ESMO 2015 Consensus on Advanced Colorectal Cancer

Eric Van Cutsem, Andres Cervantes, Dirk Arnold
Review of the ESMO consensus conference on metastatic colorectal cancer

Dirk Arnold, Instituto CUF de Oncologia, CUF Hospitals Cancer Centre, Lisboa
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 on mCRC 2015

**Chairs:**
- E Van Cutsem
- D Arnold
- A Cervantes

**Co-Chairs of working groups:**
- A Sobrero: Advanced mCRC
- R Adam: Local and ablative treatment, oligometastasis
- H Van Krieken: Molecular Pathology and Biomarkers

## Contributors

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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.
Molecular Pathology and Biomarkers

- Andrés Cervantes (Chair)
- Han Van Krieken (Chair)
- Dan Aderka
- Alberto Bardelli
- Al Benson
- Fortunato Ciardello
- Jean-Yves Douillard
- Brigette Ma
- Tim Maughan
- Nicola Normanno

- Arnaud Roth
- Ramon Salazar
- Josep Tabernero
- Julien Taieb
- Sabine Tejpar
- Aziz Zaanan
Local and ablative treatment & oligometastatic disease (omd)

- Dirk Arnold (Chair)
- René Adam (Chair)
- Enrique Aranda Aguilar
- Sergio Barroso
- André d'Hoore
- Michel Ducreux
- Thomas Grünberger
- Wasan Harpreet
- Karin Haustermans
- Claus-Henning Koehne
- Roberto Labianca
- Wim Oyen
- Tim Price
- Jens Ricke
Unresectable CLM with “conversion" as treatment goal

- Any patient with liver (+/- lung) limited disease should be considered a candidate for potential secondary resection
- In patients receiving conversion therapy, response to chemotherapy is a strong prognostic indicator
- Resectability is to be evaluated after only 2 months of (optimal) treatment so that the opportunity for resection is not missed
- R0 resection of lung metastases is recommended whenever feasible
Recommendation: Conversion therapy

- In potentially resectable disease (where conversion is the goal) a regimen associated with a high response rate / best tumour size reduction is recommended

- There is uncertainty on the best combination:
  - **RAS mutant**: FOLFOXIRI ± bevacizumab or acytotoxic doublet
  - **RAS wild type**: doublet (FOLFOX/FOLFIR) plus an anti-EGFR antibody seems to have the best benefit/risk ratio, although the combination of FOLFOXIRI ± bevacizumab may also be considered

Re-evaluate regularly to not overtreat resectable patients
Recommendation: oligometastatic disease (omd)

- In patients with (unresectable) CLM only or omd, **local ablation techniques** such as RFTA, thermal ablation or high conformal radiotherapy (e.g. SBRT, HDR-brachytherapy) as well as embolization techniques can be considered in addition to systemic therapy.

- In patients with CLM only or omd, resection and/or ablative high conformal radiotherapy, thermal ablation and others may be considered in addition to resection if this is limited by comorbidity, the extent of parenchyma resection, or other factors.

- The decision on the appropriate technique of the “**toolbox of ablative techniques**” should be taken in a MDT decision-based on local experience, tumour location / disease characteristics, patient preference.
Treatment of advanced metastatic disease

- Eric Van Cutsem (Chair)
- Alberto Sobrero (Chair)
- György Bodoky
- Eduardo Díaz Rubio
- Alfredo Falcone
- Axel Grothey
- Volker Heinemann
- Paulo Hoff

- Kei Muro
- Pia Osterlund
- Demetris Papamichael
- George Pentheroudakis
- Per Pfeiffer
- Cees Punt
- Hans Joachim Schmoll
- Takayuki Yoshino
It is clear that treatment stratification according to ESMO Groups 0, 1, 2 and 3 is no longer representative of what occurs in everyday clinical practice, where it is common there can be no clear distinction made between group 1 and 2 patients or between group 2 and 3 patients.

Increasingly often patient desire in terms of treatment goal is the main driver of treatment decisions.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Group 0: Resectable</th>
<th>Group 1: Potentially resectable</th>
<th>Group 2: Not resectable</th>
<th>Group 3: Not resectable</th>
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<tbody>
<tr>
<td>Cure (NED)</td>
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<td>Aggressive surgery</td>
<td></td>
<td>Maximum tumour shrinkage</td>
<td>Clinically relevant tumour shrinkage</td>
<td>Tumour shrinkage less relevant</td>
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<tr>
<td>Immediate surgery with induction chemotherapy or moderate (FOLFOX) perioperative chemotherapy</td>
<td>Upfront most active combination regimen</td>
<td>Aggressive treatment approach</td>
<td>Disease control</td>
<td>Less aggressive treatment approach</td>
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<tr>
<td>FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin; NED, no evidence of disease</td>
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**Drivers for decision making in 1st line treatment**

Table 4. Treatment drivers for first-line treatment

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Patient characteristics</th>
<th>Treatment characteristics</th>
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<tr>
<td>Clinical presentation:</td>
<td></td>
<td></td>
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<tr>
<td>Tumour burden</td>
<td>Age</td>
<td>Toxicity profile</td>
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<td>Tumour localisation</td>
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<tr>
<td>Tumour biology</td>
<td>Performance status</td>
<td>Flexibility</td>
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<tr>
<td><strong>RAS mutation status</strong></td>
<td>Organ function</td>
<td></td>
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<tr>
<td><strong>BRAF mutation status</strong></td>
<td>Comorbidities</td>
<td>Quality of life, patient expectation and preference</td>
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Treatment of metastatic disease

**Figure 4. Zurich treatment algorithm**

ASSESSMENT OF CLINICAL CONDITION OF THE PATIENT

- Fit
- Unfit (but may be suitable)
- Unfit

GOAL

FP + bevacizumab; reduced dose doublet; anti-EGFR

BSC

Patients with clearly resectable metastases

Surgery alone
Surgery with perioperative/postoperative CT

OMD
See Figure 2

Cytoreduction (Shrinkage)**

MOLECULAR PROFILE

- RAS wt
- RAS mt
- BRAF mt

CT doublet + anti-EGFR
Combination CT + bevacizumab
CT triplet + bevacizumab
CT doublet + biological agent
CT triplet +/- bevacizumab

Disease control (control of progression)

MOLECULAR PROFILE

RAS wt
RAS mt
BRAF mt

Re-evaluation/assessment of response every 2 months*

Re-evaluation/assessment of response every 2-3 months*

GOAL

Progressive disease

Surgery

Second-line

Cytoreduction (Shrinkage)**

Disease control

Continue

Continue; maintenance; or pause

BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; mt, mutant, NED, no evidence of disease; OMD, oligometastatic disease; wt, wild-type.

*Due to the potential for disease resistance, treatment may be continued for up to six cycles of treatment with ongoing clinical progress

**Due to the potential for disease resistance, treatment may be continued for up to six cycles of treatment with ongoing clinical progress.**
Systemic treatment: 1st line

- Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated.
- VEGF antibody bevacizumab should be used in combination with:
  - The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI
  - The cytotoxic triplet FOLFOXIRI in selected patients, predominantly where cytoreduction (tumour shrinkage) is the goal.
  - Fluoropyrimidine monotherapy (capecitabine) in patients not needing aggressive treatment.
- EGFR antibodies should be used in combination with:
  - FOLFOX/FOLFIRI
  - Capecitabine-based combinations should not be combined with EGFR antibodies.
Treatment of metastatic disease

Maintenance treatment

- Patients receiving FOLFOX or CAPOX as induction therapy should be allocated to maintenance therapy after 6–8 cycles.
- Patients receiving FOLFIRI as induction should continue for (at least) as long as tumour shrinkage continues/disease stabilisation is maintained.
- In the case of patients receiving induction therapy with single-agent 5-FU/capecitabine or capecitabine plus bevacizumab induction therapy should be maintained until progression.
- Optimal maintenance treatment after a bevacizumab-containing induction is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab monotherapy as maintenance is not recommended.
- Individualisation and discussion with the patient is essential.
- Induction therapy should be re-introduced throughout the whole treatment strategy.
Treatment of metastatic disease

Treatment of elderly patients with mCRC

- Fit older patients should be treated with systemic combination chemotherapy plus targeted agents as they derive the same benefit as younger patients.

- For older patients unfit for standard combination chemotherapy (with or without targeted agents), less intensive therapies including capecitabine plus bevacizumab or reduced dose fluoropyrimidine plus oxaliplatin or irinotecan are appropriate options.