Mayo regimen and the most frequent grade 3/4 toxicities with capecitabine were hand-foot syndrome and diarrhea.

Two phase III studies (N=1,196) have compared UFT (ftuofur, an orally active 5-FU prodrug + uracil, an inhibitor of dihydropyrimidine dehydrogenase, which is responsible for the catabolism of 5-FU) and oral leucovorin with 5-FU/LV.[27,28] The response rates were equivalent (12% vs 15% and 11% vs 9%), as were survival rates (median survival 12.2 months vs 11.9 months).[28] There was, however, a reduction in grade 3/4 mucositis, neutropenia and febrile neutropenia in favor of UFT/LV.

### *Raltitrexed*

Raltitrexed is a direct and specific thymidine synthase inhibitor that enters cells via the reduced folate carrier and undergoes intracellular polyglutamation, which increases the drug's potency and the length of time during which it is retained within cells, which allows a convenient once every 3 weeks dosing schedule. Three randomized trials have demonstrated that raltitrexed is equivalent to

5-FU + folinic acid in terms of response rate, survival, and toxicity, although the toxicity profile of raltitrexed is different from that of 5-FU/LV, producing less mucositis and leukopenia, but more frequent elevation of hepatic transaminases.[29-31] In the UK CRO-6 trial, which randomized 905 patients from 45 UK centers to receive either raltitrexed, continuous infusion 5-FU (Lokich regimen), or the de Gramont regimen, the response rates at 12 weeks and mean survival were similar (20–26%, 10 months), but the de Gramont regimen was significantly superior in terms of adverse events and quality of life.[8] There was a toxic death rate of 5.6% in the raltitrexed arm of this study. A significant number of these patients had mild to moderate renal impairment, which appears to be a risk factor for severe toxicity with this agent.

### *Oxaliplatin*

Oxaliplatin is a diaminocyclohexane platinum complex. Similar to other platinum derivatives, its mechanism of action is mediated by the formation of DNA adducts.[32] Despite this similarity, it has a different spectrum of antitumor activity and different clinical toxicity. Oxaliplatin has no renal toxicity and minimal hematologic toxicity, but it causes both a reversible, acute, cold-related dysaesthesia, and a dose-limiting cumulative peripheral sensory neuropathy that usually regresses after treatment withdrawal.[32] Experimental data have shown synergistic activity with 5-FU.[33] Two phase III trials have evaluated the addition of oxaliplatin to 5-FU + LV as first-line treatment in advanced CRC.[34,35] Both studies demonstrated a significant improvement in response rates (confirmed responses in assessable patients: 50.7% vs 22.3% and 53% vs 16%) and progression-free survival (9.0 months vs 6.2 months and 8.7 months vs 6.1 months) in patients receiving oxaliplatin. This did not, however, translate into a significant survival benefit (median survival 16.2 vs 14.7 months and 19.9 months vs 19.4 months). Grade 3/4 neutropenia, diarrhea, mucositis, and neuropathy occurred significantly more frequently in patients receiving oxaliplatin. Despite this, median quality of life scores for the two treatment arms were comparable and time to deterioration of global health status was significantly prolonged in patients receiving oxaliplatin.[34]

### *Irinotecan*

Irinotecan is a potent topoisomerase I inhibitor that blocks the DNA replication step of the enzyme, leading to multiple single-strand DNA breaks, which eventually block cell division.[36,37] Two randomized phase III studies evaluating addition of irinotecan to 5-FU/LV as first-line treatment in advanced CRC have demonstrated that irinotecan plus 5-FU/LV is superior to 5-FU/LV alone in terms of progression-free survival and overall survival.[38,39] A combined analysis of the results of these two trials reported hazard ratios for time to disease progression of 0.67 ($P<.001$) and survival of 0.79 ($P<.009$) in favor of irinotecan + 5-FU/LV.[40]

The North American study compared 5-FU/LV (Mayo regimen) with a weekly regimen of 5-FU/LV + irinotecan and weekly irinotecan alone.[38] Treatment with 5-FU/LV + irinotecan resulted in significantly longer progression-free survival than 5-FU/LV (median 7.0 months vs 4.3 months, $P=.004$), a higher rate of confirmed response (39% vs 21%, $P<.001$), and longer overall survival (median 14.8 months vs 12.6 months; $P=.04$). Results for single-agent irinotecan were similar to those for 5-FU/LV. Grade 3/4 diarrhea was more common (22.7% vs 13.2%), but grade 3/4 mucositis, neutropenia, and neutropenic fever were less frequent following treatment with 5-FU/LV + irinotecan than during treatment with 5-FU/LV alone.

The European study compared weekly or fortnightly 5-FU/LV with the same regimen plus the addition of irinotecan.[39] The response rate was significantly higher in the irinotecan group than in the no-irinotecan group (49% vs 31%, $P<.001$ for evaluable patients). Time to progression (median 6.7 months vs 4.4 months, $P<.001$) and overall survival (median 17.4 months vs 14.1 months, $P=.031$) were significantly longer in the irinotecan group than in the no-irinotecan group. Grade 3/4 diarrhea (44.4% vs 25.6% for weekly regimen and 13.1% vs 5.6% for twice-weekly regimen), neutropenia (28.8% vs 2.4% and 46.2% vs 13.4%), and asthenia (two weekly regimen only) were more frequent in patients receiving irinotecan. In both studies, the addition of irinotecan to the regimen of 5-FU/LV did not compromise quality of life, and deterioration in quality of life occurred significantly later in the irinotecan group.

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### WHEN SHOULD CHEMOTHERAPY BE STARTED?

One question that remains unanswered is whether treatment should be initiated in asymptomatic patients or delayed until onset of symptoms. In the only published study that has addressed this issue, the Nordic Gastrointestinal Adjuvant Trial Group randomly allocated 183 asymptomatic patients with metastatic CRC to early chemotherapy or expectant therapy as soon as patients had disease-related symptoms. Patients allocated to early chemotherapy survived longer (14 months vs 9 months in the expectant therapy group) and the onset of their symptoms was significantly delayed.[41] A parallel assessment of quality of life in a subset of patients demonstrated that quality of life was not reduced in asymptomatic patients who received chemotherapy.[42] Further information may be obtained from other trials of similar design, including an Australian study and a Canada study (NCIC CO-10), even though the latter closed prematurely due to poor accrual.

### WHAT IS THE OPTIMAL DURATION OF TREATMENT?

The optimal duration of chemotherapy is currently being tested in clinical trials. In MRC CR06, for example, patients with stable or responding disease after 12 weeks of chemotherapy were randomized either to stop treatment or continue until disease progression. Outside of clinical trial protocols, it is reasonable to treat responding patients for 6 months, followed by a break in treatment. Patients can then be rechallenged at relapse.

### SECOND-LINE CHEMOTHERAPY

Many patients with disease progression after first-line chemotherapy for advanced CRC maintain a relatively good performance status and may be considered for second-line chemotherapy. There is evidence for the efficacy of second-line chemotherapy with irinotecan in patients previously treated with 5-FU. Two randomized trials have demonstrated the effectiveness of single-agent irinotecan as a second-line treatment for advanced CRC.[43,44] In the first of these trials, patients were randomized to receive irinotecan plus best supportive care every 3 weeks, or best supportive care alone, until disease progression.[43] With a median follow-up of 13 months, overall survival was significantly better in the irinotecan group ($P$=.0001); 1-year survival in the irinotecan group was 36.2% vs 13.8% in the supportive care group. The survival benefit remained significant when adjusted for prognostic factors in a multivariate analysis. Survival without performance status deterioration ($P$=.0001), without weight loss of more than 5% ($P$=.018), and pain-free survival ($P$=.003) were significantly better in the patients given irinotecan. Significantly more patients receiving irinotecan experienced grade 3/4 neutropenia, nausea, vomiting and diarrhea. However, in a quality of life analysis, all significant differences, except diarrhea score,

**TABLE 2. RANDOMIZED TRIALS COMPARING RESULTS OF COMBINATION CHEMOTHERAPY REGIMENS WITH INFUSIONAL OR MODULATED 5-FU AS FIRST-LINE TREATMENT FOR ADVANCED COLORECTAL CANCER**

| Trial | Douillard et al[39] | | Saltz et al[38] | | de Gramont et al[34] | | Giacchetti et al[35] | |
|---|---|---|---|---|---|---|---|---|
| Patients (N) | 385 | | 457 | | 420 | | 200 | |
| Arm | Irinotecan+ 5-FU/LV | 5-FU/LV | Irinotecan+ 5-FU/LV | 5-FU/LV | Oxaliplatin+ 5-FU/LV | 5-FU/LV | Oxaliplatin+ 5-FU/LV | 5-FU/LV |
| Response rate (%) | 34.8 | 21.9 | 39 | 21 | 50 | 21.9 | 34 | 12 |
| *P* value | .005 | | <.001 | | .001 | | .001 | |
| Median time to progression (months) | 6.7 | 4.4 | 7.0 | 4.3 | 9.0 | 6.2 | 8.7 | 6.1 |
| *P* value | <.001 | | .004 | | .0001 | | .048 | |
| Median overall survival (months) | 17.4 | 14.1 | 14.8 | 12.6 | 14.7 | 16.2 | 19.4 | 19.9 |
| *P* value | .031 | | .04 | | .12 | | NS | |

5-FU=5-fluorouracil; LV=leucovorin; NS=not significant.

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were in favor of the irinotecan group. Time to definitive quality of life deterioration was significantly longer in the irinotecan group.

A second study randomized patients who had failed to respond to first-line 5-FU to receive irinotecan or 5-FU by continuous infusion (three different regimens).[44] Median progression-free survival was longer with irinotecan (4.2 vs 2.9 months, *P*=.030), and patients treated with irinotecan lived significantly longer than patients receiving 5-FU (*P*=.035). One-year survival increased from 32% in the 5-FU group to 45% in the irinotecan group. Median survival was 10.8 months in the irinotecan group and 8.5 months in the 5-FU group. Although irinotecan caused more grade 3/4 diarrhea, nausea, vomiting and neutropenia/neutropenic fever, quality of life assessments were similar in both groups.

## *CONCLUSIONS*

There is good evidence from pooled results of studies comparing chemotherapy with supportive care that chemotherapy can produce small but meaningful benefits in patients with advanced CRC who have good performance status. Studies of first-line treatment with combination regimens have shown that 5-FU with either irinotecan or oxaliplatin can improve response rates, progression-free survival, and overall survival (see Table 2). It is hard to explain the differing overall survival outcomes of the irinotecan and oxaliplatin first-line combination studies in light of the similar response rates and time to tumor progression produced by either drug in combination with 5-FU/LV. However, it is possible that crossover between the two treatment arms on disease progression may account for the smaller difference in median survival seen with oxaliplatin. Although the toxicity of combination regimens may be increased over 5-FU/LV alone, quality of life does not seem to be impaired, perhaps because tumor response is associated with improved symptom control.

Oral fluoropyrimidines and direct thymidylate synthase inhibitors offer advantages in terms of ease of administration in that they avoid problems associated with indwelling venous catheters. Some data now show that these drugs can be administered safely in combination with either irinotecan[45] or oxaliplatin[46] with promising activity. These agents may replace 5-FU in combination therapy in the future.

Irinotecan and oxaliplatin can be administered together safely and with good response rates. This combination is presently being evaluated in an ongoing randomized study. Three drug regimens incorporating a fluoropyrimidine may be feasible and may increase response rates further, although they are likely to be more toxic.[47] Alternating cycles of irinotecan and oxaliplatin in combination with a fluoropyrimidine may overcome some of the toxicity and may also delay onset of oxaliplatin-induced peripheral neuropathy, which is related to cumulative dose of drug received.

For patients with disease progression following first-line 5-FU chemotherapy who remain fit enough for further treatment, second-line treatment with irinotecan is beneficial. The same may also be true for oxaliplatin. Single-arm studies have demonstrated high response rates in this setting, although randomized trials addressing this question have yet to be reported. There is limited evidence suggesting that patients failing combination chemotherapy may respond to second-line treatment and an ongoing randomized trial is evaluating the efficacy and toxicity of the combination of irinotecan + 5-FU/LV followed by oxaliplatin + 5-FU/LV with the same two combinations given in the reverse sequence[48] Other approaches such as monoclonal antibody-based therapies may also prove to be of benefit in the future.

The use of molecular markers as predictors of sensitivity to chemotherapy is being explored. Some data now suggest that tumors with high thymidylate synthase expression respond poorly to 5-FU.[49-51] There is also evidence of variations in the level of topoisomerase I expression in tumors[52] as well as in vitro data that this enzyme's activity may be a predictor for sensitivity to irinotecan,[53] raising the possibility that chemotherapy could be tailored to the individual patient/tumor in the future.

Recent improvements in the effectiveness of chemotherapy resulting from the development of new agents with different intracellular targets have considerably improved median survival achieved with these regimens (16.2 to 19.9 months) compared with those achieved with best supportive care and chemotherapy (8.0 months and 11.7 months, respectively) in trials in the 1980s.They represent a quantum leap forward in the efficacy of treatment that can be offered to patients with advanced CRC

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