OPTIMISING OUTCOMES FOR PATIENTS WITH ADVANCED COLORECTAL CANCER

E-Learning Module

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Colorectal cancer (CRC)

- Second most commonly diagnosed cancer in Europe:
  - 447,000 new cases
  - 215,000 deaths

- Worldwide incidence:
  - 1.4 million new cases
  - 694,000 deaths

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

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

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 III 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
PRIME TRIAL

Randomised phase III study of FOLFOX4 +/- panitumumab for first-line treatment of patients with metastatic colorectal cancer

The first trial to hint at a detrimental effect of panitumumab in patients, whose tumours carried RAS mutations at sites other than KRAS exon 2

Additional RAS mutations were detected in the tumours of 17% of patients with mCRC originally classified as KRAS exon 2 wild-type

These patients also failed to benefit from panitumumab and had inferior progression-free survival (PFS) and OS times compared with those treated with FOLFOX4 alone
WT KRAS


<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab–FOLFOX4 (n=325)</td>
<td>256 (79)</td>
<td>23.8 (20.0–27.7)</td>
</tr>
<tr>
<td>FOLFOX alone (n=331)</td>
<td>279 (84)</td>
<td>19.4 (17.4–22.6)</td>
</tr>
</tbody>
</table>

HR = 0.83 (95% CI: 0.70–0.98)
Log-rank P-value = 0.03
Randomised phase III study of FOLFIRI +/- Cetuximab in the first-line treatment of patients with KRAS exon 2 wild-type metastatic colorectal cancer

The study demonstrated that addition of cetuximab to fluorouracil, leucovorin, and irinotecan (FOLFIRI) significantly improved overall survival, progression-free survival, and objective response in the first-line treatment of patients with KRAS codon 12/13 (exon 2) wild-type mCRC

Subgroup analysis defined by extended RAS mutation testing revealed that other RAS mutations also predicted for resistance to EGFR-targeting

This was a pivotal study in establishing the necessity for extended RAS testing before the administration of EGFR-targeted monoclonal antibodies
KRAS CODON 12 OR 13 WILD TYPE

RAS WILD TYPE (ALL LOCI)

RAS MUTATION (ANY LOCUS)

RECOMMENDATIONS FOR RAS TESTING

- RAS testing should be performed on all patients at the time of diagnosis of mCRC.
- RAS testing is mandatory prior to treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab.
- Primary or metastatic colorectal tumour tissue can be used for RAS testing.
- 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).
- Laboratories providing RAS testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited.
BRAF mutant (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)
Significant negative prognostic marker for patients with mCRC: mOS 10.4 months compared to 34.7 for patients with BRAF wild-type (Tran et al.)
The predictive significance of BRAF mutation in 1st and 2nd line is currently uncertain
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)
ANTI-EGFR THERAPY IN PATIENTS WITH (K)RAS WT/BRAF MT mCRC: RESULTS

- Meta-analysis of randomised trials of (i) anti-EGFR therapy + CT vs. CT ± bevacizumab, or (ii) anti-EGFR monotherapy vs. BSC in patients with (K)RAS wt/BRAF mt mCRC (n=469)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight, %</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPUS/CRYSTAL</td>
<td>20.7</td>
<td>0.62 (0.36–1.06)</td>
</tr>
<tr>
<td>PRIME</td>
<td>17.0</td>
<td>0.90 (0.46–1.76)</td>
</tr>
<tr>
<td>CO.17</td>
<td>6.0</td>
<td>0.84 (0.20–3.56)</td>
</tr>
<tr>
<td>PICCOLO</td>
<td>21.5</td>
<td>1.84 (1.10–3.08)</td>
</tr>
<tr>
<td>20050181</td>
<td>16.4</td>
<td>0.64 (0.32–1.28)</td>
</tr>
<tr>
<td>FIRE-3</td>
<td>18.5</td>
<td>0.87 (0.47–1.61)</td>
</tr>
<tr>
<td>Summary</td>
<td>100.0</td>
<td>0.91 (0.62–1.34)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=10.09$; df=5 (p=0.07); $I^2=50$
Test for overall effect: $Z=0.48$ (p=0.63)

- There was also no significant difference in:
  - PFS: HR=0.88 (95% CI: 0.67-1.14); p=0.33
  - ORR: OR=1.31 (95% CI: 0.83-2.08); p=0.25

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 with Pembrolizumab.
- Consequently, MSI testing is recommended in the metastatic disease setting both for genetic counselling purpose and for its predictive value for the use of immune check-point inhibitors.
PD-1 BLOCKADE IN MMR-DEFICIENT TUMOURS: PEMBROLIZUMAB PHASE II STUDY IN REFRACTORY MALIGNANCIES

To date, responses >1 yr observed, and 13 or 14 responding pts 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

<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>

THE ROLE OF MULTIDISCIPLINARY TEAMS (MDT) AND 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
- A diagnostic radiologist
- An interventional radiologist / nuclear medicine physician
Complete resection is the goal, with resectability depending on both technical and oncological criteria

<table>
<thead>
<tr>
<th>Technical criteria</th>
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<tbody>
<tr>
<td>1. Absolute</td>
</tr>
<tr>
<td>♦ Impossibility of R0 resection with ≥25–30% liver remnant</td>
</tr>
<tr>
<td>♦ Presence of unresectable extrahepatic disease</td>
</tr>
<tr>
<td>2. Relative</td>
</tr>
<tr>
<td>♦ R0 resection possible only with complex procedure (portal vein embolisation,</td>
</tr>
<tr>
<td>two-stage hepatectomy, hepatectomy combined with ablation)</td>
</tr>
<tr>
<td>♦ R1 resection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oncological criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Concomitant extrahepatic disease (unresectable)</td>
</tr>
<tr>
<td>2. Number of lesions ≥5</td>
</tr>
<tr>
<td>3. Tumour progression</td>
</tr>
</tbody>
</table>
Upfront resection or perioperative FOLFOX 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.
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.
TREATMENT GOAL

Eradication of all visible metastatic lesions using the best instrument from the toolbox of LATs, in combination with systemic therapy

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

Standard treatment algorithm for patients with OMD

OMD, oligometastatic disease; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy.
TREATMENT OF METASTATIC DISEASE

“Continuum of Care” approach within a MDT:

Approximately 5-6 months of first-line “induction” therapy
4–6 (-8) months of “maintenance” therapy – or no treatment after resection and/or ablation following first-line treatment
About 3 months re-introduction (or treatment beyond progression)

5–7 months of second-line therapy
A treatment break before initiation of a further line

Approximately 3 months of third-line therapy
Potentially a fourth line (in patients with RAS wild-type disease)
A few months of re-challenge of initial induction or first-line therapy
A few months best supportive care only
THE PRESENT: FIT PATIENTS WITH ADVANCED CRC

Two categories are evolving for the systemic treatment of ‘fit’ patients with CRC whose metastatic disease is not resectable at presentation.

Those for whom intensive treatment is appropriate and necessary, the CYTOREDUCTION group:

a) For conversion to resectable disease
b) For rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, or severe symptoms

Those for whom an intensive treatment is not necessary and where the goal is the control of disease progression, the DISEASE CONTROL group

For patients in both categories, knowledge of the RAS and BRAF mutational status of their disease is used to further refine treatment strategies.
PROPOSED ESMO CONSENSUS

Treatment goals for ‘fit’ patients (unresectable)

### 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>Toxicity profile</td>
</tr>
<tr>
<td>Tumour localisation</td>
<td>Performance status</td>
<td>Flexibility</td>
</tr>
<tr>
<td>Tumour biology</td>
<td>Organ function</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td>RAS mutation status</td>
<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIRST LINE TREATMENT

Biologics (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated.

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 is the goal - and potentially also in fit patients with tumour BRAF mutations
- Fluoropyrimidine monotherapy (capecitabine) in patients not tolerating aggressive treatment

EGFR antibodies should be used in combination with:

- FOLFOX/FOLFIRI
- Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies
OVERALL SURVIVAL: FINAL RAS* WILD-TYPE POPULATION

No. at risk:
- FOLFIRI + Cet: 199, 147, 79, 46, 23, 7
- FOLFIRI + Bev: 201, 147, 82, 34, 11, 1

Events n/N (%)
- FOLFIRI + Cetuximab: 107/199 (53.8%)
- FOLFIRI + Avastin: 133/201 (66.2%)

Median (months) 95% CI
- FOLFIRI + Cetuximab: 33.1 (24.5 – 39.4)
- FOLFIRI + Avastin: 25.0 (23.0 – 28.1)

HR 0.697 (95% CI: 0.54 – 0.90) p (log-rank) = 0.0059

Δ = 8.1 months

*KRAS and NRAS exon 2, 3 and 4 wild-type.
## INDEPENDENT EVALUATION OF SUBGROUP OF PATIENTS ASSESSABLE FOR RESPONSE

<table>
<thead>
<tr>
<th>CT evaluable population</th>
<th>FOLFIRI + cetuximab %</th>
<th>FOLFIRI + bevacizumab %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final RAS wt (N=330)</td>
<td>72.0</td>
<td>56.1</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Final RAS WT subgroup assessable for response with independent review reflects only 55% of the ITT population.

p = Fisher's exact test (two-sided).
CALGB/SWOG 80405: OS (PRIMARY ENDPOINT)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (events)</th>
<th>OS (m) median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR=0.925 (0.78-1.09)

## EFFICACY: RAS SUBGROUPS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Chemo + BV N</th>
<th>Chemo + CET N</th>
<th>Response rate %* BV vs. CET p-value</th>
<th>PFS time Hazard ratio 95% CI p-value</th>
<th>OS time Hazard ratio 95% CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS WT</td>
<td>256</td>
<td>270</td>
<td>53.8 vs. 68.6 p&lt;0.01</td>
<td>11.3 vs. 11.4† p=0.31</td>
<td>31.2 vs. 32.0† p=0.40</td>
</tr>
</tbody>
</table>

*406 RAS evaluable and 319 RAS WT patients were evaluable for response.
†Patients with KRAS codon 12/13 wild-type tumours for which tumour DNA samples were evaluable for other RAS mutations.
‡Median, months.
Clinical Performance Status of the Patient

- **Fit**: May be eligible for moderator treatment
- **Not Fit**: Eligible for treatment
- **Unfit**: Not eligible for treatment

**Treatment Aim**

- **Cytoreduction** (Tumour Shrinkage)
  - MOLECULAR PROFILE
    - RAS wt
      - Doublet + anti-EGFR
    - RAS mt
      - Combination + bevacizumab
    - BRAF mt
      - Triplet (or doublet) ± bevacizumab

- **Disease Control** (Prevention of Progression)
  - MOLECULAR PROFILE
    - RAS wt
      - CT + antibody
    - RAS mt
      - CT + bevacizumab

**Elderly Patient**

- **Fit**: CT + antibody
- **Not Fit**: Cetuximab + bevacizumab, or doublet with dose reduction

**Adapted from ESMO Pocket Guidelines 2015 Lower Gastrointestinal Cancer, Section Metastatic colorectal cancer.**
MAINTENANCE 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.

Bevacizumab as monotherapy is not recommended as maintenance therapy.
MAINTENANCE TRIALS: COMBINED ANALYSIS, VS. NO THERAPY

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log [Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO 0207</td>
<td>FP/BEV</td>
<td>-0.71334989</td>
<td>0.129711368</td>
<td>24.1%</td>
</tr>
<tr>
<td>AIO 0207</td>
<td>BEV</td>
<td>-0.4462871</td>
<td>0.12595133</td>
<td>24.5%</td>
</tr>
<tr>
<td>CAIRO-3</td>
<td>CAPE/BEV</td>
<td>-0.84397007</td>
<td>0.09065533</td>
<td>27.4%</td>
</tr>
<tr>
<td>SAKK</td>
<td>BEV</td>
<td>-0.28768207</td>
<td>0.13114787</td>
<td>24.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>100%</td>
<td></td>
<td>0.56 [0.43, .72]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log [Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO 0207</td>
<td>FP/BEV</td>
<td>-0.01005034</td>
<td>0.16961535</td>
<td>16.8%</td>
</tr>
<tr>
<td>AIO 0207</td>
<td>BEV</td>
<td>-0.12783337</td>
<td>0.1705144</td>
<td>16.6%</td>
</tr>
<tr>
<td>CAIRO-3</td>
<td>CAPE/BEV</td>
<td>-0.11653382</td>
<td>0.10111254</td>
<td>47.1%</td>
</tr>
<tr>
<td>SAKK</td>
<td>BEV</td>
<td>-0.18632958</td>
<td>0.15712878</td>
<td>19.5%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>100%</td>
<td></td>
<td>0.89 [0.78, 1.02]</td>
</tr>
</tbody>
</table>

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 antiangiogenic (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
Adding aflibercept to FOLFIRI in mCRC patients previously treated with an oxaliplatin-based regimen resulted in significant OS and PFS benefits.

**Overall results**

- **OS**
  - Placebo/FOLFIRI: Median=12.06 months
  - Aflibercept/FOLFIRI: Median=13.50 months
  - Stratified HR=0.817 [95.34% CI, 0.713-0.937]
  - Log-rank P=0.0032

- **PFS**
  - Placebo/FOLFIRI: Median=4.67 months
  - Aflibercept/FOLFIRI: Median=6.90 months
  - Stratified HR=0.758 [99.99% CI, 0.578-0.995]
  - Log-rank P=0.00007

OVERALL SURVIVAL

THIRD LINE TREATMENT

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.

The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients.

There is no unequivocal evidence to administer the alternative anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies.
THIRD LINE TREATMENT

Emerging options beyond second line:

Regorafenib is recommended in patients pre-treated 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 pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with anti-EGFR antibodies.
OVERALL SURVIVAL (UPDATED ANALYSIS)

Extended analysis shows that significant benefit is maintained after 566 events (97% of planned total)

## TAS-102 vs. Placebo in MCRC W/≥ 2 Prior Lines of Std. Chemo (Recourse): Overall Survival

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TAS-102</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>7.1</td>
<td>5.3</td>
<td>0.68 (0.58–0.81)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>2.0</td>
<td>1.7</td>
<td>0.48 (0.41–0.57)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>1.6</td>
<td>0.4</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>DCR, %</td>
<td>44.0</td>
<td>16.0</td>
<td>—</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Progressive disease, %</td>
<td>51.8</td>
<td>75.6</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

### The consensus molecular subtypes of colorectal cancer

Justin Guinney\(^1,2,21\), Rodrigo Dienstmann\(^1,2,21\), Xin Wang\(^3,4,21\), Aurélien de Reyniès\(^5,21\), Andreas Schlicker\(^6,21\),

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Overall survival**

- Log-rank P value: $3.55 \times 10^{-10}$
- CMS4 vs. CMS1: 1.55 (1.19–2.01) \( P \text{ value } 1.03 \times 10^{-33} \)
- CMS4 vs. CMS2: 1.94 (1.58–2.36) \( P \text{ value } 6.85 \times 10^{-11} \)
- CMS4 vs. CMS3: 1.72 (1.27–2.33) \( P \text{ value } 1.06 \times 10^{-24} \)

**Post-relapse survival**

- Log-rank P value: $4.01 \times 10^{-97}$
- CMS4 vs. CMS1: 0.60 (0.40–0.88) \( P \text{ value } 9.04 \times 10^{-32} \)
- CMS3 vs. CMS1: 0.69 (0.38–0.97) \( P \text{ value } 3.71 \times 10^{-10} \)
- CMS2 vs. CMS1: 0.85 (0.24–0.52) \( P \text{ value } 1.26 \times 10^{-77} \)

**Key Features**

- **CMS1** (MSI immune): MSI, CIMP high, hypermutation
- **CMS2** (Canonical): SCNA high
- **CMS3** (Metabolic): Mixed MSI status, SCNA low, CIMP low
- **CMS4** (Mesenchymal): SCNA high

**BRAF mutations**

- Immune infiltration and activation
- WNT and MYC activation
- Metabolic deregulation
- Stromal infiltration, TGF-β activation, angiogenesis

**KRAS mutations**

- Worse survival after relapse
- Worse relapse-free and overall survival

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!