Initial Management of Metastatic CRC in 2019

Axel Grothey
Director, GI Cancer Research
West Cancer Center Research Institute
Historic debates on best first-line therapy

• 1990s:
  • Best modulator of 5-FU? (MTX, IFN, folinic acid...)
  • Infusional vs bolus 5-FU

REVIEW ARTICLE

Fluorouracil in Colorectal Cancer—A Tale of Two Drugs: Implications for Biochemical Modulation

By Alberto F. Sobrero, Carlo Aschele, and Joseph R. Bertino

J Clin Oncol 1997
Historic debates on best first-line therapy

- **1990s:**
  - Best modulator of 5-FU? (MTX, IFN, folinic acid...)
  - Infusional vs bolus 5-FU

- **Early 2000s:**
  - Oxaliplatin vs Irinotecan

- **Mid-2000s-2010:**
  - Bevacizumab vs Cetuximab/ Panitumumab
The Luxury of So Many Options . . .
How Do We Personalize?

Patient X
- 5-FU
- Irinotecan
- Oxaliplatin
- Bevacizumab
- Cetuximab

Patient Y
- 5-FU
- Oxaliplatin
- Bevacizumab
- Cetuximab

Patient Z
- 5-FU
- Irinotecan
- Oxaliplatin
- Bevacizumab
- Panitumumab
- PD-1 mAb
Goal of medical therapy in mCRC

Finding the right treatment for the right patient at the right time

Individualized therapy in CRC did not start with KRAS
What influences treatment choices in mCRC?

- Patient characteristics
  - Comorbidities
  - Age
  - Prior adjuvant treatment
  - Performance status
- Tumor characteristics
  - Tumor burden
  - Tumor location
- Tumor characteristics
- Molecular characteristics
  - RAS
  - BRAF
  - MSI-high
  - HER2
- Patient preference
  - Quality of life
  - Toxicity profile

Therapy tailored according to individual patient needs
Genomic Markers in CRC

- RAS mutation ± PIK3CA/PTEN mutation: 45%
- PIK3CA/PTEN mutation: 8%
- BRAF V600E: 8%
- Kinase inhibitor: 26%
- Wild type: 26%
- Anti-HER2 Tx
- Anti-PD-1/PD-L1
- Kinase inhibitor: 8%
- Gene fusion: 2%
- MET amp: 2%
- HER2 amp: 2%
- POLE amp: 2%
- MSI+: 2%
- MSI: 2%
- BRAF non-V600: 2%
- BRAF inhibitor + anti-EGFR ± MEK inhibitor
- Anti-EGFR therapies

Current Treatment Pattern in the US

• FOLFOX + BEV undisputedly most commonly used first-line therapy in mCRC regardless of sidedness and RAS/ BRAF mutation status

• FOLFIRI + BEV mainly in academic centers

• Use of EGFR mAbs slowly increasing in left-sided RAS/ BRAF wild-type cancers
  • SOC in Europe and elsewhere (rightfully so)

• For BRAF V600E mutated cancers, FOLFOXIRI + BEV recognized as an option, but not commonly used

• In MSI-H/ MMR-D cancers, IO tested in first-line trials – but also used in front-line outside of trials

• No HER-2 targeting first-line approaches
# Treatment Options in First-line Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Sidedness restriction</th>
<th>Molecular restriction</th>
<th>Preferred indication</th>
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<tr>
<td>Cape + BEV</td>
<td>None</td>
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<td>Elderly patients, low-volume disease</td>
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*ESMO guidelines allow EGFR mAbs in R-sided cancers
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*ESMO guidelines allow EGFR mAbs in R-sided cancers
AVEX - Study design

Previously untreated mCRC, age ≥70 years  
N=280

Randomize 1:1  
Stratification factors:  
– ECOG PS (0–1 vs 2)  
– Geographic region

Capecitabine 1000 mg/m² b.i.d.  
days 1–14, q21d  
+ Bevacizumab 7.5 mg/kg  
day 1, q21d

Capecitabine 1000 mg/m² b.i.d.  
days 1–14, q21d

Key inclusion criteria
– ECOG PS 0–2  
– Prior adjuvant chemotherapy allowed if completed >6 month before inclusion  
– Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

Key exclusion criteria
– Prior chemotherapy for mCRC or prior adjuvant anti-VEGF treatment  
– Clinically significant cardiovascular disease  
– Current or recent use of aspirin (>325 mg/day) or other NSAID  
– Use of full-dose anticoagulants or thrombolytic agents

Cunningham et al, Lancet Oncol 2013
AVEX – PFS (Primary Endpoint)

HR = 0.53 (95% CI: 0.41–0.69)  
P < 0.001

Cape + BEV (n=140)
Cape (n=140)

Cunningham et al, Lancet Oncol 2013
## Treatment Options in First-line Regimen

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*ESMO guidelines allow EGFR mAbs in R-sided cancers*
CRYSTAL: FOLFIRI +/- Cetuximab

PFS

A. Progression-free survival

Left-sided mCRC

- Cetuximab + FOLFIRI (n = 142)
- FOLFIRI (n = 138)

HR, 0.50; 95% CI, 0.34-0.72; P < .001

No. at risk

- Cetuximab + FOLFIRI: 142, 99, 28, 3, 0
- FOLFIRI: 138, 73, 8, 2, 0

Months

Probability of PFS

0.0
0.2
0.4
0.6
0.8
1.0

0
6
12
18
24

B. Overall survival

Left-sided mCRC

- Cetuximab + FOLFIRI (n = 142)
- FOLFIRI (n = 138)

HR, 0.65; 95% CI, 0.50-0.86; P = .002

No. at risk

- Cetuximab + FOLFIRI: 142, 123, 83, 47, 14
- FOLFIRI: 138, 104, 63, 27, 7

Months

Probability of OS

0.0
0.2
0.4
0.6
0.8
1.0

0
12
24
36
48
60

Right-sided mCRC

- Cetuximab + FOLFIRI (n = 33)
- FOLFIRI (n = 51)

HR, 0.87; 95% CI, 0.47-1.62; P = .66

No. at risk

- Cetuximab + FOLFIRI: 33, 13, 3, 1, 0
- FOLFIRI: 51, 19, 3, 1, 0

Months

Probability of OS

0.0
0.2
0.4
0.6
0.8
1.0

0
12
24
36
48
60

Tejpar et al., JAMA Oncol 2016
OS and PFS by Sidedness in PRIME (FOLFOX +/- Pmab)

**OS**

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<td>Pmab + FOLFOX</td>
<td>30.3 (25.8, 36.1)</td>
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<td>FOLFOX</td>
<td>23.6 (18.2, 26.9)</td>
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**PFS**

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<td>12.9 (10.0, 14.6)</td>
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<td>9.2 (7.6, 10.7)</td>
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<td>HR</td>
<td>0.72 (0.57, 0.90)</td>
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CALGB/SWOG 80405: OS by Tumor Location (RAS WT)

### OS (95% CI), Months

<table>
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<th>Left</th>
<th>Right</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
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<tr>
<td>Cetux</td>
<td>39.3 (32.9-42.9)</td>
<td>13.6 (11.3-19.0)</td>
<td>0.55 (0.39-0.79)</td>
<td>0.001</td>
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<td>Bev</td>
<td>32.6 (28.3-36.2)</td>
<td>29.2 (22.4-36.9)</td>
<td>0.88 (0.62-1.25)</td>
<td>0.50</td>
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*Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

The “Perfect” Candidate for First-Line EGFR mAbs

**Negative selection (mutually exclusive)**

- KRAS/ NRAS/ HRAS exon 2, 3, 4 wild-type - 55%
- No BRAF V600E mutation - 8%
- (No HER-2 amplification - 2.5%)  

**Further exclusion criteria (not mutually exclusive)**

- Right-sided cancers 30%
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*ESMO guidelines allow EGFR mAbs in R-sided cancers
TRIBE-2 Sequencing trial

FOLFOX + bev* → PD1 → FOLFIRI + bev* → PD2

Arm A

FOLFOXIRI + bev* → PD1 → FOLFOXIRI + bev* → PD2

Arm B

R 1:1

Progression Free Survival 2 (primary EP)

* Up to 8 cycles

Cremolini et al., ASCO 2019
TRIBE-2 Sequencing trial: Primary EP

- Median follow up = 22.8 mos
  - Arm A: N = 340
  - Arm B: N = 339
- Events, N (%):
  - Arm A: 235 (69%)
  - Arm B: 188 (55%)
- Median PFS2, mos:
  - Arm A: 16.2
  - Arm B: 18.9
- HR = 0.69 [95% CI: 0.57-0.83] p<0.001

Cremolini et al., ASCO 2019
**TRIBE-2: Second PFS**

<table>
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<tr>
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<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up =</td>
<td>N = 276</td>
<td>N = 242</td>
</tr>
<tr>
<td>22.8 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, N (%)</td>
<td>223 (81%)</td>
<td>169 (70%)</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>5.5</td>
<td>6.0</td>
</tr>
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</table>

HR = 0.86 [95%CI: 0.70-1.05] p=0.120

Cremolini et al., ASCO 2019
OS and PFS by Sidedness in TRIBE (FOLFIRI+ BEV vs FOLFOXIRI + BEV)

Triplet improved outcome (only) in right-sided cancers! Cremolini, et al. Ann Oncol 2018
VISNU-1: Study Design

- Open, multicenter phase III trial in mCRC patients with ≥ 3 CTCs at baseline.

mFOLFOX6 + BEV
- Bevacizumab 5 mg/kg D1
- Oxaliplatin 85 mg/m² D1
- LV 400 mg/m² D1
- 5-FU 400 mg/m² bolus D1
- 5-FU 2400 mg/m² 46h CI

FOLFOXIRI + BEV
- Bevacizumab 5 mg/kg D1
- Irinotecan 165 mg/m² D1
- Oxaliplatin 85 mg/m² D1
- LV 400 mg/m² D1
- 5-FU 3200 mg/m² 48h CI

Stratification:
- KRAS (Ex.2,3) mut/WT
- Organs affected 1 vs >1

R

Accrual: 50 months.
- October 2012-November 2016.
- Data base cut-off: November 2018.
- Tumor evaluations every 12 weeks.
- Protocol amended to add recommended prophylactic GCS-F in the FOLFOXIRI+BEV arm (after 63 pts included).

Every 2 w until PD, unacceptable toxicity or withdrawal of IC

Primary endpoint: efficacy in terms of PFS.

Secondary endpoints: OS; ORR; Resection rate and safety analysis.
PFS by treatment arm

HR: 0.64* (95% CI 0.49-0.82)
Log-Rank p=0.0006

Time (months)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Progression</th>
<th>Death</th>
<th>Disease Progression</th>
<th>Metastasis</th>
</tr>
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<tr>
<td>FOLFOX + bevacizumab</td>
<td>177</td>
<td>119</td>
<td>35</td>
<td>14</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>FOLFOXIRI + bevacizumab</td>
<td>172</td>
<td>113</td>
<td>56</td>
<td>25</td>
<td>14</td>
<td>7</td>
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* Cox model proportional hazard assumption is not met

Sastre, et al. ASCO 2019
VOLFI: Phase II trial design

- mCRC Unresectable
- First-line
- WT RAS*
- Age ≥18 yr
- ECOG PS 0-1 (n = 96)

mFOLFOXIRI +
Panitumumab 6 mg/kg
Q2W
N = 63

FOLFOXIRI Q2W
N = 33

1 cycle FOLFOXIRI; prior R was allowed

2:1

**

Treatment until PD, resectability, or to maximum 12 cycles

If resectable: surgery, then protocol treatment to maximum 12 cycles
If CR/PR/SD after 12 cycles: reinduction (same combination) recommended on PD

- 21 active centers in Germany

Strata
Cohort 1: histologically confirmed and definitively inoperable or unresectable
Cohort 2: chance of secondary resection with curative intent (**Pretreatment liver/tumor biopsy)

*Amendment in 11/2013 to include all RAS wild-type only.
*Trial started with irinotecan 165 mg/m² (n = 2), first amendment to 130 mg/m² (n = 9), and final amendment to 150 mg/m² (n = 52).

Geissler et al., ASCO 2019
VOLFI - Primary endpoint: objective response rate

**Overall Survival**

<table>
<thead>
<tr>
<th>Months (95% CI)</th>
<th>mFOLFOXIRI + P</th>
<th>FOLFOXIRI</th>
</tr>
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<tr>
<td>ITT</td>
<td>35.7 (27.6 – 43.8)</td>
<td>29.8 (19.8 – 39.9)</td>
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<tr>
<td>Cohort 1</td>
<td>24.7 (13.3 – 39.9)</td>
<td>28.3 (13.9 – 37.7)</td>
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<tr>
<td>Cohort 2</td>
<td>52.0 (35.2 – )</td>
<td>41.7 (10.7 – 44.4)</td>
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<tr>
<td>RAS/BRAF WT</td>
<td>43.5 (35.7 – 53.3)</td>
<td>35.3 (17.7 – 41.7)</td>
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<tr>
<td>BRAF mut</td>
<td>8.0 (7.7 – 22.4)</td>
<td>9.0 (2.7 – 13.9)</td>
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<tr>
<td>Left sided</td>
<td>39.9 (32.7 – 52.0)</td>
<td>35.3 (14.3 – 41.8)</td>
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<tr>
<td>Right sided</td>
<td>11.5 (7.7 – )</td>
<td>22.0 (12.9 – 41.7)</td>
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**Full Analysis Set**

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<tr>
<th></th>
<th>N=96</th>
<th>P=0.004</th>
<th>OR=4.47</th>
<th>95%CI 1.61 – 12.38</th>
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<td><strong>by Tumor Sidedness</strong></td>
<td></td>
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<tr>
<td>Left</td>
<td>N=78</td>
<td>P=0.021</td>
<td>OR=4.52</td>
<td>1.30 – 15.72</td>
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<tr>
<td>Right</td>
<td>N=18</td>
<td>P=0.345</td>
<td>OR=3.89</td>
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**by Genotype**

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<th>RAS/BRAF wt</th>
<th>N=60</th>
<th>P=0.081</th>
<th>OR=3.36</th>
<th>0.90 – 12.55</th>
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<td>BRAF mut</td>
<td>N=16</td>
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<td>OR=21.0</td>
<td>1.50 – 293.25</td>
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Geissler et al., ASCO 2019
# Best Conversion Therapy

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<td><strong>RAS/BRAF wt (35-40%)</strong></td>
<td>FOLFOXIRI +/- BEV (FOLFOX +/- BEV)</td>
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<td><strong>RAS mut (50-55%)</strong></td>
<td>FOLFOXIRI +/- BEV (FOLFOX +/- BEV)</td>
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<td>Data in first-line pending</td>
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*ESMO guidelines allow EGFR mAbs in R-sided cancers*
BEV-containing first-line therapy active in MSI-H mCRC
Data from CALGB/ SWOG 80405

**OS**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events/Total</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>13/21</td>
<td>30.0 (23.6 to NE)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>15/16</td>
<td>11.9 (10.3 to 24.6)</td>
</tr>
<tr>
<td>Bevacizumab and cetuximab</td>
<td>14/15</td>
<td>21.5 (16.4 to 41.1)</td>
</tr>
</tbody>
</table>

Log-rank P value: .0014

**PFS (months)**

- BEV + Cetux: 7.7
- BEV: 9.3
- Cetux: 5.4

BEV vs Cetux: P<0.001

80405: mOS Chemo+BEV: 30 mos

Innocenti et al., JCO 2019
MSI-high CRCs are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)\(^1,\)*

Nivolumab ± ipilimumab (CheckMate-142, phase II)\(^2\)

- Pembrolizumab:
  - MMR-proficient CRC
  - MMR-proficient CRC

- Nivolumab ± ipilimumab:
  - Nivolumab 3mg/kg
  - Nivolumab 3mg/kg + ipilimumab 1mg/kg

*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

\(^1\) Le et al. ASCO 2016; \(^2\) Overman et al. ASCO 2016
CheckMate-142 Study Design

- CheckMate-142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory

**Primary endpoint:**
- ORR per investigator assessment (RECIST v1.1)

**Other key endpoints:**
- ORR per BICR, DCR\(^b\), DOR, PFS, OS, and safety

### Treatment Arm

#### Previously treated

- Nivolumab 3 mg/kg Q2W\(^a\)
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses and then nivolumab 3 mg/kg Q2W)\(^a\)

#### First Line

- Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W\(^a\)

\(^a\)Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; \(^b\)Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients; \(^c\)Time from first dose to data cutoff

BICR = blinded independent central review

Lenz et al., ESMO 2018
Best Reduction in Target Lesions

- 84% of patients had a reduction in tumor burden from baseline

Who are these patients? Hyperprogressors?

*Confirmed response per investigator assessment
*Evaluable patients per investigator assessment

Lenz et al., ESMO 2018
Progression-Free and Overall Survival

**PFS\(^a\)**  |  Nivolumab + ipilimumab  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 45</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (14.1–NE)</td>
</tr>
<tr>
<td>9-mo rate (95% CI), %</td>
<td>77 (62.0–87.2)</td>
</tr>
<tr>
<td>12-mo rate (95% CI), %</td>
<td>77 (62.0–87.2)</td>
</tr>
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</table>

**OS\(^a\)**  |  Nivolumab + ipilimumab  
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<tbody>
<tr>
<td>N = 45</td>
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<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NE)</td>
</tr>
<tr>
<td>9-mo rate (95% CI), %</td>
<td>89 (74.9–95.1)</td>
</tr>
<tr>
<td>12-mo rate (95% CI), %</td>
<td>83 (67.6–91.7)</td>
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</table>

*Per investigator assessment. mo = month; NE = not estimable; NR = not reached

Lenz et al., ESMO 2018
Evaluation of First-Line IO in MSI-H mCRC is Ongoing

**MMR-D mCRC**
Strat: BRAF mut, site of met, prior adj Tx

**R**
- mFOLFOX6 + BEV
- Atezolizumab
- mFOLFOX6 + BEV + Atezolizumab

**COMMIT Trial**
NRG-GI004/ SWOG 1610
N=26/347
Primary EP: PFS

PIs: James Lee, Mike Overman
Not yet reported first-line phase III IO trial

• KEYNOTE-177 (NCT02563002)
  • Pembrolizumab (200 mg IV q3w) vs SOC choice (FOLFOX or FOLFIRI +/- BEV or cetuximab)
  • 308 patients in 21 countries
  • Co-primary EP: PFS and OS
  • Accrual completed, results expected later this year (?)
### Treatment Options in First-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>
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*ESMO guidelines allow EGFR mAbs in R-sided cancers
BRAF Mutations in CRC

- BRAF is primary effector of KRAS signaling
- BRAF mutations:
  - Occur most frequently in exon 15 (V600E)
  - Found in 4%-14% of patients with CRC
  - Mutually exclusive with KRAS mutations

PETACC-3: Survival after relapse according to BRAF mutation status

Median OS:
- BRAF mut: 7.49 m
- BRAF wt: 25.2 m
(p = 1.9e-11)

Tejpar et al, ASCO 2010
Roth et al. JCO 2010
BEACON CRC: A Randomized, 3-Arm, Phase 3 Study of Encorafenib and Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI, plus Cetuximab in $BRAF^{V600E}$ Mutant Metastatic Colorectal Cancer


BEACON CRC: Binimetinib, Encorafenib, And Cetuximab COMbined to Treat BRAF-mutant ColoRectal Cancer
Final Study Design

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–mutant 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

**Phase 3**

- **Triplet therapy**  
  ENCO + BINI + CETUX  
  n = 205

- **Doublet therapy**  
  ENCO + CETUX  
  n = 205

- **Control arm**  
  FOLFIRI + CETUX, or irinotecan + CETUX  
  n = 205

**Primary Endpoints:**

- OS  
- ORR (Blinded Central Review)

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

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

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

Kopetz et al, ESMO GI 2019
1º Endpoint Overall Survival: Triplet vs Control (all randomized patients)

Median OS in months (95% CI)

- **Triplet**: 9.0 (8.0–11.4)
- **Control**: 5.4 (4.8–6.6)

HR (95% CI), 0.52 (0.39–0.70)

2-sided \( P < 0.0001 \)

Kopetz et al, ESMO GI 2019
Waterfall Plots of Best Change in Sum of Diameters (based on central review)

*Patients whose SoD was contraindicated by assessment of PD. SoD = sum of longest diameter. Includes patients with measurable disease with a baseline and at least one post-baseline scan.

Control

N=73

Triplet

N=87

Doublet

N=98

Kopetz et al, ESMO GI 2019
ANCHOR: Single Arm Phase II Study of First-line Encorafenib + Binimetinib + Cetuximab

CLINICAL STUDY PROTOCOL

The ANCHOR CRC Study: encorafenib, binimetinib and Cetuximab in subjects with previously untreated BRAF-mutant Colorectal Cancer

Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated BRAF\(_{V600E}\)-mutant Metastatic Colorectal Cancer

N = 90, Primary Endpoint: ORR (Goal > 41%)

NCT03693170.

Grothey et al., TIP ESMO GI 2019
Tropomyosin Receptor Kinase (TRK): Role in Normal Biology and Cancer

• **TRK receptors**[1]:
  - In normal biology, expressed in neuronal tissue; roles in development, nervous system function via activation by neurotrophins
  - Rarely expressed in normal nonneuronal or cancerous tissues

• **TRK fusions**[1]:
  - Rearrangement of NTRK gene couples tyrosine kinase domain with a 5’ fusion partner to generate a chimeric TRK protein lacking ligand binding domain
  - Leads to overexpression or constitutive activation of TRK receptor kinase domain

<table>
<thead>
<tr>
<th>Receptor[2-4]</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRKA</td>
<td>NTRK1</td>
<td>Pain, thermoregulation</td>
</tr>
<tr>
<td>TRKB</td>
<td>NTRK2</td>
<td>Movement, memory, mood, appetite, weight</td>
</tr>
<tr>
<td>TRKC</td>
<td>NTRK3</td>
<td>Proprioception</td>
</tr>
</tbody>
</table>

Tropomyosin Receptor Kinase (TRK) Fusions Observed Across Diverse Cancer Types in Both Adults and Children

- Brain cancers (glioma, GBM, astrocytoma)
- Thyroid cancer
- Salivary (MASC)
- Lung cancer
- Secretory breast cancer
- Pancreatic
- Cholangiocarcinoma
- GIST
- Colon
- Melanoma
- Sarcoma (multiple)

NTRK fusions are rare events: 0.21% across 11,116 patients with tumors of all types
## Multiple TRK Inhibitors in Advanced Stages of Development

<table>
<thead>
<tr>
<th>Target(s)</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRK-specific inhibitors</td>
<td>Larotrectinib – FDA approved Nov 2018</td>
</tr>
<tr>
<td></td>
<td>LOXO-195</td>
</tr>
<tr>
<td></td>
<td>PLX7486*</td>
</tr>
<tr>
<td>TRK/ALK/ROS1-specific inhibitors</td>
<td>Entrectinib – FDA Breakthrough Designation</td>
</tr>
<tr>
<td></td>
<td>TPX-0005</td>
</tr>
<tr>
<td></td>
<td>DS-6051b</td>
</tr>
<tr>
<td>Nonspecific TKIs that may also cover TRK</td>
<td>Cabozantinib†</td>
</tr>
<tr>
<td></td>
<td>Sitravatinib (MGCD516)</td>
</tr>
<tr>
<td></td>
<td>Merestinib (LY2801653)</td>
</tr>
</tbody>
</table>

*Also selectively inhibits colony-stimulating factor-1 receptor.

†Approved by FDA for advanced RCC (in tablet form) or for progressive, metastatic medullary thyroid cancer (in capsule form).

Larotrectinib in Cancers with NTRK Fusion

A  Maximum Change in Tumor Size, According to Tumor Type

- Thyroid tumor
- Soft-tissue sarcoma
- Colon tumor
- Lung tumor
- Appendix tumor
- Salivary-gland tumor
- IFS
- Cholangiocarcinoma
- Breast tumor
- Melanoma
- GIST
- Pancreatic tumor

Drilon et al., NEJM 2018
Conclusions

• Individualization of first-line chemotherapy plus biologics is warranted based on mutational status, sidedness, treatment goals, prognosis, patient disposition
  • Triplet chemotherapy approaches (+/- biologics) are likely underutilized

• Targeted agents, beyond EGFRi and VEGFi, are moving into first-line therapy
  • IO and IO combos for MSI-H/ MMR-D cancers
  • Combination of MAPK inhibitors in BRAF V600E mutated mCRC
  • NTRK inhibitors for mCRC with NTRK fusion (<0.5%)
  • Potentially HER-2 targeted agents (no trials in first-line yet)