Research Review
SPEAKER SERIES

Management of advanced colorectal cancer in 2011

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Axel Grothey is a Professor of Oncology and Consultant in the Division of Medical Oncology in the Department of Oncology at the Mayo Clinic in Rochester, Minnesota, US. His areas of interest are gastrointestinal (GI) cancers (in particular, colorectal cancer), gynecological cancers, breast cancer, and neuroendocrine tumours.

Prof. Grothey received his medical degree from Ruhr University Bochum in Germany. He then completed his residency in internal medicine at the West German Tumor Center at the University of Essen. He also completed residencies in pathology and internal medicine at prestigious universities in Germany and was awarded a fellowship in the Department of Hematology-Oncology at the University of Bochum. Subsequently, Prof. Grothey was awarded a postdoctoral research fellowship at the MD Anderson Cancer Center, University of Texas, to address the effect of kinase-mediated signaling on the actin cytoskeleton and phenotypic properties of cancer cells.

Prof. Grothey is the Vice Chair of the North Central Cancer Treatment Group (NCCTG) and the Co-Chair of the NCCTG gastrointestinal GI committee. He is also a member of the Association of German Internists, the American Association of Cancer Research, the American Society for Cell Biology, the American Society of Clinical Oncology, the European Association for Cancer Research and the European Society for Medical Oncology. He serves on the review board of numerous professional journals and is widely published in many peer-reviewed journals.

This publication is a summary of a presentation by Professor Axel Grothey, Professor of Oncology and Consultant in Medical Oncology at the Mayo Clinic, Rochester, Minnesota, US. He spoke throughout New Zealand in March 2011 about the management of advanced colorectal cancer.

The past 15 years have seen major advances in the treatment of colorectal cancer (CRC), with novel agents becoming available such as the cytotoxic agents, irinotecan, oxaliplatin and capecitabine, and later the monoclonal antibodies bevacizumab, cetuximab and panitumumab. In the 1980s, when CRC was treated with either 5-fluorouracil (5-FU) or best supportive care (BSC), the median overall survival (OS) for stage IV CRC was 6 months. During the `modern era' of CRC therapy, with the introduction of the novel cytotoxic agents in the 1990s, and the monoclonal antibodies early this century, the median OS for this disease has risen to more than 2 years. Nevertheless, while there has been a drug-driven improvement in survival, there have been no new drugs for the treatment of this disease since 2004. Prof. Grothey says that there is a desperate need for new drugs to further advance care for patients with CRC.

Treatment paradigms for metastatic CRC

It is evident that some patients with stage IV metastatic CRC can be cured by an interdisciplinary approach. This is a unique situation for a major tumour and is not usually seen with other types of metastatic cancer. Prof. Grothey believes that in the palliative setting, the combinations of 5-FU, leucovorin (LV) and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (XELOX) and infusional 5-FU, LV and irinotecan (FOLFIRI) are fairly equal in their efficacy. Current strategy for patients with advanced CRC is to optimise the opportunity for patients to receive and benefit from all available active agents while minimising toxicity, thereby improving both survival and quality of life.

Oxaliplatin

The Mayo Clinic NCCTG/Intergroup Trial N9741 involving five National Cancer Institute cooperative oncology groups, including the North Central Cancer Treatment Group (NCCTG), compared three regimens: FOLFOX (comprising both bolus and infused 5-FU); irinotecan, bolus 5-FU plus LV (IFL); and irinotecan plus oxaliplatin (IROX).[1] This pivotal study, published in 2004, introduced oxaliplatin into the American market. The study, involving 795 patients with previously untreated metastatic CRC, showed that FOLFOX was active and comparatively safe in patients with advanced CRC, with FOLFOX outperforming IFL in median time to progression of disease (8.7 months vs 6.9 months; $p = 0.0014$), median OS (19.5 months vs 15 months; $p = 0.0001$) and response rate (RR) (45% vs 31%; $p = 0.002$). Prof. Grothey points out that the IFL regimen used in the N9741 trial (irinotecan 125 mg/m^2, bolus 5-FU 500 mg/m^2 plus LV 20 mg/m^2 administered on days 1, 8, 15 and 22 every 6 weeks) is now considered to be a fairly weak regimen.

Another phase III trial, the GERCOR study, compared oxaliplatin with irinotecan for metastatic CRC, with both regimens using bolus and infused 5-FU plus LV.[2] That study, involving 220 patients, evaluated the FOLFOX6 and FOLFIRI regimens in order to determine the best sequence to treat patients with metastatic CRC. Patients received FOLFIRI as first-line therapy and FOLFOX6 as second-line therapy, or vice versa. The study showed that both sequences achieved a similar median progression-free survival (PFS) for first-line therapy (8.5 months vs 8.1 months). However, with both sequences there was a substantial decrease in RR from 54-56% with first-line therapy to 4-15% with second-line therapy. This loss of activity is commonly seen when moving from first- to second- to third-line chemotherapy. Prof. Grothey points out that another common phenomenon seen in the study was the large drop-out rate of patients between first- and second-line chemotherapy, with only approximately two-thirds of patients making it to second-line therapy.

Three-drug therapy

Prof. Grothey emphasises that patients benefit from being exposed to all relevant active chemotherapeutic agents and that duration of therapy is very important. In fact, analysis undertaken by Grothey and Sargent demonstrated that among 11 published phase III trials involving 5768 patients with advanced CRC, there was a strong positive correlation between median OS and the percentage of patients who received the three agents 5-FU, irinotecan and oxaliplatin in the course of their disease.[3] Two subsequent studies, one investigating sequential versus combination capecitabine, irinotecan and oxaliplatin (CAIRO),[4] and the other comparing folinic acid, 5-FU, oxaliplatin and irinotecan (FOLFOXIRI) with FOLFIRI,[5] supported the finding of a positive correlation between the percentage of patients receiving three drugs and the median OS (see **Figure 1**).

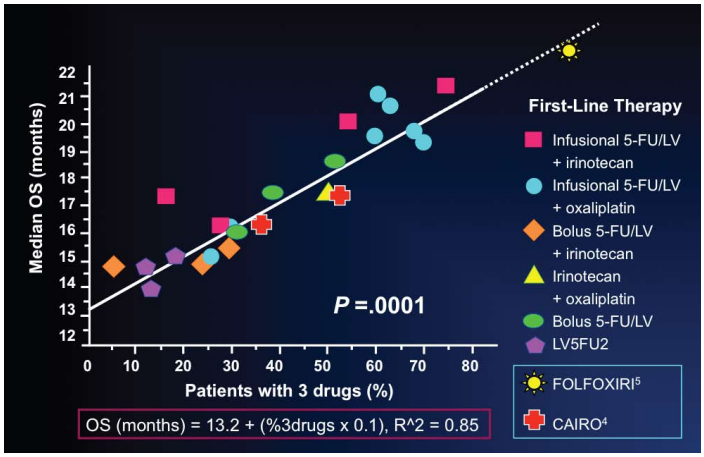

Figure 1: Regression plot and relationship between percentage of patients receiving fluorouracil/leucovorin, irinotecan and oxaliplatin (3 drugs) in the course of their disease and the reported median overall survival (OS). An analysis of 11 studies involving 5768 patients. The findings of two additional studies are superimposed.[4,5] Adapted from Grothey and Sargent, 2005.[3]

5-FU = 5-fluorouracil; LV = leucovorin

Biologic agents

Even with exposure to multiple chemotherapeutic agents, the best median OS seen in phase III trials in metastatic CRC has been approximately 2 years.[5] Prof. Grothey says that in order to go beyond this time point, the use of biologic agents is required, the vascular endothelial growth factor receptor (VEGFR) antibody bevacizumab, and the epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab.

Bevacizumab

The antiangiogenic agent bevacizumab showed proof of efficacy in a phase III trial by Hurwitz and colleagues involving 813 patients with previously untreated metastatic CRC.[6] In the study, patients were randomly assigned to receive either IFL plus bevacizumab (n = 402), or IFL plus placebo (n = 411). The median OS was 20.3 months for IFL plus bevacizumab recipients compared with 15.6 months for IFL plus placebo recipients ($p < 0.001$). Furthermore, the median PFS was 10.6 months for IFL plus bevacizumab recipients, compared with 6.2 months for IFL plus placebo recipients (HR 0.54; $p < 0.001$). The IFL regimen used in the study was a fairly weak chemotherapy regimen and the addition of bevacizumab clearly improved its efficacy. Prof. Grothey says that this study did not allow crossover which was a key feature of the study. He also presented data from initial phases of the study that showed that of 110 patients who received 5-FU and LV plus bevacizumab, the median survival was 18.3 months and that the regimen was almost as effective in terms of survival as IFL plus bevacizumab. The question may therefore be raised as to whether irinotecan is necessary in the IFL plus bevacizumab regimen.

The positive interaction between the fluoroyrimidines and bevacizumab appears to be very strong. The international phase III MAX study comparing capecitabine, capecitabine plus bevacizumab, and capecitabine plus bevacizumab plus mitomycin confirmed this by showing that capecitabine and bevacizumab with or without mitomycin was an effective regimen in the treatment of previously untreated, unresectable metastatic CRC, and that PFS significantly ($p < 0.001$) improved without major additional toxicity or impairment of patient quality of life (median PFS; capecitabine 5.7 months, capecitabine plus bevacizumab with or without mitomycin 8.4 months and 8.5 months, respectively).[7]

The concept that it may be unnecessary to add any other agent than a fluoropyrimidine such as capecitabine or 5-FU to bevacizumab, for the treatment of metastatic CRC, is the rationale behind the current Mayo Clinic US Intergroup phase III trial N0949. This trial, involving 380 elderly patients aged ≥ 70 years, is designed to test if oxaliplatin is a necessary first-line agent in a fluoropyrimidine plus bevacizumab regimen. In the study, patients will be randomised to receive modified FOLFOX7 plus bevacizumab, XELOX plus bevacizumab, 5-FU/LV plus bevacizumab or capecitabine plus bevacizumab. These regimens will be continued until progression of disease, unacceptable toxicity or patient withdrawal, and study participants will be able to receive oxaliplatin as a second-line agent.

Currently in the US, the dominant first-line regimen for metastatic CRC is a combination regimen, with more than 90% of US physicians using FOLFOX. Only a small proportion of US physicians use FOLFIRI in first-line therapy. FOLFIRI plus bevacizumab in first-line therapy in a study by Fuchs et al, has been shown to be a superior regimen compared with IFL plus bevacizumab.[8] In part of the phase III study, 117 patients were randomised to receive either FOLFIRI plus bevacizumab (n = 57) or modified IFL (mIFL) plus bevacizumab (n = 60). They found that the median OS was significantly ($p = 0.037$) greater for FOLFIRI plus bevacizumab recipients than mIFL plus bevacizumab recipients (28 months vs 19.2 months). Prof. Grothey says that in the US, FOLFIRI plus bevacizumab has become one of the standards of care in metastatic CRC.

The combination of FOLFOX plus bevacizumab has been in use since bevacizumab was introduced in the US in 2004. Bevacizumab was initially approved for use with IV 5-FU-based chemotherapy and at that time, the IFL versus FOLFOX study[1] had just been published showing superior efficacy for FOLFOX. The FOLFOX combination was therefore considered to be the strongest regimen available at the time and it was considered that adding bevacizumab would make a `super' regimen. Prof. Grothey says that this was not without problems, as the FOLFOX regimen has been shown to have neurotoxicity issues with long-term treatment.

The N016966 study involving 1401 patients with metastatic CRC evaluated the efficacy and safety of bevacizumab when added to first-line oxaliplatin-based chemotherapy (either XELOX or FOLFOX4).[9] The study followed a 2 x 2 placebo-controlled design where patients were randomised to either XELOX plus placebo (n = 350), FOLFOX4 plus placebo (n = 351), XELOX plus bevacizumab (n = 350) or FOLFOX4 plus bevacizumab (n = 350). Analysis of PFS showed that XELOX was not inferior to FOLFOX4 and that the addition of bevacizumab to oxaliplatin-based chemotherapy significantly ($p = 0.0023$) increased mean progression free survival; 9.4 months with bevacizumab versus 8 months without (HR 0.83; 97.5% CI 0.72-0.95). Prof. Grothey points out that the HR of 0.83 is a relatively small effect. In a subset analysis, statistical superiority of bevacizumab versus placebo was evident in the XELOX subgroup but not in the FOLFOX4 subgroup, with a mean PFS of 9.3 months versus 7.4 months (HR 0.77; 97.5% CI 0.63-0.94) and 9.4 months versus 8.6 months (HR 0.89; NS), respectively. The study authors suggested that the small or insignificant effect size was due to the fact that a large proportion of patients discontinued therapy with bevacizumab prior to disease progression and earlier than planned. In a pre-planned on-treatment subgroup analysis of PFS, the magnitude of the benefit of bevacizumab was larger, with an HR of 0.61 (97.5% CI 0.48-0.78) for the XELOX plus bevacizumab versus XELOX plus placebo subgroup and an HR of 0.65 (97.5% CI 0.50-0.84) for the FOLFOX4 plus bevacizumab versus FOLFOX4 plus placebo subgroup.

Prof. Grothey says that in the N016966 study, when patients stopped oxaliplatin after 5-6 months due to cumulative toxicity, they also stopped bevacizumab. He points out that bevacizumab does not kill tumour cells, but rather works by delaying tumour progression (i.e., it is a cytostatic agent rather than a cytotoxic agent). When bevacizumab is stopped tumours progress. He emphasises that it is extremely important to treat patients until disease progression.

Avoiding oxaliplatin neurotoxicity- a `stop-and-go' strategy

The benefits of oxaliplatin may be accompanied by toxicities, including dose-limiting neurotoxicity, and the cumulative neurotoxicity of the agent often requires treatment to be stopped in patients who are still exhibiting a response. Tournigand and colleagues investigated a `stop-and-go' strategy, aimed at avoiding oxaliplatin neurotoxicity, in their OPTIMOX1 study involving 620 previously untreated patients who were randomised to receive either continuous FOLFOX4 (n = 311) administered every 2 weeks until disease progression or the occurrence of unacceptable toxicity, or FOLFOX7 for six cycles followed by maintenance with 12 cycles of an oxaliplatin-free regimen (LV plus 5-FU2), followed by six cycles of FOLFOX7 (n = 309).[10] The study showed no difference in efficacy between the two regimens (median duration of disease control 9 months vs 10.6 months), but that there was a substantial decrease in the incidence of grade 3 neurotoxicity with the intermittent regimen (see **Figure 2**).

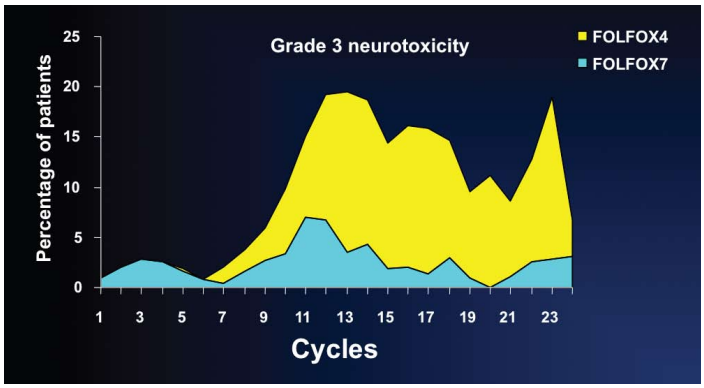

Figure 2: The percentage of patients developing a grade 3 neurotoxicity while receiving one of two chemotherapy regimens for metastatic CRC, either FOLFOX4 administered every 2 weeks or FOLFOX7 administered every 2 weeks for 6 cycles followed by LV/5-FU (an oxaliplatin-free regimen) every 2 weeks from cycle 7 to 18, then FOLFOX7 for a further 6 cycles. Adapted from Tournigand et al, 2006.[10]

An optimal regimen

In his clinical practice, Prof. Grothey treats patients with advanced CRC with eight cycles of an oxaliplatin-containing bevacizumab regimen (mainly modified FOLFOX7). This regimen contains infusional 5-FU and he believes this to be more effective than bolus 5-FU. In the palliative setting, he always stops oxaliplatin after eight cycles, as he believes 98% of those patients who have responded by then, will continue to respond on bevacizumab alone. He adds that it is extremely important to not inflict neurotoxicity on these patients by prolonging their oxaliplatin exposure. His patients are then maintained on capecitabine plus bevacizumab or 5-FU plus bevacizumab. He does not reintroduce oxaliplatin and says that the maximum cumulative dose with this protocol will be 680 mg/m^2. He says that at that dose, only 2-3% of patients will experience grade 3 or 4 neurotoxicity.

The question arises as to whether maintenance therapy with a bevacizumab-containing regimen works. The Dutch CRC Group is currently investigating this with patients receiving an induction regimen of six cycles of oxaliplatin, capecitabine and bevacizumab, and then randomising those patients to observation alone or low-dose capecitabine plus bevacizumab. Prof. Grothey expects this trial (CAIRO3) to be positive for the continued therapy arm.

Bevacizumab beyond disease progression

While it is clear that we need to treat to disease progression, it may be that patients benefit from bevacizumab continued across first- and second-line treatments. This will be investigated in the Roche ML18147 multinational European randomised, open-label, phase III trial that will look at the effect of adding bevacizumab to crossover fluoropyrimidine-based chemotherapy in patients with metastatic CRC and disease progression under a first-line standard chemotherapy/bevacizumab combination.

EGFR inhibitors and the *KRAS* gene

In metastatic CRC, the *KRAS* gene has been shown to be a biomarker that can predict how well a patient may respond to therapy. In tumours, the *KRAS* gene can be wild-type or mutated. Amado and colleagues showed the importance of *KRAS* mutations in CRC with their phase III study in which patients with metastatic CRC who had EGFR expression in ≥ 1% of tumour cells and documented evidence of disease progression after failure of fluoropyrimidines and prespecified exposure to irinotecan and oxaliplatin, received panitumumab plus best supportive care (BSC) or BSC alone.[11] Of the 427 patients assessed for *KRAS* status, 184 (43%) exhibited the *KRAS* mutation (84 panitumumab plus BSC recipients and 100 BSC alone recipients). The study findings showed that median PFS was significantly ($p < 0.001$) increased in patients with wild-type *KRAS* who received panitumumab plus BSC (n = 124), compared with those who received BSC alone (n = 119; 12.3 weeks vs 7.3 weeks; HR 0.45: 95% CI 0.34-0.59) and that patients with mutant *KRAS* did not benefit from treatment with panitumumab (7.4 weeks vs 7.3 weeks; NS).

A subsequent randomised phase III study by Karapetis and colleagues investigating the effect of *KRAS* status on the efficacy of cetuximab in advanced CRC showed similar findings to the panitumumab study, with a significant difference in PFS between patients receiving BSC alone versus cetuximab plus BSC evident in patients with a wild-type *KRAS* and not in those with mutated *KRAS*.[12] This study involved patients for whom all other chemotherapy had failed, and in those with wild-type *KRAS*, the addition of cetuximab to BSC was seen to double both median PFS and OS (3.7 months vs 1.9 months and 9.5 months vs 4.8 months, respectively; $p < 0.001$).

While the Karapetis study demonstrated the efficacy of cetuximab later in therapy, the question arose as to what would happen if cetuximab was added to earlier lines of therapy. Van Cutsem and colleagues investigated this in their multicentre phase III trial, Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL).[13] In their study, 599 patients with metastatic CRC and immunohistochemical evidence of tumour EGFR expression received cetuximab plus FOLFIRI and 599 patients received FOLFIRI alone. The median PFS in the cetuximab plus FOLFIRI group was 8.9 months versus 8 months in the FOLFIRI only group (HR 0.85; 95% CI 0.72-0.99). When *KRAS* status was included in the analysis, only the wild-type group exhibited a significant difference in PFS between the two groups; median PFS of 9.9 months in the cetuximab plus FOLFIRI group, compared with 8.7 months in the FOLFIRI only group (HR 0.68; 0.50-0.94).

Effect of EGFR inhibitors on FOLFOX, XELOX and FLOX in *KRAS* mutant tumours

Two recent trials have shown a detrimental effect of adding an EGFR inhibitor to FOLFOX as first-line therapy in patients who exhibit a *KRAS* mutation. Prof. Grothey says that the reasons for this phenomenon are unknown.

The first study, the randomised phase II OPUS trial of oxaliplatin and cetuximab in first-line treatment of metastatic CRC, revealed that patients with wild-type *KRAS* status exhibited a significant benefit in median PFS from the addition of cetuximab to FOLFOX4 (7.7 months [n = 61] vs 7.2 months [n = 73]; HR 0.567; $p = 0.02$).[14] However, this benefit was not seen in patients who had a mutant *KRAS* status and, in fact, the addition of cetuximab decreased the median PFS from 8.6 months (with FOLFOX alone [n = 47]) to 5.5 months (n = 52; HR 1.83; $p = 0.02$).

The second study, the randomised phase III multicentre PRIME study designed to test the efficacy and safety of FOLFOX4 plus panitumumab as first-line therapy in chemotherapy-naïve patients with metastatic CRC (n = 1183), revealed that patients with wild-type *KRAS* status benefited from the addition of panitumumab to FOLFOX4 (median PFS 9.6 months vs 8 months for FOLFOX4 alone; HR 0.80; 95% CI 0.66-0.97), but that patients with mutant *KRAS* status exhibited an inferior median PFS with the addition of panitumumab to their FOLFOX4 regimen (median PFS 7.3 months vs 8.8 months for FOLFOX4 alone; HR 1.29; 95% CI 1.04-1.62).[15]

The largest study ever conducted in first-line therapy for metastatic CRC was the phase III COIN trial comparing either continuous chemotherapy plus cetuximab or intermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine (XELOX or FOLFOX).[16] The study involving 2445 patients was conducted in the UK and Ireland, and *KRAS* status assessed. When analysis was undertaken for patients with *KRAS* wild-type tumours, the median PFS between those who had received XELOX/FOLFOX and those who had received XELOX/FOLFOX plus cetuximab was identical (8.6 months).

A subsequent study, the phase III NORDIC VII trial showed similar findings with cetuximab not adding significant benefit to a regimen of 5-FU, folinic acid and oxaliplatin (FLOX).[17] The study randomised 566 patients with untreated metastatic CRC to first-line therapy with either continuous FLOX, continuous FLOX plus cetuximab or intermittent FLOX plus continuous cetuximab. While the study showed that FLOX was effective with a median PFS of 8 months, the addition of

cetuximab did not provide significant additional benefit. Further analysis of PFS by *KRAS* status revealed that neither patients with wild-type or mutant *KRAS* tumours benefited from the addition of cetuximab to continuous FLOX.

Prof. Grothey says that if we consider the results of previous phase III studies investigating the EGFR monoclonal antibodies cetuximab and panitumumab, we see a trend towards better results with later treatment. He emphasises that he prefers to use the EGFR antibodies later rather than earlier in the treatment of his patients.

Dual antibody therapy: bevacizumab plus cetuximab

Prof. Grothey presents the CAIRO2 trial as a study from which we can learn a lot with regard to how to treat patients with monoclonal antibodies.[18] The trial randomly assigned 755 patients with previously untreated metastatic CRC to treatment with capecitabine, oxaliplatin and bevacizumab (n = 378) or the same regimen plus weekly cetuximab (n = 377). The study revealed that the addition of cetuximab significantly (p = 0.01) reduced the median PFS from 10.7 to 9.4 months. However, when the analysis was performed based on *KRAS* status, there was only a significant difference in median PFS between the two treatment regimens for those who had a mutant *KRAS* status (median PFS decreased from 12.5 months to 8.1 months with the addition of cetuximab [p = 0.003], and median OS decreased by approximately 7 months). Prof. Grothey says that while it has been suggested that the negative findings in this study are due to an interaction with oxaliplatin, he does not believe this to be the case. He points out that in the study oxaliplatin was discontinued after 6 cycles (i.e. after 4.5 months) and whatever happened after that time was not influenced by oxaliplatin. He also emphasises that the median PFS times seen with capecitabine, oxaliplatin plus bevacizumab in this study (10-12 months) were favourable.

Take-home messages

Optimised medical therapy for advanced CRC

Identify the goal of therapy

- Response rate only matters for conversion therapy of liver metastases or if the patient is symptomatic from his/her tumour burden.
- For most patients gain of time and maintaining quality of life is the most important issue.

Treat to progression

- Be mindful about toxicities, stop oxaliplatin before neurotoxicity develops.
- Some select patients can have chemotherapy-free intervals.

Expose patients to all potentially active agents

- These agents are the oncologist's tools to keep patients alive.
- Use fluoropyrimidine-based combinations as default backbone.
- Reserve sequential single-agent therapy for select patients.

Reutilise chemotherapeutic agents (in different combinations?) in the course of therapy

- Continuum-of-care vs distinct lines of therapy

We need new drugs (our tools to keep patients alive!)

In Summary

Prof. Grothey says that for his patients with advanced CRC he first identifies the goal of therapy. He starts his patients on FOLFOX and bevacizumab or capecitabine, oxaliplatin and bevacizumab. He informs them that they will come off oxaliplatin after a certain number of cycles in order to avoid neurotoxicities.
Prof. Grothey emphasises that treating to progression is important and that the duration of therapy really matters. He suggests using bevacizumab in first-line therapy and beyond, and exposing all patients to all potentially active agents. He says that it is also possible to give some patients with slowly growing tumours a break from therapy, but that they must be monitored closely. He says that in some cases it is also a good idea to reutilise prior therapy.

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