

special article

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

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# ESMO consensus on mCRC 2016

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## ***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)

## 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]

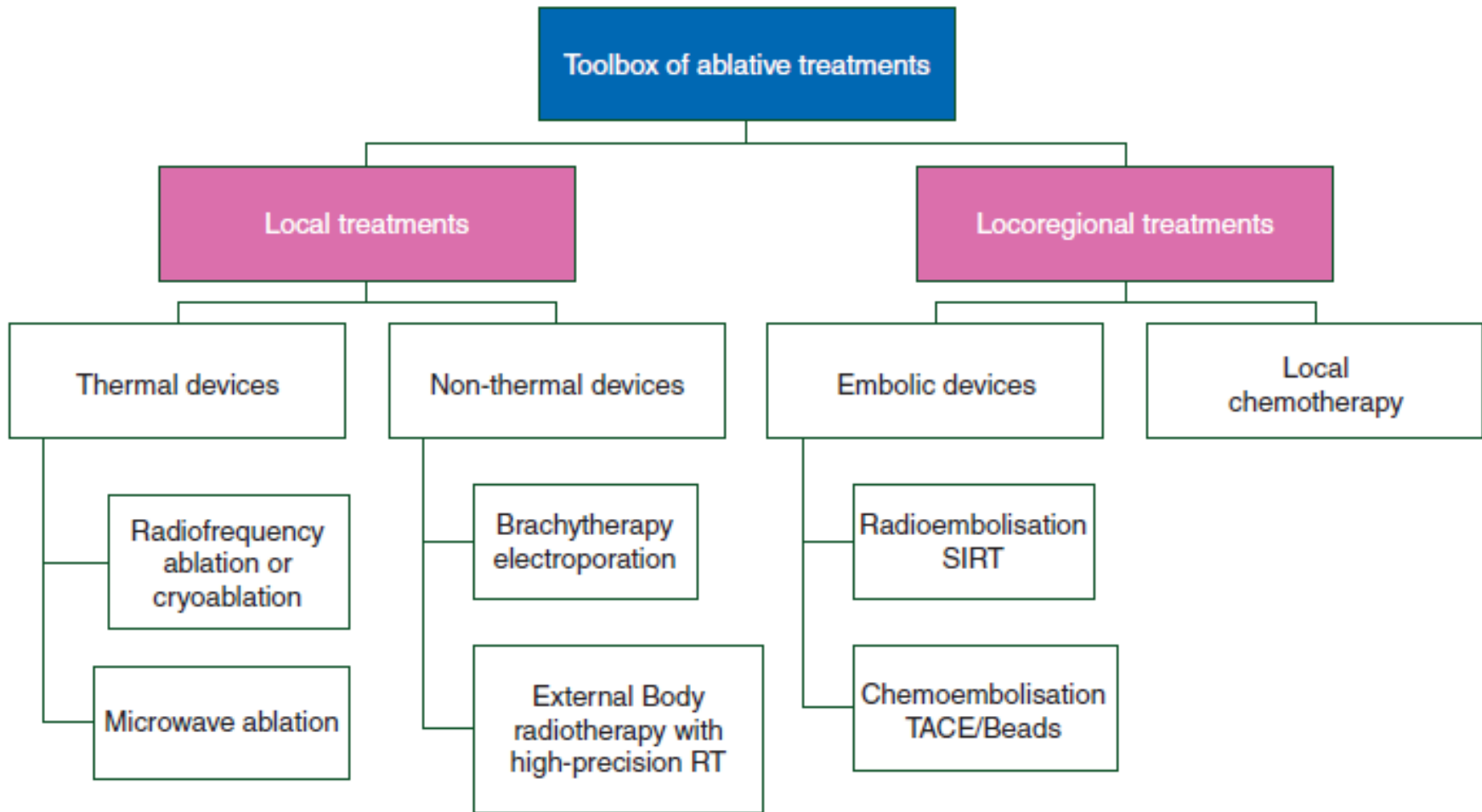
## Recommendation 6: MSI testing

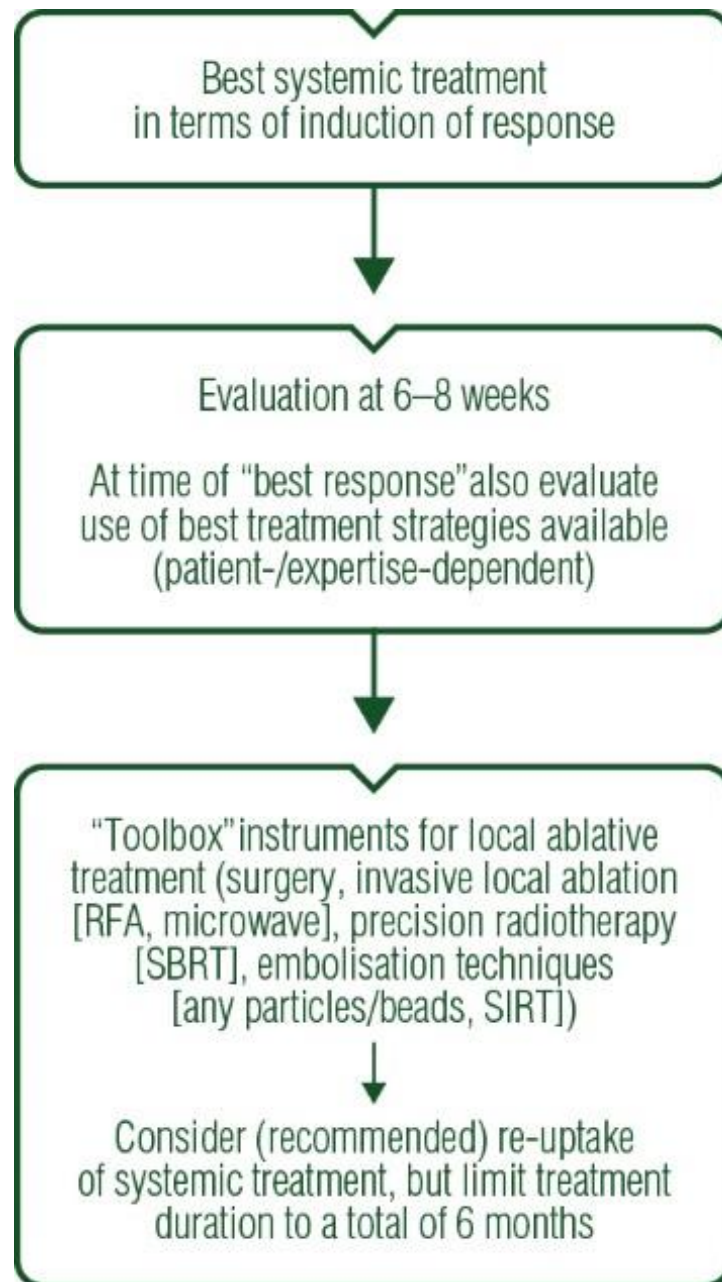
- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B]
- MSI testing has strong predictive value for the use of immune checkpoint inhibitors in the treatment of patients with mCRC [II, B]

## 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 1: Toolbox of ablative treatments





RFA = radiofrequency ablation;  
SBRT = stereotactic body radiation therapy  
SIRT = selective internal radiation therapy

Figure 3. Standard treatment algorithm for patients with oligometastatic disease.

# Local and ablative treatment (including surgery)

## Recommendation 12: Perioperative treatment.

- Both technical criteria for resection and prognostic considerations define the need for systemic perioperative therapy [IV, B].
- In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [I, C; consensus >75%].
- In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (FOLFOX or CAPOX) should be administered [I, B; consensus >75%].
- Targeted agents should not be used in resectable patients where the indication for perioperative treatment is prognostic in nature [II, E].



# Local and ablative treatment (including surgery)

## **recommendation 12: Perioperative treatment.**

- In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [IV, B] (Figure 2). Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.
- In patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from adjuvant treatment [III, B].
- In patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX or CAPOX is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy) [IV, B].
- Decision-making should include patients' characteristics and preferences [IV, B].

# Local and ablative treatment (including surgery)

## 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.

# 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].

# Local and ablative treatment (including surgery)

## 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].

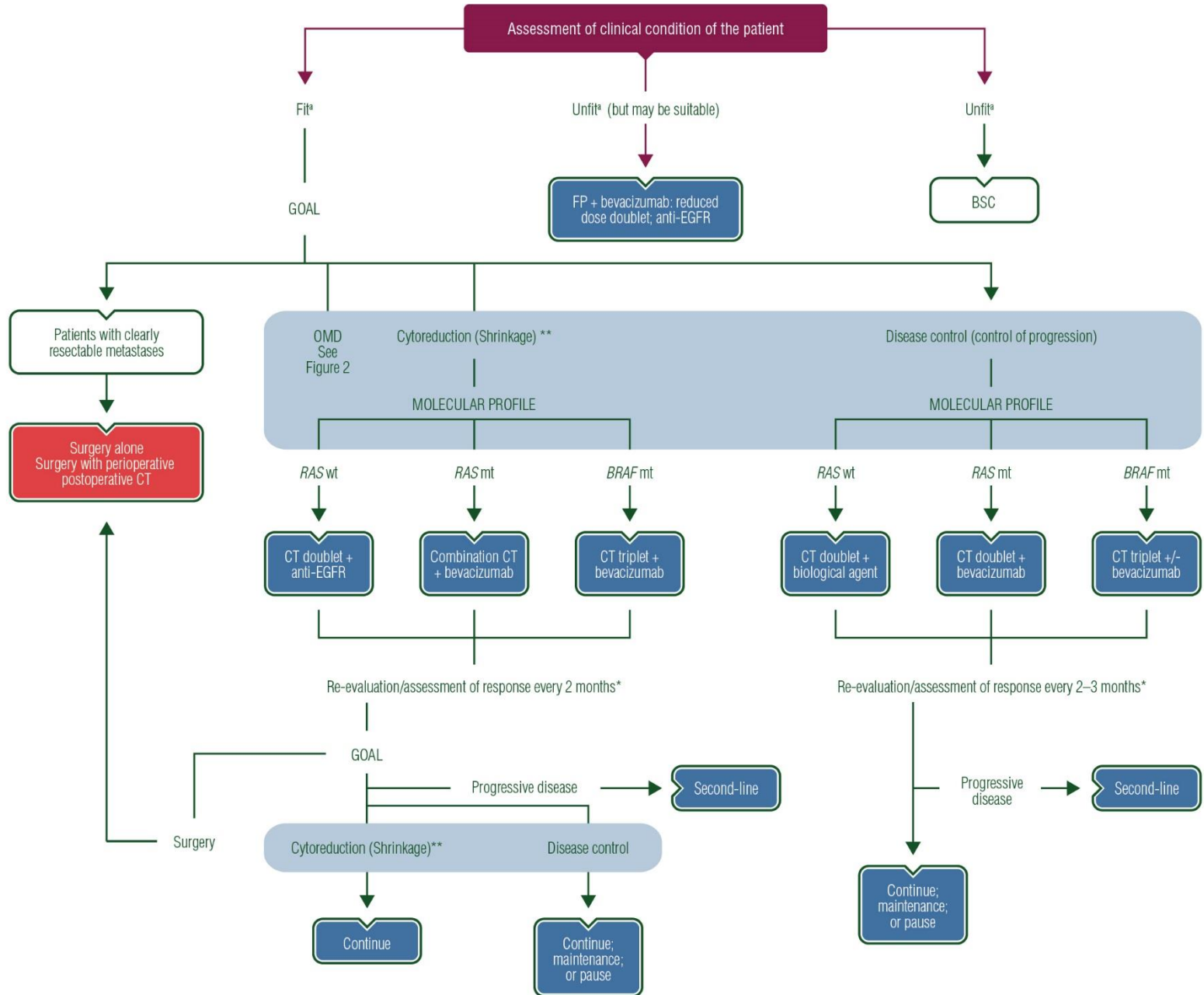
**Table 4.**  
Drivers for first-line treatment

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

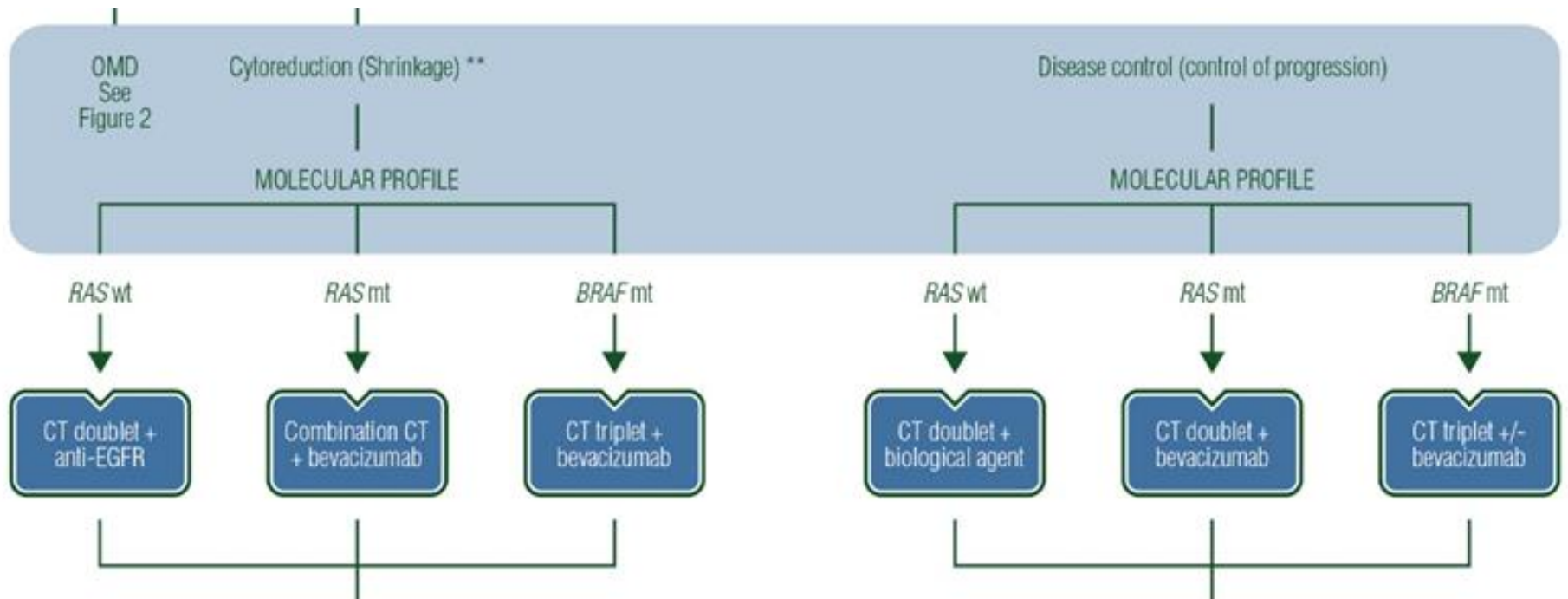
**Table 6.**  
Revised ESMO groups for treatment stratification of patients according to whether patients are 'fit' or 'unfit'

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

# Treatment of metastatic disease



# Treatment of metastatic disease





# Treatment of metastatic disease

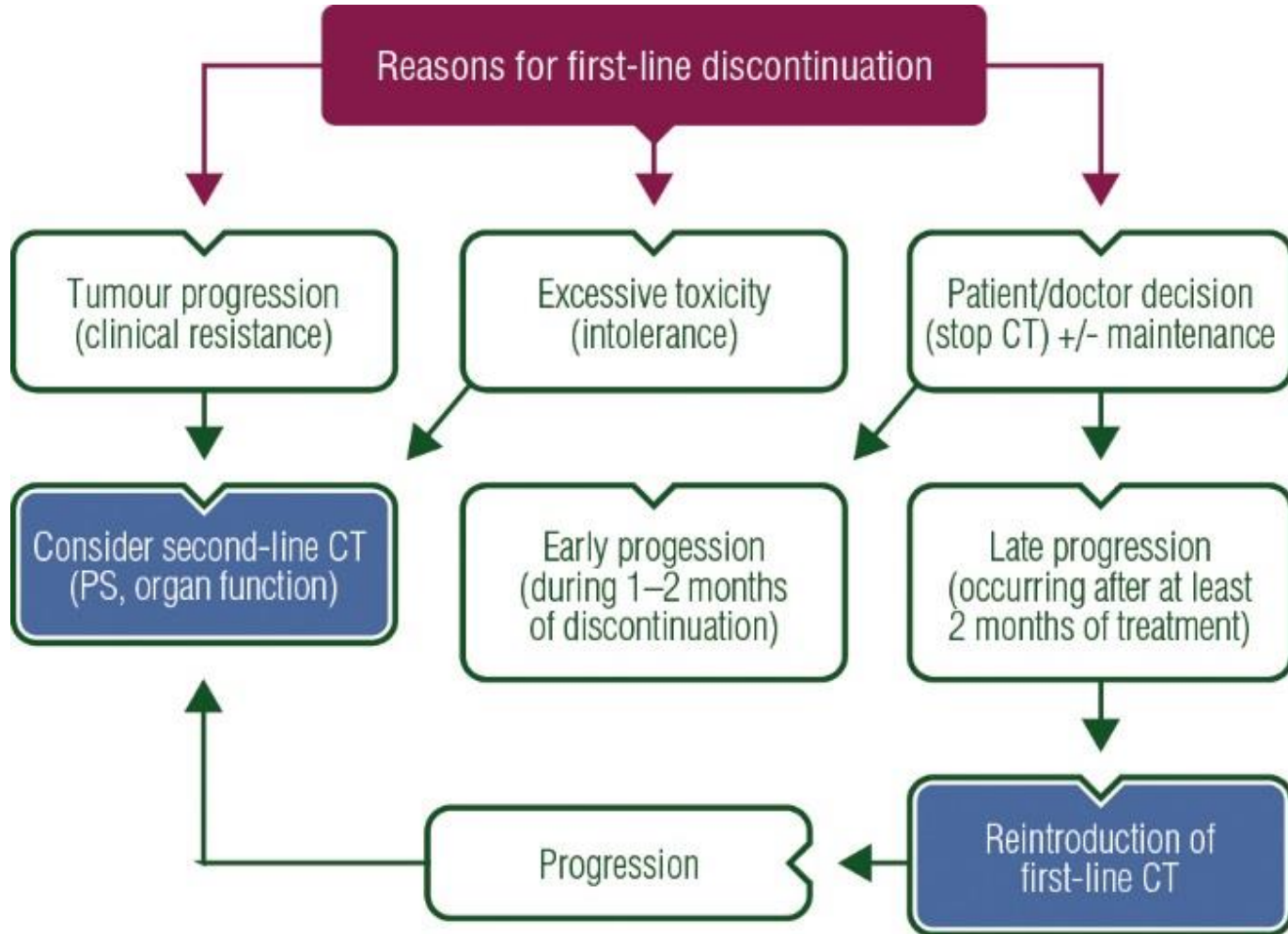


Figure 5. Maintenance and second-line treatment options. CT, chemotherapy; PS, performance status.

## 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].

## 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].**

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