Andrés Cervantes
Professor of Medicine

COLORECTAL CANCER: STATE OF THE ART
DECLARATION OF INTERESTS

Consulting and advisory services, speaking or writing engagements, public presentations

Merck Serono : 500€ - 20'000€ p.a.
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Roche : 500€ - 20'000€ p.a.
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Strategic changes in the treatment of mCRC

• Changes in clinical presentation due to follow up after primary resection and earlier detection of metastatic disease
• Improvement in systemic therapies
• Integration of surgery and ablative therapies in a multidisciplinary team approach
• “Continuum of care” treatment
Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making


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ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

ESMO consensus on mCRC 2015

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D Arnold  
A Cervantes

Co-Chairs of working groups  
A Sobrero  
R Adam  
H Van Krieken

Advanced mCRC  
Local and ablative treatment, oligometastasis  
Molecular Pathology and Biomarkers

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G Pentheroudakis  
P Pfeiffer  
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PL Puig  
C Punt  
J Ricke  
A Roth  
R Salazar  
HJ Schmoll  
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Consensus report: Methodology

• An international group of experts from a range of disciplines, was convened in December 2014 to update the existing ESMO consensus guidelines for the management of patients with mCRC

• A set of pre-formulated topics was prepared and 3 working groups convened in the areas of molecular pathology and biomarkers, local and ablative treatment (including surgery) and treatment of advanced/metastatic disease.

• The experts in each group were invited to submit their recommendations in advance to structure the on-site discussions.

• On-site discussions within each of the working groups resulted in a set of recommendations being presented to all participants and a final set of consensus recommendations being formulated.

• Levels of evidence and grades of recommendation: assigned by the meeting chairpersons.
<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td></td>
<td>B: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td></td>
<td>C: Insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, …) optional</td>
</tr>
<tr>
<td>II</td>
<td>D: Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td></td>
<td>E: Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

*By permission of the Infectious Diseases Society of America.*
Recommendation 1:  Tissue handling

Recommendation 2:  Selection of specimens for biomarker testing

Recommendation 3:  Tissue selection
**Recommendation 3: RAS testing**

- RAS mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A]
- RAS testing should be carried out on all patients at the time of diagnosis of mCRC [I, A]
- RAS analysis should include at least KRAS exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and NRAS exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117)
- **Turnaround time for RAS testing** (expanded RAS analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

**Recommendation: RAS testing**

- **RAS** is a predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [1, A].
- **RAS testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab [1, A].
- Primary or metastatic colorectal tumour tissue can be used for RAS testing (see also *Recommendation 3*).
- **RAS analysis** should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for RAS testing** (expanded RAS analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.
Recommendation 5: BRAF testing

- Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B]

Recommendation 6: MSI testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B]
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [II, B]

Recommendation 9: emerging technologies

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].
- Whole genome, whole exome and whole transcriptome analysis should be carried out only in a research setting [V, D].

Figure 2. Categorisation of patients according to technical and oncological criteria. FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin.
Recommendation 13: conversion therapy.

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or a large tumour size reduction (shrinkage) is recommended [II, A].

- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
  - In patients with RAS wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A].
  - In patients with RAS-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab [II, A].

- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

Figure 1: toolbox of ablative treatments

- Local treatments
  - Thermal devices
    - Radiofrequency ablation or cryoablation
    - Microwave ablation
  - Non-thermal devices
    - Brachytherapy electroporation
    - External Body radiotherapy with high-precision RT
- Locoregional treatments
  - Embolic devices
    - Radioembolisation SIRT
    - Chemoembolisation TACE/Beads
  - Local chemotherapy

Online Ann Oncol, July 2016
Figure 3. Standard treatment algorithm for patients with oligometastatic disease.

Online Ann Oncol, July 2016

Best systemic treatment in terms of induction of response

Evaluation at 6–8 weeks

At time of “best response” also evaluate use of best treatment strategies available (patient-/expertise-dependent)

“Toolbox” instruments for local ablative treatment (surgery, invasive local ablation [RFA, microwave], precision radiotherapy [SBRT], embolisation techniques [any particles/beads, SIRT])

Consider (recommended) re-uptake of systemic treatment, but limit treatment duration to a total of 6 months

RFA = radiofrequency ablation
SBRT = stereotactic body radiation therapy
SIRT = selective internal radiation therapy
Local and ablative treatment (including surgery)

**recommendation 15: local ablation techniques.**

- In patients with unresectable liver metastases only, or OMD, local ablation techniques such as thermal ablation or high conformal radiation techniques (e.g. SBRT, HDR-brachytherapy) can be considered. The decision should be taken by an MDT based on local experience, tumour characteristics and patient preference [IV, B].

- In patients with lung only or OMD of the lung, ablative high conformal radiation or thermal ablation may be considered if resection is limited by comorbidity, the extent of lung parenchyma resection, or other factors [IV, B].

- SBRT is a safe and feasible alternative treatment for oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [IV, B].

- RFA can be used in addition to surgery with the goal of eradicating all visible metastatic sites [II, B].

Recommendation 16: embolisation.

- For patients with liver-limited disease failing the available chemotherapeutic options
- Radioembolisation with yttrium-90 microspheres should be considered [II, B].
- Chemoembolisation may be also considered as a treatment option [IV, B].

Recommendation 17: cytoreductive surgery and HIPEC

- Complete cytoreductive surgery and HIPEC can be considered for patients with limited peritoneal metastases in centres which are very experienced in the use of HIPEC [III, B].

## Table 4.
Drivers for first-line treatment

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Patient characteristics</th>
<th>Treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour burden</td>
<td>Age</td>
<td>Toxicity profile</td>
</tr>
<tr>
<td>Tumour localisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour biology</td>
<td>Performance status</td>
<td>Flexibility of treatment administration</td>
</tr>
<tr>
<td>RAS mutation status</td>
<td>Organ function</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
</tr>
</tbody>
</table>

Online Ann Oncol, July 2016
Metastatic colorectal cancer (mCRC) is not a single disease

- Patient and tumor characteristics vary widely
- Tumor cell heterogeneity is what makes tumors challenging to treat:
  - Multiple molecular alterations occur during tumor progression
  - Various molecular signaling pathways are involved
- Development of drugs which target and inhibit key molecular pathways is an essential step towards personalized cancer care
Table 6.
Revised ESMO groups for treatment stratification of patients according to whether patients are ‘fit’ or ‘unfit’

<table>
<thead>
<tr>
<th>Patient’s classification</th>
<th>‘Fit’ patients</th>
<th>‘Unfit’ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No impending</td>
</tr>
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<td></td>
<td></td>
<td>clinical threat</td>
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<tr>
<td></td>
<td></td>
<td>Resection not an</td>
</tr>
<tr>
<td></td>
<td></td>
<td>option</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td>Best supportive</td>
</tr>
<tr>
<td>A. Conversion and</td>
<td>Treatment</td>
<td>care</td>
</tr>
<tr>
<td>achievement of NED</td>
<td>biomarker driven:</td>
<td></td>
</tr>
<tr>
<td>B. Impending clinical</td>
<td>RAS wt, RAS mt,</td>
<td></td>
</tr>
<tr>
<td>threat, impending</td>
<td>BRAF mt patient</td>
<td></td>
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<tr>
<td>organ dysfunction and</td>
<td>subgroups</td>
<td></td>
</tr>
<tr>
<td>severe (disease-related)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment biomarker driven:</td>
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<tr>
<td>Treatment biomarker driven:</td>
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<td></td>
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<tr>
<td>‘Unfit’ patients</td>
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<td>Palliative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disease control</td>
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<tr>
<td></td>
<td></td>
<td>and hence</td>
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<tr>
<td></td>
<td></td>
<td>prolonged survival</td>
</tr>
<tr>
<td>Treatment goal</td>
<td></td>
<td>Palliative</td>
</tr>
<tr>
<td>A. Cytoreduction,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>followed by R0 resection;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NED achieved by LAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Improvement of</td>
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<td>symptoms and hence</td>
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<td>avoidance of rapid</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>prolonged survival</td>
<td></td>
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</tr>
</tbody>
</table>

Selecting patients for Cytoreduction

- Candidates for liver mets surgery: Conversion therapy
- Liver only disease: aiming at “potential resection”
- Symptomatic patients who need a quick improvement
- Asymptomatic but at risk of impending symptoms
- If only “one shot” is available…
- If they may not receive 2nd line treatment, due to rapid progression
- If patients do accept the risk of some toxicity and they are motivated to get the most efficacious treatment option
Figure 5. Maintenance and second-line treatment options. CT, chemotherapy; PS, performance status.

Recommendation 18: First-line systemic therapy combinations according to targeted agent used

- Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [I, A].
- The VEGF antibody bevacizumab should be used in combination with:
  - The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI
  - The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal - and potentially also in fit patients with tumour BRAF mutations [II, B]
  - Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [I, B].
- EGFR antibodies should be used in combination with:
  - FOLFOX/FOLFIRI [I, A]
  - Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [I, E].

The Facts on Colon Cancer Sideness: Prognosis

Right versus Left differences are reflected in epidemiology, etiological factors, pathogenesis, molecular alterations, embryology, clinical presentation and outcome.

Right colon cancer has worse prognosis from Stage IIIC to IV, but prognosis is not different in patients with stage I-IIIB.

BRAF mutant tumours are unequally distributed among those two sides (30% versus 2).

MSI is more prevalent in right sided tumours in stage II patients (18 versus 3%) having a favourable prognostic effect on these patients.

Patients with metastatic MSI colon tumours do poorly with CT and prognosis is bad.

## Prognostic analysis in anti-EGFR arm: Overall survival

<table>
<thead>
<tr>
<th>Category</th>
<th>No. deaths / No. entered</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>26/33</td>
<td>102/142</td>
<td></td>
</tr>
<tr>
<td>FIRE-3</td>
<td>31/38</td>
<td>86/157</td>
<td></td>
</tr>
<tr>
<td>PEAK</td>
<td>19/22</td>
<td>29/53</td>
<td></td>
</tr>
<tr>
<td>PRIME</td>
<td>34/39</td>
<td>126/169</td>
<td></td>
</tr>
<tr>
<td>20050181</td>
<td>28/31</td>
<td>129/150</td>
<td></td>
</tr>
<tr>
<td>CALGB80405</td>
<td>56/71</td>
<td>119/173</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>194/234</strong></td>
<td><strong>591/844</strong></td>
<td><strong>2.03 [1.69–2.42];</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $P = 0.46$, $I^2 = 0\%$
How can this prognostic information influence our practice?

Very little, but …

It could help in better informing patients

It may modify the way we plan or design research:

- Making trials in only left or right-sided tumours

- Stratifying patients according to side

- Mixing up patients with such different outcomes may lead us to misleading results
Predictive analysis: Overall Survival

<table>
<thead>
<tr>
<th>Category</th>
<th>No. deaths / No. entered</th>
<th>Hazard ratio</th>
<th>HR interaction [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT + anti-EGFR</td>
<td>CT +/- bev</td>
<td></td>
</tr>
<tr>
<td>CRYSTAL - Left</td>
<td>102/142</td>
<td>112/138</td>
<td>1.66 [0.93–2.97]; P = 0.09</td>
</tr>
<tr>
<td>CRYSTAL - Right</td>
<td>26/33</td>
<td>42/51</td>
<td></td>
</tr>
<tr>
<td>FIRE3 - Left</td>
<td>86/157</td>
<td>106/149</td>
<td>2.08 [1.19–3.63]; P = 0.01</td>
</tr>
<tr>
<td>FIRE3 - Right</td>
<td>31/38</td>
<td>38/50</td>
<td></td>
</tr>
<tr>
<td>PEAK - Left</td>
<td>29/53</td>
<td>33/54</td>
<td>0.86 [0.33–2.25]; P = 0.77</td>
</tr>
<tr>
<td>PEAK - Right</td>
<td>19/22</td>
<td>12/14</td>
<td></td>
</tr>
<tr>
<td>PRIME - Left</td>
<td>126/169</td>
<td>136/159</td>
<td>1.19 [0.71–2.00]; P = 0.51</td>
</tr>
<tr>
<td>PRIME - Right</td>
<td>34/39</td>
<td>44/49</td>
<td></td>
</tr>
<tr>
<td>20050181 - Left</td>
<td>129/150</td>
<td>123/148</td>
<td>1.19 [0.67–2.10]; P = 0.55</td>
</tr>
<tr>
<td>20050181 - Right</td>
<td>28/31</td>
<td>36/39</td>
<td></td>
</tr>
<tr>
<td>CALGB80405 - Left</td>
<td>119/173</td>
<td>119/152</td>
<td>1.77 [1.11–2.80]; P = 0.02</td>
</tr>
<tr>
<td>CALGB80405 - Right</td>
<td>56/71</td>
<td>58/78</td>
<td>(1.50 [1.19–1.88]; P &lt; 0.001)</td>
</tr>
<tr>
<td>Total - Left</td>
<td>591/844</td>
<td>629/800</td>
<td>0.75 [0.67–0.84]; P &lt; 0.001</td>
</tr>
<tr>
<td>Total - Right</td>
<td>194/234</td>
<td>230/281</td>
<td>1.12 [0.87–1.45]; P = 0.381</td>
</tr>
</tbody>
</table>

Between HR interaction heterogeneity: P = 0.47
The Facts on Colon Cancer Sideness: Prediction of treatment effect in all RAS wt

Consistent indication across trials that patients with left sided tumours may be more extensively benefitted from anti-EGFR therapies

Patients with right sided tumours may get little benefit, if any from anti-EGFR therapies

The effect of bevacizumab may be more favourable in patients with right sided tumours

All set of data point in the same direction: consistency
How are these data going to influence our practice?

The use of anti-EGFRs antibodies in first line could be reinforced in patients with all RAS wild-type left sided tumours, particularly when cytoreduction is needed. Bevacizumab based combinations could be used thereafter upon progression or intolerance.

Patients with all RAS wild-type right sided tumours could be better treated in first line with bevacizumab-based doublets or triplets, but there is no reason to avoid anti-EGFRs upon progression or intolerance.

We should consider always the “Continuum of Care” concept, using sequentially in all patients all available therapies, which made us to advance in improving outcomes in advanced colorectal cancer patients.
Recommendation 19: Maintenance therapy

- Patients receiving FOLFOX or CAPOX plus bevacizumab-based therapy as induction therapy, should be considered for maintenance therapy after 6 cycles of CAPOX or 8 cycles of FOLFOX. The optimal maintenance treatment is a combination of a fluoropyrimidine (plus bevacizumab). Bevacizumab as monotherapy is not recommended [I, B].
- Patients receiving FOLFIRI can continue on induction therapy – at a minimum – for as long as tumour shrinkage continues and the treatment is tolerable [V, B].
- For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy.
- For patients receiving initial therapy with single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [V, A]. Individualisation and discussion with the patient is essential [V, A].
- Initial induction therapy or a second-line therapy have to be reintroduced at radiological or first signs of symptomatic progression. If a second-line therapy is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no residual toxicity is present [III, B].

Recommendation 20: Second-line combinations with targeted agents

- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].
- Patients who received bevacizumab first-line should be considered for treatment with:
  - Bevacizumab post-continuation strategy [I, A]
  - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A]
  - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type (BRAF wild-type) disease
    - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [II, A].
- Patients who are fast progressors on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and - in the case of patients with RAS wild-type disease and no pre-treatment with anti-EGFR therapy - EGFR antibody therapy, preferably in combination with chemotherapy [II, B].
Recommendation 21: Third-line therapy

- In RAS wild-type and BRAF wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
  - Cetuximab and panitumumab are equally active as single agents [I, A]
  - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
  - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies [I, C].

- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B]
  - Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.

- Trifluridine/tipiracil is recommended for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B].
Recommendation 21: Third-line therapy (continued)

- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B]
  - Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.
- TAS-102 (trifluridine/tipiracil) is a new option for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies [I, B].

Van Cutsem E, Arnold D, Cervantes A et al, ESMO Consensus submitted Ann Oncol
2017: A classical case of mCRC

- 3 months preterminal phase
- 3 months "rechallenge"
- 3 months second line
- 3 months break
- 4 months second line
- 3 months reintroduction (or treatment beyond progression)
- 6 months maintenance
- 5 months first-line induction
- OS 30 months
Ongoing advances in personalized treatment of mCRC

- Targeting multiple signaling pathways involved in tumorigenesis
  - **RAS pathway**
    - Anti-EGFR antibodies
  - **BRAF pathway**
    - combination therapy
      - e.g.: anti-EGFR, BRAF and MEK inhibitors
  - **HER2**
    - Trastuzumab + lapatinib

- Induction of immune responses to target tumor cells

- Further molecular definition of individual patient subgroups

**MSI tumors:**
- Anti-PD(L) antibodies
  - *Pembrolizumab, Nivolumab*