OPTIMISING OUTCOMES FOR PATIENTS WITH ADVANCED COLORECTAL CANCER

E-Learning Module

George Zarkavelis¹, Anna-Lea Amylidi¹, Demetris Papamichael², George Pentheroudakis¹, Henk van Halteren³

1. Department of Medical Oncology, Medical School, University of Ioannina, Greece
2. Department of Medical Oncology, Bank Of Cyprus Oncology Centre, Nicosia, Cyprus
3. Department of Medical Oncology, Admiraal de Ruyter Hospital, Goes, The Netherlands
DEMOGRAPHICS

Third most commonly diagnosed cancer worldwide:
1,849,518 new cases worldwide
499,667 new cases in Europe

Second cause of death among cancers
880,792 deaths worldwide
242,483 deaths in Europe

Metastatic disease a major cause of cancer-related mortality
Median Overall Survival (mOS) of mCRC patients ≥30 months

1. Current state-of-the-art systemic therapy for unresectable advanced colorectal cancer

2. Tumour sidedness, molecular pathology and new actionable targets

3. Oligometastatic advanced colorectal cancer
CURRENT STATE-OF-THE-ART SYSTEMIC THERAPY FOR UNRESECTABLE ADVANCED COLORECTAL CANCER
ESMO TREATMENT ALGORITHM FOR METASTATIC COLORECTAL CANCER

Zurich treatment algorithm

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

*Patients assessed as fit or unfit according to medical condition not due to malignant disease. *After two re-evaluations, consider maintenance. **(A) Includes two subgroups: (1) those for whom intensive treatment is appropriate with the goal of cyto reduction (tumour shrinkage) and conversion to resectable disease; (2) those who need an intensive treatment, although they will never make it to resection or LAT, since they need a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, severe symptoms.

Reprinted from Ann Oncol, 27(8), Van Cutsem E, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer, 1386–422. Copyright 2016, with permission from the European Society for Medical Oncology.
THE ROLE OF MULTIDISCIPLINARY TEAMS (MTD) AND MULTIDISCIPLINARY MOLECULAR TUMOUR BOARDS

Several studies have shown improved clinical outcomes, including improved OS, when patients with CRC are managed by MDTs

An ideal MDT should include:

- Medical and radiation oncologists
- A colorectal surgeon
- A specialist hepatobiliary and/or, lung surgeon
- A pathologist / molecular pathologist / biologist
- A diagnostic radiologist
- An interventional radiologist / nuclear medicine physician
“Evolving Continuum of Care” approach within a MDT:

First line
- Patient characteristics
- Tumour characteristics
- Treatment goal

Maintenance therapy
Optimise benefit from first-line agents

Second and further lines of treatment
Patients should receive all active agents for which they are eligible

The optimal sequencing of currently available therapies remains to be elucidated (toxicity and patient's tolerance, biomarkers)
# 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: Tumour burden</td>
<td>Age</td>
<td>Treatment goal, 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>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>
<tr>
<td><strong>Emerging:</strong> MSI, NTRAK, HER2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### CURRENT FIRST-LINE OPTIONS

#### Fit – Cytoreduction

<table>
<thead>
<tr>
<th>Primary tumour location</th>
<th>RAS/BRAF wild type</th>
<th>RAS mutated</th>
<th>BRAF mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left sided</td>
<td>Doublet + anti-EGFR</td>
<td>Doublet + Beva</td>
<td>Doublet or Triplet + Beva</td>
</tr>
<tr>
<td>Right sided</td>
<td>Doublet + Beva</td>
<td>Doublet + Beva</td>
<td>Doublet or Triplet + Beva</td>
</tr>
</tbody>
</table>

#### Fit – Disease control

<table>
<thead>
<tr>
<th>Primary tumour location</th>
<th>RAS/BRAF wild type</th>
<th>RAS mutated</th>
<th>BRAF mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left sided</td>
<td>Doublet + anti-EGFR</td>
<td>Doublet + Beva</td>
<td>Doublet or Triplet + Beva</td>
</tr>
<tr>
<td>Right sided</td>
<td>Doublet + Beva</td>
<td>Doublet + Beva</td>
<td>Doublet or Triplet + Beva</td>
</tr>
</tbody>
</table>
FIRST-LINE CHEMOTHERAPY

Does a combination strategy outperform sequential treatment?

Strategies of sequential therapies in unresectable metastatic colorectal cancer: a meta-analysis¹

Five RCTs performed encompassing FU/capecitabin, oxaliplatin and irinotecan

Combination vs sequential treatment:
Progression-free survival: HR 0.74 (95% CI: 0.67, 0.81; p<0.00001)
Overall Survival: HR 0.95 (95% CI: 0.86, 1.02; p=0.15)

Combination strategy outperforms sequential treatment with regard to response rate and PFS.
But no significant difference in OS and higher toxicity rates (i.e., polyneuropathy, diarrhoea, nausea, vomiting)

FIRST-LINE CHEMOTHERAPY
What does bevacizumab add to the outcome?

Efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated advanced or metastatic colorectal cancer: a systematic review and meta-analysis¹

Improved Progression-free Survival: HR 0.61 (95% CI: 0.51, 0.74; p<0.00001)
Improved Overall Survival: HR 0.86 (95% CI: 0.75, 0.98; p=0.03)

However……
No proven PFS/OS benefit of bevacizumab, if added to schedules containing oxaliplatin

What do EGFR inhibitors add to outcome in case of KRAS WT colorectal cancer?

**Additive value of cetuximab:**

- Improved Progression-free Survival: HR 0.79 (95% CI: 0.65, 0.95; p=0.01)
- Improved Overall Survival: HR 0.85 (95% CI: 0.74, 0.98; p=0.02)

**Additive value of panitumumab:**

- Improved Progression-free Survival: HR 0.80 (95% CI: 0.67, 0.95; p=0.01)
- Improved Overall Survival: HR 0.83 (95% CI: 0.70, 0.98; p=0.03)

RECOMMENDATIONS FOR RAS GENE TESTING

Tumour RAS mutational status is predictive for response to anti-EGFR directed targeted therapies

KRAS activating mutations detected in approximately 40% of metastatic colorectal cancers

Mutations in KRAS exons 2, 3 and 4 and NRAS exons 2, 3 and 4 predict for lack of response to EGFR-targeted monoclonal antibodies

Evidence from Phase 3 trials suggest that these therapies may even have a detrimental effect in patients with RAS-mutant disease, especially when combined with an oxaliplatin-based cytotoxic backbone
BRAF MUTATION PRECLUDES ADDITIONAL BENEFIT OF ANTI-EGFR THERAPY

Meta-analysis of outcome results of 469 patients with advanced KRAS WT BRAF\textsubscript{mut} colorectal cancer who were treated in RCTs comparing chemotherapy vs. chemotherapy + EGFR inhibitor

**No additional benefit of EGFR inhibitor in these patients:**

- **Overall Survival:** HR 0.91 (95% CI: 0.62, 1.34; p=0.63)
- **Progression-free Survival:** HR 0.88 (95% CI: 0.67, 1.14; p=0.33)
- **Overall Response Rate:** OR 1.31 (95% CI: 0.83, 2.08; p=0.25)
RECOMMENDATIONS FOR BRAF TESTING

BRAF mutation (usually V600E) occurs in 8–12% of patients with mCRC

Almost exclusively non-overlapping with KRAS mutations

2/3 of BRAF mutant tumours located in right colon; associated with increased incidence of lymph node and peritoneal but fewer pulmonary metastases

1/3 of BRAF mutant tumours also have microsatellite instability (MSI)

Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for its prognostic and predictive significance, choice of therapy and/or participation in clinical trials
RECOMMENDATIONS FOR BRAF TESTING

Prognostic significance:
• Significant negative prognostic marker for patients with mCRC: mOS 10.4 months compared with 34.7 for patients with BRAF wild-type

Predictive significance:
• Response to anti-EGFR mAbs is unlikely even if tumour is RAS wild type
• Two meta-analyses have shown that the efficacy benefit of anti-EGFR mAbs to be greater in patients with RAS wild type/BRAF wild type tumours than RAS wild type/BRAF mutant tumours
• A recent meta-analysis provides evidence that there is no increased benefit from the use of triplet chemotherapy + bevacizumab as first-line choice in patients with BRAF mutant tumours versus doublet + bevacizumab
• There is now evidence that resistance to anti-EGFR moAbs in BRAF mutated tumours can be overcome with the use of BRAF inhibitors

ATYPICAL BRAF MUTATIONS
BRAF non-V600E mutations

One fifth of all BRAF mutations in colorectal cancer. May rise in younger adults, less often found in women, less often high grade, significantly better median overall survival compared with BRAF V600E mutations¹

Atypical non-V600E BRAF mutations represent a distinct subgroup with regards to gender, tumour location, metastatic pattern and MSI status, showing shorter OS and PFS compared with BRAF wild type, but better than BRAF V600E. They also may be a negative predictive marker for the application of anti-EGFR therapy. Further investigation is warranted²

FIRST-LINE CHEMOTHERAPY

Should we add bevacizumab or an EGFR inhibitor in case of RAS WT colorectal cancer?

Bevacizumab vs Panitumumab: a meta-analysis of 3 trials:

• No significant differences found with regard to ORR, PFS, OS and adverse events

EGFR INHIBITOR MAY BE SUPERIOR IN THE CASE OF LEFT SIDED CANCER

Overall survival

Forest plots for predictive analyses of tumour location (right vs left side) in trials comparing chemotherapy plus EGFR antibody therapy (experimental arm) with chemotherapy alone or chemotherapy plus bevacizumab (control arm)

Reprinted from Ann Oncol, 28(8), Arnold D, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials, 1713–29. Copyright 2017, with permission from the European Society for Medical Oncology.
FIRST-LINE SYSTEMIC THERAPY: CONTINUOUS VS. INTERMITTENT

Meta-analysis of studies encompassing (combinations of) irinotecan, FU/capecitabine, oxaliplatin and bevacizumab

Meta-analysis for overall survival: all trials

MAIN CONCLUSIONS OF META ANALYSIS…

Intermittent strategies of administering first-line systemic therapies do not result in a reduction in OS and either improve or maintain QoL compared with continuous administration

Characteristics of identified randomized, controlled trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary outcome</th>
<th>Type of trial</th>
<th>Treatment</th>
<th>Number of patients randomized (evaluated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muggen et al.</td>
<td>Overall survival</td>
<td>Superiority</td>
<td>Interim (12 weeks)</td>
<td>178</td>
</tr>
<tr>
<td>Loi et al.</td>
<td>OS</td>
<td>Superiority</td>
<td>Continuous (12 weeks)</td>
<td>176</td>
</tr>
<tr>
<td>Combination trials: intermittent chemotherapy with 5-FU maintenance therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tournigand et al. (OPTIMOX)</td>
<td>Duration of disease control</td>
<td>Superiority</td>
<td>Interim (FOLFOX4, 12 weeks) vs. 5-FU, 12 weeks</td>
<td>309</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (FOLFOX4 every 2 weeks until PD)</td>
<td>311</td>
</tr>
<tr>
<td>Cangi et al. (COPPER)</td>
<td>Time to treatment failure</td>
<td>Superiority</td>
<td>Interim (mFOLFOX6 + BEV alternate every 4 weeks with and without oxaliplatin + CaMg)</td>
<td>180 (139) (in total)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (mFOLFOX6 + BEV every 2 weeks + CaMg until PD)</td>
<td></td>
</tr>
<tr>
<td>Combination trials: intermittent chemotherapy with no maintenance therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alempol and Kiess [6]</td>
<td>OS</td>
<td>Superiority</td>
<td>Interim (FOLFIGI, 12 weeks; CFi: restart</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cont FOLFIGI FPE)</td>
<td></td>
</tr>
<tr>
<td>Chitale et al. (OPTIMOX2)</td>
<td>Duration of disease control</td>
<td>Superiority</td>
<td>Interim (mFOLFOX4, 12 weeks; CFi: restart</td>
<td>108 (108)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mFOLFOX4 at PD, 12 weeks)</td>
<td></td>
</tr>
<tr>
<td>Adams et al. (COSMOS)</td>
<td>Overall survival</td>
<td>Noninferiority</td>
<td>Interim (FOLFOX4 or CapeOx, 12 weeks; CFi: restart same chemo at PD)</td>
<td>815</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (FOLFOX4 or CapeOx until PD)</td>
<td>815</td>
</tr>
<tr>
<td>Labianca et al. [11]</td>
<td>Overall survival</td>
<td>Noninferiority</td>
<td>Interim (FOLFIGI every 2 weeks until PD)</td>
<td>167 (147)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (BEV + CapeOx, 18 weeks; CFi: restart BEV + CapeOx at PD)</td>
<td>170 (146)</td>
</tr>
<tr>
<td>Koopman et al. (GAIBO3) (12)</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Interim (BEV + CapeOx, 18 weeks; BEV + CapeOx at PD)</td>
<td>279 (278)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (BEV + CapeOx, 18 weeks; BEV + CapeOx at PD)</td>
<td></td>
</tr>
<tr>
<td>Combination trials: intermittent chemotherapy with a biologic maintenance therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaz et al. (MAGO) (13)</td>
<td>Progression-free survival</td>
<td>Noninferiority</td>
<td>Interim (BEV + CapeOx, 18 weeks; BEV only until PD)</td>
<td>241</td>
</tr>
<tr>
<td>Twite et al. (NORDIC IV) (14)</td>
<td>Progression-free survival</td>
<td>Superiority</td>
<td>Interim (Cetuximab + FOLFOX6, 16 weeks; Continue FOLFOX6 at PD)</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (Cetuximab + FOLFOX6 until PD)</td>
<td>239</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuous (Cetuximab + FOLFOX6, 16 weeks; Continue FOLFOX6 at PD)</td>
<td>185</td>
</tr>
</tbody>
</table>

BEV, bevacizumab; CaMg, calcium magnesium; cape, capecitabine; CapeOx, capecitabine/oxaliplatin; CFI, chemotherapy-free interval; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid (leucovorin)/5-FU/irinotecan; FLOX, folinic acid (leucovorin)/5-FU/oxaliplatin; m, modified; NR, not reported; PD, disease progression; PS, performance status; s, simplified; WHO, World Health Organization; 5-FU, 5-fluorouracil.

CONTINUOUS VS. INTERMITTENT FIRST-LINE THERAPY

Individualisation and discussion with the patient is essential:

For patients receiving FOLFOX or CAPOX plus bevacizumab-based therapy, consider maintenance therapy after 6–8 cycles with a combination of a fluoropyrimidine plus bevacizumab.

As overall survival has not been improved by maintenance strategies, treatment holidays are a valid option and should be discussed with the patient.

Patients receiving FOLFIRI can continue on induction therapy for as long as tumour shrinkage continues and the treatment is tolerable.

For patients receiving initial therapy with a single agent fluoropyrimidine (plus bevacizumab) induction therapy should be maintained.

Maintenance panitumumab was found to be inferior to combined panitumumab plus a fluoropyrimidine in a Phase 2 study, whereas maintenance cetuximab achieved a PFS rate noninferior to continuation of doublet chemotherapy plus cetuximab. Data from Phase 3 trials are lacking regarding the role of anti-EGFRs as maintenance therapy.

Bevacizumab as monotherapy is not recommended as maintenance therapy.

SECOND-LINE THERAPY AND BEYOND
SECOND-LINE TREATMENT

Initial induction therapy or a second-line therapy have to be reintroduced at radiological or first signs of symptomatic progression

Bevacizumab-naïve

- Consider for an anti-angiogenic (bevacizumab or aflibercept) second-line. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen

Bevacizumab as first-line

- Consider:
  - Aflibercept or bevacizumab post-continuation strategy
  - Ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin
  - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wild-type disease

Consider the molecular profile of the tumour. There are emerging targeted options:

- Immunotherapy for MMR deficient/MSI-H tumours
- BRAF inhibitors for BRAF-mutated tumours
- Anti-HER2-targeted therapy for HER2 overexpressing tumours
- Larotrectinib, entrectinib for NTRK-fused tumours
VELOUR STUDY

Overall results

Adding aflibercept to FOLFIRI in mCRC patients previously treated with an oxaliplatin-based regimen resulted in significant OS and PFS benefits (1226 patients from primary analysis population):

<table>
<thead>
<tr>
<th></th>
<th>Placebo/FOLFIRI</th>
<th>Aflibercept/FOLFIRI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (median, months)</td>
<td>12.06</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>HR (94.34% CI)</td>
<td></td>
<td>0.817 (0.713, 0.937)</td>
<td>0.0032</td>
</tr>
<tr>
<td>PFS (median, months)</td>
<td>4.67</td>
<td>6.90</td>
<td></td>
</tr>
<tr>
<td>HR (94.34% CI)</td>
<td></td>
<td>0.758 (6.51, 7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2-year survival rate (%)</td>
<td>18.7</td>
<td>28.0</td>
<td></td>
</tr>
</tbody>
</table>
RAISE TRIAL: RAMUCIRUMAB + FOLFIRI OVERALL SURVIVAL

RAM, ramucirumab.
BEACON: ENCORAFENIB + CETUXIMAB ± BINIMETINIB FOR BRAF V600E-MUTANT MCRC

Multicentre, randomised, open-label, 3-arm Phase 3 trial
Patients with BRAF V600E+ mCRC with PD after 1–2 prior regimens (no prior RAF/MEK/EGFR inhibitors), no symptomatic brain metastases

**Primary endpoints:** OS and ORR for triplet vs control
**Secondary endpoints:** OS and ORR for doublet vs control, triplet vs doublet; PFS; safety

Arm A: Binimetib + Encorafenib + Cetuximab
Arm B: Encorafenib + Cetuximab
Arm C: Investigators Choice → FOLFIRI + Cetuximab or Irinotecan + Cetuximab

Kopetz S, et al. BEACON CRC: A randomized, three-arm, phase 3 study of encorafenib plus cetuximab with or without binimetinib vs choice of either irinotecan or FOLFIRI plus cetuximab in patients with BRAF V600E metastatic colorectal cancer. Presented at 2020 ASCO Annual Meeting, abstract 4001. Reproduced with permission from Scott Kopetz, MD, PhD.
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 OS although there are toxicity concerns in frail patients.

TAS-102 (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.

Rechallenge strategies may be applied, taking into consideration patient’s performance status, tolerability and toxicity.

Retrospective studies have provided positive results when applying chemotherapy rechallenge in further lines of treatment.\(^1\)

Randomized trials are currently under recruitment investigating this strategy.

Consider the molecular profile of the tumour. There are emerging targeted options.

- Immunotherapy for MMR deficient/MSI-H tumours
- BRAF inhibitors for BRAF mutated tumours
- Anti-HER 2 targeted therapy for HER2 overexpressing tumours
- TRK inhibitors for NTRK fusions

Primary endpoint met prespecified stopping criteria at second interim analysis (P≤0.009279)

Reprinted from The Lancet, 381(9863), Grothey A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial, 303–12. Copyright 2013, with permission from Elsevier.
**RE COURSE: TAS 102 VS. PLACEBO OS**

TUMOUR SIDEDNESS, MOLECULAR PATHOLOGY AND NEW ACTIONABLE TARGETS
Tissue handling

Standardisation of tissue processing for patients with mCRC still remains a challenge.

The pathologist plays a central role in:

- Preparing the tissue samples for standard histology assessment
- Choosing the most appropriate material for biomarker testing
- Reviewing the adequateness of the selected material for molecular testing:
  - A neoplastic cell content of at least 50% is recommended when using a technique with low sensitivity
  - Enrichment of samples by macro-dissection to maximise tumour cell content prior to DNA extraction is recommended
  - In that regard, laser capture micro-dissection may also be used
MOLECULAR ABERRATIONS IN METASTATIC COLORECTAL CANCER

Genomic alterations level I/II/III according to ESCAT in metastatic colorectal cancer (mCRC)

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Reprinted from Ann Oncol, 31(11), Mosele F, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group, 1491–505. Copyright 2020, with permission from the European Society for Medical Oncology.
### PRIMARY TUMOUR SIDEDNESS

- For patients with RAS wild-type tumours, recent data suggest that the sidedness of the primary tumour may be of prognostic and predictive significance.
- Right-sided tumours seem to be associated with inferior outcomes.
- Age, MMR status, BRAF status and methylation phenotype are associated with right-sided primaries.

<table>
<thead>
<tr>
<th>Right-sided tumours ~40% (increasing)*</th>
<th>Left-sided tumours ~60%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Older patients</td>
<td>• 18q loss</td>
</tr>
<tr>
<td>• Female patients</td>
<td>• 20q gain</td>
</tr>
<tr>
<td>• Late symptoms onset</td>
<td>• p53 mutation</td>
</tr>
<tr>
<td>• Peritoneal metastases</td>
<td>• COX2 expression</td>
</tr>
<tr>
<td>• <strong>Higher incidence in female patients</strong></td>
<td>• Aneuploidy</td>
</tr>
<tr>
<td>• Mucinous, signet ring histology</td>
<td>• EGFR gain</td>
</tr>
<tr>
<td>• Microsatellite instability</td>
<td>• HER2 gain</td>
</tr>
<tr>
<td>• Poorly differentiated</td>
<td>• High EGFR ligand expression (EREG expression)</td>
</tr>
<tr>
<td>• PI3KCA</td>
<td></td>
</tr>
<tr>
<td>• <strong>KRAS mutations</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>BRAF mutations</strong></td>
<td></td>
</tr>
</tbody>
</table>

---

*High-incidence CRC populations.
ASSESSMENT OF OVERALL SURVIVAL OF LEFT VS. RIGHT SIDE IN PATIENTS WITH COLON CANCER

Meta-analysis of 66 studies, including >1.4 million patients
Left-sided primary tumour location was associated with a significant 20% reduced risk of death (HR 0.82; 95% CI: 0.79, 0.84; p<0.001)

A. Since most level I alterations are hotspot mutations in KRAS, NRAS and BRAF, and considering that MSI status is determined by IHC or PCR, there is no need to test samples using multigene NGS in the context of daily practice.

B. Nevertheless, multigene NGS can be an alternative to PCR tests only if it does not generate extra cost compared with standard techniques already implemented in routine practice.

C. This would allow detection of ERBB2 amplifications, and, in some panels, detect MSI status with high accuracy. If large panel NGS is carried out, it should include detection of NTRK fusions.

D. Patients with mCRC can present oncogenic alterations for which drugs are being developed and it is therefore recommended for clinical research centres to include patients in molecular screening programmes to propose access to innovative agents in clinical trials.

MSI, microsatellite instability; NGS, next-generation sequencing; PCR, polymerase chain reaction.
MICROSATELLITE INSTABILITY (MSI)

4–8% of tumours in patients with mCRC have MSI due to a deficiency in their MMR system.

mCRC patients with MSI tumours and stage IV disease tend to present at a younger median age and their tumours are usually poorly differentiated.

1/3 of tumours that exhibit MSI are also BRAF-mutant.

MSI is a negative prognostic marker for PFS and OS in the metastatic setting, while it may also be a negative predictive marker for response to chemotherapy.

Recent data, however, suggest that MSI is a positive predictive marker for response to immunotherapy.

Consequently, MSI testing is recommended in the metastatic disease setting both for genetic counselling purposes and for its predictive value for the use of immune check-point inhibitors.
PD-1 BLOCKADE IN MMR-DEFICIENT TUMOURS
Pembrolizumab Phase 2 study in refractory malignancies

<table>
<thead>
<tr>
<th>Efficacy outcome (RECIST), %</th>
<th>MMR-deficient CRC (n=13)</th>
<th>MMR-proficient CRC (n=25)</th>
<th>MMR-deficient other tumours (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>62</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>92</td>
<td>16</td>
<td>70</td>
</tr>
</tbody>
</table>

To date, responses >1 year observed, and 13 or 14 responding patients continue to maintain response

Other efficacy outcomes in MMR-deficient vs. MMR-proficient tumours

- Median PFS: not yet reached vs. 2.3 mos
- Median OS: not yet reached vs. 5 mos

KEYNOTE 177: FIRST-LINE PEMPROLIZUMAB IN MMR-D/MSI-H METASTATIC COLORECTAL CANCER

Randomized, open label Phase 3 trial

Patients with treatment-naive MSI-H (PCR)/dMMR (IHC) stage IV CRC

Dual primary endpoints: PFS, OS

Secondary endpoints: ORR, safety

Chemotherapy options included mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab

Crossover permitted at disease progression
Note the crossing of the curves, indicating a subgroup of patients with primary resistance to immunotherapy.
CHECKMATE 142: NIVOLUMAB ± IPILIMUMAB IN MMR-D/MSI-H CRC

Investigator-Assessed Response With Nivo Monotherapy (n = 74)
- ORR: 31%
- 62% of patients had a reduction in tumor burden from baseline
- Median TTR: 2.8 mos
- Median DoR: not reached; 83% (19/23) responses ongoing

Best Reduction in Target Lesion Size With Nivo + Ip
- 80% of patients had a reduction in tumor burden from baseline

8887 CRC (colonic 85.5% and rectal 14.5%) evaluated by comprehensive genomic profiling for genomic alterations in 315 cancer-related genes

569 mCRC were positive for ERBB2 and/or ERBB3 and featured ERBB amplification, short variant (SV) alterations, or a combination of the two

In the HERACLES-A study 48/914 (5%) of patients with KRAS exon 2 wild type harboured amplification/overexpression

HER2 OVEREXPRESSION

Overexpression of HER2 ~5% of colorectal cancers

IHC for HER2 protein, *in situ* hybridization or RT-PCR

There is accumulating data that targeted therapy with anti-HER2 agents can provide benefit

To date trastuzumab + lapatinib, trastuzumab + pertuzumab and trastuzumab deruxtecan have been investigated in HER2 overexpressing metastatic colorectal cancer
HERACLES: PHASE 2 TRIAL OF TRASTUZUMAB + LAPATINIB IN METASTATIC CRC

Best tumour response

- KRAS wild type, HER2 positive
- Colorectal cancer refractory to standard of care
- Primary endpoint: objective response

Reprinted from The Lancet, 17(6), Sartore-Bianchi A, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. 738–46. Copyright 2016, with permission from Elsevier.
DESTINY: PHASE 2 TRIAL OF TRASTUZUMAB DERUXTECAN

- Patients with unresectable-metastatic CRC HER2 expressing and RAS/BRAF wild type
- ≥2 previous lines of therapy
- Primary endpoint: ORR in Cohort A

## SUMMARY: ANTI-HER2 TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Molecular Target</th>
<th>HER2 Regimen</th>
<th>PFS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERACLES A</td>
<td>KRAS wt</td>
<td>Trastuzumab + Lapatinib</td>
<td>4.9</td>
</tr>
<tr>
<td>My Pathway</td>
<td>none</td>
<td>Trastuzumab + Pertuzumab</td>
<td>2.9</td>
</tr>
<tr>
<td>HERACLES B</td>
<td>RAS/RAF wt</td>
<td>Pertuzumab + TDM-1</td>
<td>4.8</td>
</tr>
<tr>
<td>MOUNTAINEER</td>
<td>RAS wt</td>
<td>Trastuzumab + Tucatinib</td>
<td>8.1</td>
</tr>
<tr>
<td>TRIUMPH</td>
<td>RAS wt</td>
<td>Trastuzumab + Pertuzumab</td>
<td>4.0</td>
</tr>
<tr>
<td>DESTINY-CRC01</td>
<td>RAS wt</td>
<td>T-DXd</td>
<td>6.9</td>
</tr>
</tbody>
</table>

NTRK FUSIONS

- Translocations leading to the activation of tropomyosine receptor kinase
- 1% of metastatic colorectal cancers
- NTRK fusions associated with poor prognosis
- Use of TRK inhibitors, larotrectinib and entrectinib may be beneficial for patients

*One patient had a tropomyosin receptor kinase (TRK) solvent front resistance mutation (NTRK3 G623R) at baseline owing to previous therapy; †One patient had a pathological complete response.

**Summary**

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS/NRAS/BRAF WT – left-sided tumours</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td>Panitumumab</td>
</tr>
<tr>
<td>dMMR/MSI-H</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>Nivolumab ± ipilimumab</td>
</tr>
<tr>
<td>BRAF mutant</td>
<td>Encorafenib + cetuximab</td>
</tr>
<tr>
<td>HER2+ and RAS/BRAF WT</td>
<td>Dual anti-HER2 therapy, T-DXd</td>
</tr>
<tr>
<td>NTRK fusion positive and RAS/BRAF WT</td>
<td>Larotrectinib, entrectinib</td>
</tr>
<tr>
<td>Unknown status</td>
<td>Anti-VEGFs</td>
</tr>
<tr>
<td>RAS mutated</td>
<td>RAS inhibitors under investigation</td>
</tr>
</tbody>
</table>
EGFR INHIBITOR RECHALLENGE THERAPY?

Characterising the patterns of clonal selection in circulating tumour DNA from patients with colorectal cancer refractory to anti-EGFR treatment

---

Figure 1. KRAS codon mutation distribution in treatment-naïve patients versus patients with acquired EGFR-inhibitor resistance (EGFR-TKI resistant). Atypical KRAS codon 61 and codon 146 mutations were more frequent in metastatic colorectal cancer patients with acquired KRAS mutations after anti-EGFR mAb treatment than in treatment-naïve patients with KRAS mutations (*P < 0.05).

Figure 3. Time from last treatment with EGFR mAbs correlates with quantification of KRAS mutations detected in ctDNA. Time from last dose of EGFR mAbs correlated with the percentage of KRAS mutation reads detected in ctDNA from the plasma of metastatic colorectal cancer patients who developed resistance to treatment (P = 0.038).

LIQUID BIOPSIES IN CRC

Cell-free DNA is detectable in most late stage cancers (100% in mCRC)

Estimates of PFS and OS according to RAS and BRAF ctDNA status:

- Patients with RAS wild-type ctDNA (n=13) had significantly longer PFS than those with RAS mutated ctDNA (n=12) (median PFS **4.0** vs. **1.9** months (HR 0.44 [95% CI: 0.18, 0.98]; p=0.03)

- No significant differences reported in terms of OS (median OS **12.5** vs. **5.2** months (HR 0.58 [95% CI: 0.22, 1.52]; p=0.24)
Clinical relevance of intrinsic biologic processes implicated in each subtype

- **CMS1 tumours**: more frequent in females, right sided tumours, higher grade, poor survival after relapse
- **CMS2 tumours**: mainly left sided, superior survival after relapse
- **CMS3 tumours**: frequent KRAS mutations
- **CMS4 tumours**: diagnosed at more advanced stages, display worse overall survival
OLIGOMETASTATIC ADVANCED COLORECTAL CANCER
THE MANAGEMENT OF OLIGOMETASTATIC DISEASE (OMD)

Treatment strategies for patients with OMD should be based on the possibility of achieving complete ablation of all tumour masses, using surgical R0 resection and/or LAT, either initially or possibly after induction treatment with systemic therapy, for both the primary tumour and metastases.

Numerous case series have shown that in this setting long-term survival or even cure can be attained in 20–50% of patients who undergo complete R0 resection of their metastases.
COLORECTAL LIVER METASTASES (CLM)

Complete resection is the goal, with resectability depending on both technical and oncological criteria

### Technical criteria

| 1. Absolute | ♦ Impossibility of R0 resection with ≥30% liver remnant  
| ♦ Presence of unresectable extrahepatic disease |
| 2. Relative | ♦ R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation)  
| ♦ R1 resection |

### Oncological criteria

| 1. Concomitant extrahepatic disease (unresectable) |
| 2. Number of lesions ≥5 |
| 3. Tumour progression |

Upfront resection or perioperative chemotherapy and resection are the recommended approaches in resectable CLM.

When facing technically unresectable liver metastases, systemic conversion chemotherapy should be used to render liver disease resectable.

Resectability is first evaluated after 2 months of optimal treatment and again after 4 months, when maximal tumour shrinkage is deemed to have occurred in most patients, so that the opportunity for resection is not missed.

Up to 75% of these patients will suffer a relapse following resection of their hepatic metastases, with the majority occurring in the liver.

INDUCTION CHEMOTHERAPY FOR BORDERLINE RESECTABLE PATIENTS

**Doublets** of fluorouracil with either oxaliplatin or irinotecan show equal potential.

No evidence for better long-term results if both agents are combined in a **triplet** regimen.

Beware of chemotherapy-associated liver injury.

No clear cut evidence underlining benefit from adding **biologics**, such as bevacizumab and EGFR inhibitors.
CONCLUSIONS

The survival of patients with metastatic colorectal cancer can be optimised via the integration of systemic therapy, surgical resection and ablative modalities, where appropriate, preferably in a MDT setting.

Insights in the biology of the disease and biomarker-driven therapeutic strategies are expected to improve survival and rationalise therapeutic approaches.

Basic and translational cancer research leading to well-defined hypotheses that are going to be tested in appropriately stratified and molecularly-enriched clinical trials, is the way forward.
THANK YOU!