Applying the ESMO Colorectal Cancer Consensus to different clinical scenarios

Dirk Arnold

CUF Hospitals Cancer Centre
Lisbon, Portugal
Disclosure slide

- Participate on Advisory Board with:
  Roche, Merck Serono, Amgen, Bayer, sanofi, BTG, Lilly

- Speaker and Chairman for educational events with:
  Roche, Merck Serono, Bayer, Lilly

- Investigator and researcher in data generating activities supported and sponsored by
  Roche, Mologen, Lilly, BTG, AstraZeneca, Bayer
Most recent formats for guidance of mCRC treatment

**Clinical practice guidelines**

**Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

E. Van Cutsem\(^1\), A. Cervantes\(^2\), B. Nordlinger\(^3\) & D. Arnold\(^4\), on behalf of the ESMO Guidelines Working Group*

*1Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; 2Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; 3Department of General Surgery and Surgical Oncology, Hôpital Ambroise Paré, Assistance Publique - Hôpitaux de Paris, Paris, France; 4Klinik für Tumorchirurgie, Medizinische Universität zu Lübeck, Lübeck, Germany.*

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**ESMO consensus guidelines for the management of patients with metastatic colorectal cancer – anno 2015**

E. Van Cutsem\(^1\), A. Cervantes\(^2\), R. Adam\(^3\), A. Sobrero\(^4\), H. Van Krieken\(^5\), D. Aderka\(^6\), E. Artemova\(^7\), H. Asunción Aguilar\(^7\), A. Bardelli\(^8\), A. Benson\(^9\), G. Bodoky\(^10\), F. Ciardiello\(^11\), A. D’Hoore\(^12\), E. Díaz Rubio\(^13\), J. Y. Douillard\(^14\), M. Ducreux\(^15\), A. Falcone\(^16\), A. Grothey\(^17\), T. Grünberger\(^18\), K. Haustermans\(^19\), V. Heinemann\(^20\), P. Hoff\(^21\), C.-H. Kömpe\(^23\), R. Labianca\(^23\), P. Laurent-Puig\(^24\), B. Ma\(^25\), T. Maughan\(^26\), K. Merrill\(^27\), A. Minervini\(^28\), R. S. Oosterwijk\(^29\), T. Overholt\(^30\), R. A. Pauwels\(^31\), M. Pehamberger\(^32\), G. Penteroudakis\(^32\), P. Pfeiffer\(^33\), T. Price\(^34\), C. Punt\(^35\), J. Rieche\(^36\), A. Roth\(^37\), R. Salazar\(^38\), W. Scheithauer\(^39\), H. J. Schmoll\(^40\), J. Tabernero\(^41\), J. Taïeb\(^24\), S. Tejpar\(^1\), H. Wasan\(^42\), T. Yoshino\(^43\), A. Zaanan\(^44\) & D. Arnold\(^44\)
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

- Medical Oncologist
- Pathologist
- Radiologist
- Surgeon
- Interventionalist
- Radiotherapist
- all others.....
ESMO consensus on mCRC 2015

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- A Sobrero: Advanced mCRC
- R Adam: Local and ablative treatment, oligometastasis
- H Van Krieken: Molecular Pathology and Biomarkers

Contributors
- D Aderka
- E Aranda
- A Bardelli
- S Barroso
- A Benson
- G Bodoky
- F Ciardiello
- A D'Hoore
- A Diaz Rubio
- JY Douillard
- M Ducreux
- A Falcone
- A Grothey
- T Gruenberger
- K Haustermans
- V Heinemann
- P Hoff
- K Köhne
- R Labianca
- B Ma
- T Maughan
- K Muro
- N Normanno
- P Österlund
- W Oyen
- D Papamichael
- G Pentheroudakis
- P Pfeiffer
- T Price
- PL Puig
- C Punt
- J Ricke
- A Roth
- R Salazar
- HJ Schmoll
- J Tabernero
- J Taieb
- S Tejpar
- H Wassan
- T Yoshino
- A Zaanan
Consensus report: Methodology

- An international group of experts from a range of disciplines, was convened 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.
ESMO 2015 Advanced CRC Consensus Conference

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
**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.

- **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: 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 [1, B].

Recommendation: MSI testing

- Except in the setting of genetic counselling, *MSI testing* is not yet recommended routinely in the metastatic disease setting.
- MSI testing has strong predictive value for the use of immune-checkpoint-inhibitors.
NOT routinely recommended:

- Chemotherapy sensitivity / toxicity biomarkers (DPD, UGT1A1, ERCC1 Expression, TS activity and genotyping)
- Emerging biomarkers like TS activity and TSER genotyping are not recommended for use in clinical practice (PiK3CA, amphiregulin, …)
- Emerging technologies like CTC, cfDNA, whole genome / exome / transcriptome sequencing
ESMO 2015 Advanced CRC Consensus Conference

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
- Kees Punt
- Hans Joachim Schmoll
- Takayuki Yoshino
ESMO 2015 Advanced CRC Consensus Conference

Local and ablative treatment & oligometastatic disease

- 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
Our Consensus Guideline:
What is NOT meant and NOT intended
NCCN Guidelines Version 2.2015
Colon Cancer

Initial Therapy

- FOLFOX³
  - or
  - CapeOX⁴
  - or
  - FOLFOX³ + bevacizumab⁵,⁶
  - or
  - CapeOX⁴ + bevacizumab⁵,⁶

Patient appropriate for intensive therapy²

- FOLFOX³ + cetuximab or panitumumab⁶,⁷
  - (KRAS/NRAS WT gene only)⁸,⁹

or

- Patient appropriate for intensive therapy²

or

- Initial Therapy
  - FOLFIRI¹⁰
  - or
  - FOLFIRI¹⁰ + bevacizumab⁵,⁶

Initial Therapy

- Patient appropriate for intensive therapy²

or

- FOLFIRI¹⁰ + cetuximab or panitumumab⁶,⁷
  - (KRAS/NRAS WT gene only)⁸,⁹

or

- Patient appropriate for intensive therapy²

or

- Initial Therapy
  - 5-FU/leucovorin¹⁄₈
  - or
  - Capecitabine¹⁹
  - ± bevacizumab⁵,⁶,²⁰

NCCN Guidelines Version 2.2015
as of Sept 12, 2015
NCCN Guidelines Version 2.2015
Colon Cancer

Initial Therapy

Patient appropriate for intensive therapy

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± bevacizumab⁵,⁶,²⁰

or

FOLFOXIRI ± bevacizumab⁵,⁶
Our Consensus Guideline:
What is NOT meant and NOT intended
Clinical scenario #1

- 64 y/o male patient, PS 1
- Liver metastases and lung metastases, metachronous
- 9 mos after resection of sigmoid cancer
- RAS wild type, BRAF wild type

„Should this patient be treated with x (or with y...) ?“
The questions to select the most appropriate induction treatment

- **Is the patient fit** enough to receive *standard* treatment?
- **Which treatment goals** exist?
  - All *treatment decisions* involving patients categorised as clinically fit *must* be made at a *tumour board* meeting by a MDT
- **Which treatment intensity** is the most appropriate?
  - Chemo monotherapy +/- bevacizumab
  - Chemo doublet +/- any monoclonal antibody
  - Chemo triplet +/- bevacizumab
- **Which information are available from the appropriate molecular analyses?**
## Treatment of metastatic disease

### Drivers for decision making in 1st 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</td>
</tr>
<tr>
<td><em>RAS</em> mutation status</td>
<td>Organ function</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td><em>BRAF</em> mutation status</td>
<td>Comorbidities</td>
<td>Quality of life, patient expectation and preference</td>
</tr>
</tbody>
</table>

Table 4. Treatment drivers for first-line treatment
Fit patients: Treatment goals

- **Fit patients with „disease control“ as goal**
  - Long OS, “chronic disease“ in palliative care
  - No disease-related symptoms, and not at risk to develop them soon
    - Few treatment-related symptoms as important argument

- **Fit patients with „cytoreduction“ as goal**
  - Cure (potentially)
  - No disease-related symptoms
    - Potentially accept slightly more treatment-related symptoms, but then have the option to de-escalate or to undergo ablation / eradication

ESMO Consensus 2015; in preparation
Clinical scenario #1

- 64 y/o male patient, PS 1
- Liver metastases and lung metastases, metachronous
- 9 mos after resection of sigmoid cancer
- RAS wild type, BRAF wild type

„Should this patient be treated with...”?
Which treatment goal exists?
Is the patient fit enough to undergo any treatment?
What is his RAS / BRAF status?
Is he willing to tolerate „toxic“ treatment (for a while)?
Fit patients with cytoreduction or shrinkage as a goal

- For potentially resectable patients…with *RAS* wild-type tumours, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice.

- For those with *RAS* mutant tumours should…a cytotoxic triplet plus bevacizumab (or cytotoxic doublet plus bevacizumab)…are the preferred options.

- If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage, patients should be recommended for potentially curative surgery with a view to eliminating all evidence of disease (R0 resection and/or ablative strategy).

ESMO Consensus 2015; in preparation
Treatment of metastatic disease

Fit patients with „disease control“ as goal

- The recommendation…for whom surgery (or induction --> local ablative treatment) was not an option…is… that they should receive chemotherapy (single-agent/doublet) plus bevacizumab first-line, with EGFR antibody therapy as an option for patients with RAS wild-type disease.

- Patients should be re-evaluated every 2–3 months. Where there is evidence of good disease control, patients should continue on therapy and if after two re-evaluations, active maintenance should be preferrably considered.

ESMO Consensus 2015; in preparation
„Special situations, special questions....“

What to do....

...in RAS WT ?
...in RAS mut ?
...in BRAF mut ?
...in other molecular / clinical subsets ?
...if tumour shrinkage is the goal ?
„Special situations, special questions....“

What to do....

...in RAS WT ?
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...if tumour shrinkage is the goal ?
Evidence for a benefit of anti-EGFR moAb in patients with RAS WT tumours

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N RAS wt other mut.</th>
<th>OS (HR)</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEAK</td>
<td>FOLFOX</td>
<td>170 23%</td>
<td>0.63</td>
<td>Phase II no hypothesis tested. OS data mature ??</td>
</tr>
<tr>
<td></td>
<td>Beva vs. Pani</td>
<td></td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>FIRE-3</td>
<td>FOLFIRI</td>
<td>400 15.8%</td>
<td>0.70</td>
<td>Secondary endpoint</td>
</tr>
<tr>
<td></td>
<td>Beva vs. Cet</td>
<td></td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>CALGB</td>
<td>any</td>
<td>670 15.3%</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beva vs. Cet</td>
<td></td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

Schwartzberg et al., J Clin Oncol 2014; Stintzing, ESMO 2014; Lenz & Venook ESMO 2014

Arnold, ESMO 2014 (oral presentation, Special Symposium)
• For patients with RAS wt mCRC: “All combination chemotherapy –antibody combinations should be regarded as a standard,
For patients with RAS wt mCRC: “All combination chemotherapy –antibody combinations should be regarded as a standard
For patients with RAS wt mCRC: “All combination chemotherapy—antibody combinations should be regarded as a standard, and the decision making will be a complex surrogate, taking into account many clinical factors, toxicity, as well as patient preferences”
„Special situations, special questions....“

What to do....

...in RAS WT ?
...in **RAS mut** ?
...in BRAF mut ?
... in other molecular / clinical subsets ?
...if tumour shrinkage is the goal ?
IFL +/- Bevacizumab phase III trial
KRAS analysis subgroup (N=230)

PFS

Group: Wild-Type

HR 0.44

Group: Mutant

HR 0.41

OS

Group: Wild-Type

HR 0.58

Group: Mutant

HR 0.69

Hurwitz et al., The Oncologist 2009
# FIRE 3: Bevacizumab in RAS mutant

<table>
<thead>
<tr>
<th></th>
<th>RAS wt (n=201)</th>
<th>RAS mutant (n=188)</th>
<th>HR/Odds ratio</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>FOLFIRI + Bevacizumab</td>
<td>FOLFIRI + Cetuximab</td>
<td>FOLFIRI + Bevacizumab</td>
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</tr>
<tr>
<td><strong>ORR (95%-CI)</strong></td>
<td>56 % (48 – 64)</td>
<td>38.1 % (28.5 – 48.6)</td>
<td>50.5 % (39.9 – 61.2)</td>
<td>0.60 (0.34-1.08)</td>
</tr>
<tr>
<td><strong>PFS (95% CI)</strong></td>
<td>10.2 mo (9.3 – 11.5)</td>
<td>7.5 mo (5.7 – 8.5)</td>
<td>9.6 mo (8.5 – 10.9)</td>
<td>1.25 (0.93-1.68)</td>
</tr>
<tr>
<td><strong>OS (95% CI)</strong></td>
<td>25.0 mo (23.0 – 28.1)</td>
<td>20.2 mo (16.4 – 23.4)</td>
<td>20.6 mo (17.1 – 26.3)</td>
<td>1.05 (0.77 – 1.44)</td>
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Stintzing et al. ESMO 2014
# FIRE 3: Bevacizumab in RAS mutant

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3rd line EGFR > 60%

Stintzing et al. ESMO 2014
TML strategy: „no benefit...in KRAS mutants....?”

Kubicka et al., Ann Oncol 2014
„Special situations, special questions....“

What to do....

...in RAS WT ?
...in RAS mut ?
...in BRAF mut ?
...in other molecular / clinical subsets ?
...if tumour shrinkage is the goal ?
FOLFOXIRI/bev vs. FOLFIRI/bev
all WT, RAS mut, BRAF mut subgroups

Cremolini et al., Lancet Oncol 2015
## Treated patients with FOLFOXIRI/bev: Results

<table>
<thead>
<tr>
<th>Study Description</th>
<th>N</th>
<th>RR</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOIB</td>
<td>10</td>
<td>90%</td>
<td>12.8</td>
<td>23.8</td>
</tr>
<tr>
<td>Masi, Lancet Oncol 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective phase II</td>
<td>15</td>
<td>60%</td>
<td>9.2</td>
<td>24.1</td>
</tr>
<tr>
<td>Loupakis, Eur J Cancer 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIBE</td>
<td>16</td>
<td>56%</td>
<td>7.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Cremolini et al, Lancet Oncol 2015</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
**RAS wt/BRAF mut pts.: Effect of anti-EGFR**

### Overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>0.90 [0.46, 1.76]</td>
</tr>
<tr>
<td>CRYSTAL and OPUS</td>
<td>0.62 [0.36, 1.06]</td>
</tr>
<tr>
<td>CO.17</td>
<td>0.84 [0.20, 3.58]</td>
</tr>
<tr>
<td>PICCOLO</td>
<td>1.84 [1.10, 3.08]</td>
</tr>
<tr>
<td>20050181</td>
<td>0.64 [0.32, 1.28]</td>
</tr>
<tr>
<td>COIN</td>
<td>1.18 [0.76, 1.81]</td>
</tr>
<tr>
<td>Summary:</td>
<td>0.97 [0.67, 1.41]</td>
</tr>
</tbody>
</table>

Test for effect: $P = 0.88$

Heterogeneity: $I^2 = 53\%, \ P = 0.06$

No significant treatment × BRAF status interaction for OS ($p=0.43$)
„Special situations, special questions....“

What to do....

...in RAS WT ?
...in RAS mut ?
...in BRAF mut ?
...in other molecular / clinical subsets ?
...in oligometastatic disease ?
 „Special situations, special questions....“

What to do....

...in RAS WT ?
...in RAS mut ?
...in BRAF mut ?
...in other molecular / clinical subsets ?
...in oligometastatic disease ?
Recommendation: oligometastatic disease

- In patients with (unresectable) CLM or with oligometastatic disease (...), local ablation techniques ...can be considered in addition to systemic therapy

- 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
Local and ablative treatment (including surgery)

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
„Toolbox“ of (palliative) ablative treatments

**Local cytoreduction**
- Thermal devices
  - Radiofrequency
  - Microwave
- Non-thermal devices
  - Brachytherapy/SBRT
  - IR-Electroporation

**Locoregional cytoreduction**
- Embolic devices
  - Radioembolisation SIRT
- Local chemotherapy
  - Chemoembolisation TACE/Beads

**Toolbox of ablative treatments**

---

Courtesy of Jens Ricke, Magdeburg
Clinical scenario #2

- 57 y/o female patient, PS 1
- **2 resectable** liver metastases
- Metachronous 2 yrs. after resection of primary
- RAS wild type, BRAF wild type

„Should this patient be treated with chemo or undergo upfront surgery?“
Clinical scenario #3

• 57 y/o female patient, PS 1
• 3 technically irresectable liver metastases (centrally)
• Metachronous 2 yrs. after resection of primary
• RAS wild type, BRAF wild type

„This patient should be treated – but with which chemo? (and how long....)?
Clinical scenario #2

• 57 y/o female patient, PS 1
• 2 resectable liver metastases
• Metachronous 2 yrs. after resection of primary
• RAS wild type, BRAF wild type

„Should this patient be treated with chemo or undergo upfront surgery?“
Clinical scenario #4

- 57 y/o female patient, PS 1
- **2 resectable** liver metastases
- Occuring 2 mos. after finishing adjuvant FOLFOX (6 mos.)
- RAS wild type, BRAF wild type

„Should this patient be treated with chemo or undergo upfront surgery?“

„This patient should be treated – but with *which* chemo? (and how long....) ?“
Local and ablative treatment (including surgery)

prognostic information

bad

preop FOLFOX or „best induction“

periop FOLFOX (EORTC trial)

no preop (or adjuvant?)

Conversion „best induction“

everal criteria

„easy“

„best induction“

„difficult“

ESMO Consensus 2015; in preparation
Local and ablative treatment (including surgery)

Upfront resectable CLM: Perioperative treatment

- In the case…the recommendation was that they can either be referred immediately for potentially curative surgery or for perioperative chemotherapy according to the schedule and regimen used in the EPOC study.

- The preference of the panel was for surgery up front with the recognition that the schedule of systemic therapy used perioperatively in the EPOC study was no longer seen as the only standard of care.

- The overall recommendation was for adjuvant therapy in patients with no evidence of disease who had received no preoperative chemotherapy and no previous treatment [low level of evidence, high level of recommendation].

ESMO Consensus 2015; in preparation
Local and ablative treatment (including surgery)

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 a cytotoxic doublet
  - **RAS wild type:** as above, or doublet (FOLFOX/FOLFIRI) plus an anti-EGFR antibody
    - seems to have the best benefit/risk ratio,
    - although the combination of FOLFOXIRI ± *bevacizumab* may also be considered
Fudan University, rand. phase II trial: Pts. with irresectable liver-limited disease (KRAS WT)

A

Overall Survival (probability)

HR = 0.54 (95% CI, 0.33 to 0.89); P = .013

B

Progression-Free Survival (probability)

HR = 0.60 (95% CI, 0.41 to 0.87); P = .004

Ye et al., J Clin Oncol 2013
OLIVIA, rand. phase II trial: Pts. with irresectable liver-limited disease

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + FOLFOXIRI (n=41)</th>
<th>Bevacizumab + mFOLFOX-6 (n=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>48.8 (32.9–64.9)</td>
<td>23.1 (11.1–39.3)</td>
<td>0.017</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>80.5 (65.1–91.2)</td>
<td>61.5 (44.6–76.6)</td>
<td>0.061</td>
</tr>
<tr>
<td>Histopathological response*</td>
<td>50.0 (27.2–72.8)</td>
<td>50.0 (23.0–77.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Grüntberger et al., ASCO 2013; Ann Oncol 2015
Recommendation: Cytoreductive surgery and HIPEC

- **Complete cytoreductive surgery** - and hyperthermic intraperitoneal chemotherapy - can be considered for patients with limited peritoneal metastases in very experienced expertise centers.
2nd line treatment: Chemotherapy

- Sequence: FOLFOX $\rightarrow$ FOLFIRI or FOLFIRI $\rightarrow$ FOLFOX
- Induction therapy should be considered for re-introduced throughout the whole treatment strategy
Bevacizumab-naïve should be considered for bevacizumab 2\textsuperscript{nd} line

Who received bevacizumab 1\textsuperscript{st} line should be considered for treatment with:

- Bevacizumab “post continuation (TML) strategy”
- Aflibercept (or ramucirumab, if available) in combination with FOLFIRI when treated in first line with oxaliplatin

EGFR antibodies in combination with FOLFIRI for patients with RAS wild-type (& BRAF wild-type) in 2\textsuperscript{nd} line

Patients who are fast progressors should be considered for treatment with the (likely) most active treatment
Treatment of metastatic disease

Anti-EGFR’s in later lines

■ 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 equally active as single agents
  ■ The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients
  ■ There is no unequivocal evidence to administer the alternate anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies.
Regorafenib is recommended in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies.

- Regorafenib is superior to placebo in terms of overall survival, although there are safety / toxicity concerns in frail patients.

- Trifluridine / tipiracil is a (potential) new option for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies.
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 therapy (with or without targeted agents), less intensive therapies including capecitabine plus bevacizumab or reduced dose fluoropyrimidine plus oxaliplatin or irinotecan are appropriate options.
Thanks for listening!