Current standards and practise changing studies in metastatic CRC:
Towards a personalized treatment in mCRC

Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
Leuven, Belgium

Eric.VanCutsem@uzleuven.be
Patients with unresectable metastatic CRC: strategy and continuum of care

**Classification**

- **Upfront resectable**
  - Resection
  - Curative surgery
  - Overall survival / long-term disease control
  - Required outcome
  - Treatment strategy

- **Borderline resectable**
  - CT + biologic
  - Relapse
  - Overall survival / long-term disease control

- **Unresectable**
  - CT + biologic
  - Relapse

- **Treatment strategy**
  - Curative surgery
  - Overall survival / long-term disease control

References:
Progress in the treatment of mCRC

- CHEMOTHERAPY: combination of cytotoxic and biological targeted drugs

<table>
<thead>
<tr>
<th>Cytotoxic agents</th>
<th>Biological agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ 5-FU</td>
<td>✓ bevacizumab / aflibercept / ramucirumab</td>
</tr>
<tr>
<td>✓ capecitabine/S1</td>
<td>✓ cetuximab / panitumumab</td>
</tr>
<tr>
<td>✓ irinotecan</td>
<td>✓ regorafenib</td>
</tr>
<tr>
<td>✓ oxaliplatin</td>
<td>✓ pembrolizumab / nivolumab</td>
</tr>
<tr>
<td>✓ raltitrexed</td>
<td>✓ ipilimumab</td>
</tr>
<tr>
<td>✓ (mitomycin)</td>
<td>✓ vemurafenib / encorafenib</td>
</tr>
<tr>
<td>✓ trifluridine/tiparicil</td>
<td>✓ cobimetinib / binimetinib</td>
</tr>
<tr>
<td></td>
<td>✓ lapatinib +</td>
</tr>
<tr>
<td></td>
<td>trastuzumab / pertuzumab</td>
</tr>
<tr>
<td></td>
<td>trastuzumab-deruxtecan</td>
</tr>
<tr>
<td></td>
<td>✓ larotrectinib / entrectenib</td>
</tr>
<tr>
<td></td>
<td>✓ early in development…………....</td>
</tr>
</tbody>
</table>

- Other contributing factors to improved outcome:
surgery, locoregional treatment....,
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:</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 of treatment administration</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>
</tbody>
</table>

Ann Oncol, July 2016
## Table 6. Revised ESMO groups for treatment stratification of patients according to whether patients are ‘fit’ or ‘unfit’

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

LAT, local and ablative therapy; mt, mutant; NED, no evidence of disease; wt, wild-type.
Treatment of metastatic disease

Assessment of clinical condition of the patient

FP®

Unfit® (but may be suitable)

FP + bevacizumab, reduced dose doublet, anti-EGFR

BSC

GOAL

Patients with clearly resectable metastases

Surgery alone
Surgery with perioperative postoperative CT

OMD
See Figure 2

Cytoreduction (Shrinkage) **

MOLECULAR PROFILE

RAS wt

CT doublet + anti-EGFR

RAS mt

Combination CT + bevacizumab

BRAF mt

CT triple + bevacizumab

RAS wt

CT doublet + biological agent

RAS mt

CT doublet + bevacizumab

BRAF mt

CT triple +/- bevacizumab

Re-evaluation/assessment of response every 2 months*

Surgery

Progressive disease

Second-line

GOAL

Continue

Continue; maintenance; or pause

Progressive disease

Second-line

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Sidedness restriction</th>
<th>Molecular restriction</th>
<th>Preferred indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cape + BEV</td>
<td>None</td>
<td>None</td>
<td>Elderly patients, low-volume disease</td>
</tr>
<tr>
<td>FOLFOX/ CAPOX/ FOLFIRI + BEV</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>FOLFOXIRI + BEV</td>
<td>None</td>
<td>None</td>
<td>Aggressive cancers (w.g. BRAF mut, R-sided)</td>
</tr>
<tr>
<td>FOLFOX/ FOLFIRI + EGFR mAb</td>
<td>Left-sided*</td>
<td>RAS/ BRAF wt (HER-2 neg?)</td>
<td>SOC left-sided cancers</td>
</tr>
<tr>
<td>FOLFOXIRI + EGFR mAb</td>
<td>Left-sided*</td>
<td>RAS/ BRAF wt (HER-2 neg?)</td>
<td>Left-sided cancers with high tumor load</td>
</tr>
<tr>
<td>PD-1 antibody/ IO combo</td>
<td>None</td>
<td>MSI-H/ MMR-D</td>
<td>Pts with MSI-H cancers not considered for chemo</td>
</tr>
<tr>
<td>BEACON(-like)</td>
<td>None</td>
<td>BRAF V600E mut</td>
<td>Data in first-line pending</td>
</tr>
</tbody>
</table>

*ESMO guidelines allow EGFR mAbs in R-sided cancers

Adapted from Van Cutsem E et al, ESMO Consensus - Ann Oncol, July 2016 and from A Grothey
Head to Head-Meta-Analysis based on three phase 2/3 RCTs in the first-line setting of mCRC patients.

<table>
<thead>
<tr>
<th>Trial</th>
<th>KRAS Status</th>
<th>Intervention A</th>
<th>Intervention B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRE-3</strong> (Phase 3)</td>
<td>KRAS-WT</td>
<td>Cetuximab + FOLFIRI</td>
<td>Bevacizumab + FOLFIRI</td>
</tr>
<tr>
<td></td>
<td>(n = 592)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>†Retrospектив RAS-Analyse</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PEAK</strong> (Phase 2)</td>
<td>KRAS-WT</td>
<td>Panitumumab + mFOLFOX6</td>
<td>Bevacizumab + mFOLFOX6</td>
</tr>
<tr>
<td></td>
<td>(n = 285)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>†Präspezifizierte RAS-Analyse</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CALGB/SWOG 80405</strong></td>
<td>KRAS-WT</td>
<td>Cetuximab + FOLFOX/FOLFIRI</td>
<td>Bevacizumab + FOLFOX/FOLFIRI</td>
</tr>
<tr>
<td></td>
<td>(n = 1137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>†Explorative RAS-Analyse</td>
<td></td>
<td>Ein dritter Bevacizumab + Cetuximab + FOLFOX/FOLFIRI Studienarm wurde am 10.09.2009 geschlossen</td>
</tr>
</tbody>
</table>

Metaanalysis: Head to Head studies of anti-VEGF vs anti-EGFR therapy in first line RAS-WT mCRC


OS in RAS-WT Patients, per trial and total

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% KI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRE-3</td>
<td>0.70 (0.53–0.92)</td>
<td>37.01</td>
</tr>
<tr>
<td>PEAK</td>
<td>0.63 (0.39–1.02)</td>
<td>15.87</td>
</tr>
<tr>
<td>CALGB</td>
<td>0.90 (0.70–1.10)</td>
<td>47.12</td>
</tr>
<tr>
<td>total</td>
<td>0.77 (0.63–0.95)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

p= 0.016

PFS and ORR in RAS-WT Patients, total

<table>
<thead>
<tr>
<th></th>
<th>HR (95% KI)</th>
<th>% Weight</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.92 (0.71–1.18)</td>
<td>100</td>
<td>0.50</td>
</tr>
<tr>
<td>ORR</td>
<td>1.46 (1.13–1.90)</td>
<td>100</td>
<td>0.004</td>
</tr>
</tbody>
</table>

A first line anti-EGFR-strategy in patients with mCRC and RAS-WT status might be superior in terms of OS and ORR compared to anti-VEGF-based treatment

### Biomarker testing for metastatic CRC in 2020

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Percentage</th>
<th>Therapy Option</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS/NRAS/BRAF Wild-Type (KRAS and NRAS exon 2, 3, 4)</strong></td>
<td>40%</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panitumumab</td>
</tr>
<tr>
<td><strong>BRAF V600E Mutation</strong></td>
<td>8%</td>
<td>Encorafenib + Cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Encorafenib + Panitumumab</td>
</tr>
<tr>
<td><strong>HER2 Positive (IHC 3+ or 2+ with ISH+; or NGS panel)</strong></td>
<td>3%</td>
<td>Trastuzumab + Pertuzumub *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trastuzumab + Lapatinib *</td>
</tr>
<tr>
<td><strong>MSI-High (PCR or NGS panel) / Deficient Mismatch Repair</strong></td>
<td>8%</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab + Ipilimumab</td>
</tr>
<tr>
<td><strong>NTRK Gene Fusion</strong></td>
<td>&lt;0.5%</td>
<td>Larotrectinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entrectinib</td>
</tr>
</tbody>
</table>

* If KRAS and NRAS WT

NCCN Guidelines Version 3.2020
Initially: *KRAS* testing identifies mutations in codons 12 and 13 of exon 2.

<table>
<thead>
<tr>
<th></th>
<th><strong>EXON 2</strong></th>
<th><strong>EXON 3</strong></th>
<th><strong>EXON 4</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS</strong></td>
<td>★★</td>
<td>✓</td>
<td>★★</td>
</tr>
<tr>
<td>Codons</td>
<td>12, 13</td>
<td>61</td>
<td>117, 146</td>
</tr>
<tr>
<td>Frequency</td>
<td>30-35%</td>
<td>~8%</td>
<td>6–7%</td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td>★★</td>
<td>✓</td>
<td>★★</td>
</tr>
<tr>
<td>Codons</td>
<td>12, 13</td>
<td>61</td>
<td>117, 146</td>
</tr>
<tr>
<td>Frequency</td>
<td>3–5%</td>
<td>4–6%</td>
<td>0–1%</td>
</tr>
</tbody>
</table>

*KRAS/NRAS* mutations outside *KRAS* exon 2 are now tested before using cetuximab and panitumumab.

*RAS*
Excluding additional mutant tumors increases the relative proportion of responsive wt tumors.

Detection of additional mutant tumors that are resistant to EGFR mAbs (cetuximab, panitumumab)

Increasing relative proportion of wild (wt) population responsive to EGFR mAbs

Enhanced benefit profile for EGFR inhibitors in the more selected population
Molecular subtypes in CRC

Can predict lack of response to therapy

- "pan-WT"
- KRAS ex2
- Fusions (e.g. NTRK)
- Amplifications (e.g. HER2)
- BRAF
- NRAS
- KRAS ex3,4

No RAS mutation
Any RAS mutation

Van Cutsem et al, JCO 2015
Summary of common clinical and molecular characteristics of right- and left-sided colon tumors and associations with dietary factors. CIMP = CpG island methylator phenotype; HNPCC = hereditary non-polyposis colorectal cancer; APC = adenomatous polyposis coli; K-ras = Kirsten-ras; DCC = deleted in colorectal cancer; FAP = familial adenomatous polyposis.
• Left sided tumors have a better prognosis than right sided tumors.
• Sidedness is predictive in first line treatment of RAS Wt tumours:
  – Left sided tumors benefit more for anti-EGFR antibodies.
  – Right sided tumors benefit slightly more from bevacizumab
## Preferred choices in first line treatment of mCRC

<table>
<thead>
<tr>
<th>Goal / condition</th>
<th>Molecular</th>
<th>Prefered 1st line regimen</th>
</tr>
</thead>
</table>
| **Cytoreduction** (conversion/symptom relief) | all WT     | Left: Doublet (FOLFOX)/EGFR AB  
|                                   |            | Right: FOLFOX/beva or FOLFOXIRI/beva (or FOLFOX/EGFR)  
|                                   | RAS mut    | FOLFOX/beva or FOLFOXIRI/beva  
|                                   | BRAF mut V600E | FOLFOXIRI/beva or FOLFOX/beva  |
| **Disease stabilization**         | all WT     | Left: Doublet (FOLFOX)/EGFR AB  
|                                   |            | Right: Doublet (FOLFOX)/beva  
|                                   | RAS mut    | Doublet (FOLFOX)/beva  
|                                   | BRAF mut V600E | Doublet (FOLFOX)/beva or FOLFOXIRI/beva  |
| „frail“, or chosen sequential treatment | no BRAF ! | Capecitabine/beva  |

**Preferred choices in second line treatment of mCRC**

<table>
<thead>
<tr>
<th>Goal / condition in first line</th>
<th>Molecular</th>
<th>Prefered 2nd line regimen</th>
</tr>
</thead>
</table>
| Cytoreduction                  | all WT    | 1st line doublet + EGFR AB: doublet + bevacizumab  
1st line doublet + bev.: doublet + bevacizumab  
Oxaliplatin → irinotecan based  
Irinotecan → oxaliplatin based |
| Disease stabilization          | RAS mut   | FOLFOX/beva or FOLFIRI/beva  
alternatives FOLFIRI/aflibercept or ramucirumab |
|                                | MSI-H     | Pembrolizumab / nivolumab ± ipilimumab  
Cetuximab/encorafenib          |
|                                | BRAF mut v600E | Pembrolizumab / nivolumab ± ipilimumab  
Cetuximab/encorafenib          |
| Subgroups                      | HER-2 amplified | Second line or later line? Combination anti-HER2 |
|                                | NTRAK alterations | Second line or later line? NTRAK-TKI |
| Other: experimental            | Trial     |                           |
| „frail“                        |           | 5FU or Capecitabine/beva if first line EGFR antibody based |

ESMO consensus guideline:  
Third-line treatment

Clinical Update in thinking based on data:  
* molecular analysis esp. for druggable markers: MSI, BRAF, HER2, NTRAK fusions, POLE mutation: targeted agents or IO agents

Ann Oncol, July 2016
Genomic markers

- PIK3CA/PTEN mut: 8%
- RAS mut +/- PIK3CA/PTEN mut: 45%
- Wild-type: 26%
- BRAFT V600E: 8%
- BRAF inh + anti-EGFR +/- MEK inh: 26%
- anti-EGFR therapies
- anti-PD1/L1
- anti-HER2
- PODE mut
- MSI + other
- MSI
- BRAF non-V600
- MET ampl
- MET inh
- Gene fusion
- Kinase inh

Dienstmann et al, ASCO Ed Book 2018
MSI predictive value in mCRC
Studies in pretreated patients

Prevalence ~ 5%

PEMBROLIZUMAB

NIVOLUMAB

NIVOLUMAB + IPILIMUMAB

RR: cohort A: 33% (21-46%)
cohort B: 33% (22-46%)

Le E, Kim T, Van Cutsem E et al, J Clin Oncol, 2019

Overman... Van Cutsem et al. J Clin Oncol 2018;
Overman et al. Lancet Oncol 2017
Non-randomized cohort: checkmate 142 study  
N=45

- Overall RR: 69% (53–82)  
  CR: 13%
- 24-month PFS rate: 74%
- 24-month OS rate: 79%
**Keynote-177: Pembrolizumab vs chemotherapy in first line MSI-H mCRC**

**KEYNOTE-177 Study Design (NCT02563002)**

**Key Eligibility Criteria**
- MSI-H (PCR)/dMMR (IHC) Stage IV CRC
- Treatment naïve
- ECOG PS 0 or 1
- Measurable disease by RECIST v1.1

**Pembrolizumab 200 mg Q3W for up to 35 cycles**

**Investigator-Choice Chemotherapy**
- mFOLFOX6 IV Q2W
- mFOLFOX6 + Bevacizumab IV Q2W
- mFOLFOX6 + Cetuximab IV Q2W
- FOLFIRI IV Q2W
- FOLFIRI + Bevacizumab IV Q2W
- Cetuximab + Bevacizumab IV Q2W

**Optional crossover to pembrolizumab 200 mg Q3W for up to 35 cycles for patients with centrally verified PD by RECIST v1.1, central review**

**Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision**

**Safety and survival follow-up**

**Dual-Primary endpoints:**
- PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints:
  - ORR per RECIST v1.1 by BICR, safety
  - Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

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*Chosen before randomization; 5 Bevacizumab 5 mg/kg IV; Cetuximab 400 mg/m² over 2 hours then 250 mg/m² IV over 1 hour weekly.
IHC: immunohistochemistry with MLH1, MSH2, MSH6, PMS2, PCR: polymerase chain reaction; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

**Presented at:** 2020 ASCO ANNUAL MEETING

**Presented by:** Thierry Andre, MD

Andre T et al, ASCO 2020, LBA4
Keynote-177: Pembrolizumab vs chemotherapy in first line MSI-H mCRC

Progression-Free Survival

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>54%</td>
</tr>
<tr>
<td>Chemo</td>
<td>73%</td>
</tr>
</tbody>
</table>

Median (95% CI)
- Pembrolizumab: 16.5 mo (6.4-32.4)
- Chemotherapy: 8.2 mo (6.1-10.2)

Median study follow-up: 32.4 months (range: 24.0 - 48.3); PFS time from randomization to first documented disease progression or death assessed per RECIST v1.1 by BIRC. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.017. Data cut-off: 16th Oct 2020.

PRESENTED AT: 2020 ASCO ANNUAL MEETING
#ASCO20
PRESENTED BY: Thierry Andre, MD

Andre T et al, ASCO 2020, LBA4
Radiographic Response in Target Lesions

Response Rate: 43.8% vs 33.1% (p = 0.027)

Keynote-177: Pembrolizumab vs chemotherapy in first line MSI-H mCRC

Andre T et al, ASCO 2020, LBA4
Keynote-177: Pembrolizumab vs chemotherapy in first line MSI-H mCRC

Duration of Response

- Median DOR: NR (2.3+ to 41.4+)
- Median DOR: 10.6 (2.8 to 37.5+)
- 24-mo response duration: 83%
- 35%

Duration of Response assessed per REGIST v1.1 by BCR. Data cut-off: 19Feb2020.

Presented by: Thierry Andre, MD

Andre T et al, ASCO 2020, LBA4
**MAPK signalling pathway:**

**multiple blocking necessary**

---

**BRAF^V600E** mutation in mCRC

- Occurs in 8%–12% of patients and confers a poor prognosis
- Standard therapies have limited benefits after ≥1 line of treatment
- BRAF inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation: Feedback may be overcome by targeting multiple pathway nodes, ie BRAF/MEK/EGFR
- In the BEACON CRC safety-lead in study, the triplet regimen of Encorafenib (ENCO) + Binimetinib (BINI) + Cetuximab (CETUX) had manageable safety profile and encouraging activity in patients with **BRAF^V600E** mCRC

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Van Cutsem E et al, J Clin Oncol 2019
Best Percentage Change in Tumor Measurements from Baseline

- Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.
- One patient had no baseline sum of longest diameters and is not presented.


Van Cutsem E et al, *J Clin Oncol* 2019
Phase 3

Primary Endpoints:

Triplet vs Control

Overall Survival

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

Patients with $BRAF^{V600E}$ mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Safety Lead-in
ENCO + BINI + CETUX
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

Secondary Endpoints: Doublet vs Control OS & ORR, PFS, Safety

A separate Safety Lead-in cohort of $n=7$ in Japan was enrolled subsequently. Results will be reported at a later time.

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Van Cutsem E et al, J Clin Onc 2019 – safety lead in
Kopetz S, Van Cutsem E, …., Tabernero J, NEJM 2019
Primary Analysis: Overall Survival and Objective Response Rate

**ENCO/BINI/CETUX vs Control**

- HR (95% CI): 0.52 (0.39-0.70)
- 2-sided P<0.0001
- Median OS in months (95% CI):
  - ENCO/BINI/CETUX: 9.0 (8.0-11.4)
  - Control: 5.4 (4.8-6.6)

**ENCO/CETUX vs Control**

- HR (95% CI): 0.60 (0.45-0.79)
- 2-sided P=0.0003
- Median OS in months (95% CI):
  - ENCO/CETUX: 8.4 (7.5-11.0)
  - Control: 5.4 (4.8-6.6)

**Objective Response Rate (First 331 Randomized Patients)**

<table>
<thead>
<tr>
<th>Confirmed Response by blinded central review</th>
<th>ENCO/BINI/CETUX N=111</th>
<th>ENCO/CETUX N=113</th>
<th>Control N=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>26%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(18%, 35%)</td>
<td>(13%, 29%)</td>
<td>(&lt;1%, 7%)</td>
</tr>
<tr>
<td>p-value vs. Control</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Overall survival analysis conducted in all randomized patients.

Kopetz S, Van Cutsem E, Tabernero et al, NEJM 2019
Updated Overall Survival: ENCO/BINI/CETUX vs ENCO/CETUX vs Control

BEACON Study in BRAF V600E mutated CRC

Kopetz S, Van Cutsem E, Tabernero et al, ASCO 2020
Non-V600 BRAF mutations

- Codon 594/596 kinase activity impaired
- Favorable prognosis
- L-sided
- Male > female
- Low grade; not mucinous
- (+) KRAS mut; (-) MSI
- No peritoneal spread

Molecular subtypes in CRC

Can predict response to therapy

- "pan-WT"
- KRAS ex2
- Fusions (e.g. NTRK)
- Amplifications (e.g. HER2)
- BRAF
- NRAS
- KRAS ex3,4
- HER2 amplification
- NTRK fusion

Trastuzumab + lapatinib

Larotrectinib

Sartore-Bianchi et al, Lancet Oncology 2016; Drilon et al, NEJM 2018
Anti-HER2 combinations in chemorefractory HER2+ mCRC

Patient selection (n=57):
• FISH or CISH + (HER2/Ch17 > 2 or HER2 GCN > 6)
• NGS: HER2 amplification based on copy number gain
• IHC 3+

Patient selection (n=27):
• IHC: 3+ HER2 score in more than 50% of cells
• IHC: 2+ and a HER2:CEP17 ratio > 2 in more than 50% of cells by FISH

RR: 30% (14-50)
Med duration of response 8.7 mo (5.5 – 21.6+)

RR: 32% (20-45)
Med duration of response 6.1 mo (2.9 – 11.1)

Meric-Bernstam F et al, Lancet Oncol 2019
DESTINY study: Trastuzumab/deruxtecan (ADC) in HER2 expressing mCRC

**DESTINY-CRC01**

**Best Change in Tumor Size**

RR: 45.3% (95%CI: 31.6-59.6%)

PFS: 6.9 mo
Outcomes have progressively improved with the evolution of metastatic CRC treatment options