ESMO PRECEPTORSHIP ON COLORECTAL CANCER

17-18 MAY 2019
VALENCIA, SPAIN
The role of maintenance treatment – and what to do after 1st line?

Instituto CUF de Oncologia
Lisboa, Portugal

Aklepios Tumorzentrum Hamburg
AK Altona, Abt. Onkologie, Hämatologie und Palliativmedizin
Disclosures Dirk Arnold, 2014-2019

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

- Speaker and Chairman for educational events with:
  Boston Scientific, BTG, Roche, Merck Serono, Bayer, Lilly, Servier, Sanofi

- Investigator and researcher in data generating activities supported and sponsored by
  Roche, Mologen, AstraZeneca, Bayer
Ways to improve OS in metastatic CRC

- Diagnostic work-up and biomarkers
- Choice of treatment in 1st line
- Integration of local and ablative treatments
- The principle of „continuum of care“ in mCRC

Van Cutsem E, Cervantes A, ......Arnold D. ESMO Consensus; Ann Oncol 2016
Metastatic CRC: Main principles in 1st line

**Induction**

- Best systemic treatment
- where? response?

**Post induction**

- Several manifestations, "palliative"
- Best maintenance
  - De-escalation?
  - pause?
  - other compound?

- Best ablation
  - resection
  - "ablation toolbox"

Oligometastatic disease "ablative"

Arnold et al, Clin Colorect Cancer 2017
„First generation maintenance trials“

- **OPTIMOX/1'**
  - N=620'
  - FOLFOX'4'un: I'TF'
  - FOLFOX'7'
  - sLV5FU2'
  - Tournigand'et al.,'J'Clin'Oncol'2006'

- **OPTIMOX/2'**
  - N=202'
  - mFOLFOX'7'
  - mFOLFOX'7'
  - sLV5FU2'
  - mFOLFOX'7'
  - Chemo'free'interval'
  - Chibaudel'et al.,'J'Clin'Oncol'2009'

*Van Cutsem E, Cervantes A, … Arnold D. ESMO Consensus; Ann Oncol 2016*
„First generation maintenance trials“: OPTIMOX-2

No treatment („CFI“) vs. FP after 3 mos. combination CT

HR 0.88; p=0.42
Median 19.5 vs. 23.8 mos
(=4.3 mos. shorter OS)
“Deescalation maintenance”: Trials

SAKK 41/06²

Previously untreated mCRC (n=262) → Bev + CT (16-24 weeks) → Bev N=131 → PD

Primary endpoint: non-inferiority in TTP (from randomisation)

CAIRO3¹

Previously untreated mCRC n=558 → XELOX + Bev (18 weeks, x6) With CR/PR/SD → Cape + Bev N=278 → PD

Primary endpoint: superiority in PFS2 (maintenance and reinduction treatment)

AIO 0207²

Previously untreated mCRC (n=852²/452) → FP + oxaliplatin + Bev (24 weeks) With CR/PR/SD → Bev N=156 → PD

Primary endpoint: non-inferiority in TFS (maintenance and reinduction treatment)
De-escalation maintenance: „Time to failure of strategy“ (TFS)

HR nihil vs. FP/Bev: \(0.76\); \(p<0.04\)

HR nihil vs. FP/Bev: \(0.67\); \(p<0.0001\)

DCCG: Koopman, et al., ASCO 2014; Simkens et al., Lancet 2015
De-escalation maintenance: „Time to first progression (PFS)"

**HR nihil vs. FP/Bev:** 0.49; p<0.0001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floxuripirimide plus bevacizumab</td>
<td>131</td>
<td>6.3 months (5.8-7.6)</td>
</tr>
<tr>
<td>Bevacizumab alone</td>
<td>149</td>
<td>4.6 months (4.0-5.3)</td>
</tr>
<tr>
<td>No treatment</td>
<td>150</td>
<td>3.5 months (2.9-4.1)</td>
</tr>
</tbody>
</table>

**HR nihil vs. FP/Bev:** 0.43; p<0.0001

**AIO:** Arnold, et al. ASCO 2014; Hegewisch-Becker et al., Lancet Oncol 2015

**DCCG:** Koopman, et al., ASCO 2014; Simkens et al., Lancet 2015
De-escalation maintenance: Overall survival (OS)

HR nihil vs. FP/Bev: exploratory, n.s.

HR nihil vs. FP/Bev: 0.83; p=0.06

DCCG: Koopman, et al., ASCO 2014; Simkens et al., Lancet 2015
Maintenance or observation after induction?

Arnold et al., ASCO 2016 (oral presentation)
Stein and Arnold, Clin Colorectal Cancer 2017
ESMO Guideline: Maintenance treatment

• Patients receiving FOLFOX or CAPOX as induction therapy should be allocated to maintenance therapy after 6–8 cycles.

• Patients receiving FOLFIRI as induction should continue for (at least) as long as tumour shrinkage continues.

• Optimal maintenance treatment after a bevacizumab-containing induction is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab monotherapy as maintenance is not recommended.

• Individualisation and discussion with the patient is essential.

Van Cutsem E, Cervantes A, ......Arnold D. ESMO Consensus; Ann Oncol 2016
Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-Free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9)

![Graphs showing progression-free survival and overall survival over time for maintenance and observation groups.](image-url)
Clinical factors influencing outcome in metastatic colorectal cancer patients treated with fluoropyrimidine and bevacizumab (FP+Bev) maintenance treatment vs observation: a pooled analysis of the phase 3 CAIRO3 and AIO 0207 trials

Kaitlyn Goey  Sjoerd Elias  Axel Hinke  Martijn van Oijen  Kees Punt  
Susanna Hegewisch-Becker  Dirk Arnold  Miriam Koopman

Goey et al., ESMO 2016; poster discussion session
<table>
<thead>
<tr>
<th>Events (n/N)</th>
<th>HR (95%CI)</th>
<th>(P_{\text{interaction}})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>247/251</td>
<td>247/259</td>
</tr>
<tr>
<td>Female</td>
<td>139/142</td>
<td>115/129</td>
</tr>
<tr>
<td><strong>Age at randomisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>268/273</td>
<td>281/301</td>
</tr>
<tr>
<td>≥70</td>
<td>118/120</td>
<td>85/87</td>
</tr>
<tr>
<td><strong>WHO/ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>218/221</td>
<td>212/229</td>
</tr>
<tr>
<td>1–2</td>
<td>168/172</td>
<td>154/159</td>
</tr>
<tr>
<td><strong>Response to induction treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>251/257</td>
<td>238/254</td>
</tr>
<tr>
<td>SD</td>
<td>135/136</td>
<td>128/134</td>
</tr>
<tr>
<td><strong>Site primary tumour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>220/223</td>
<td>189/206</td>
</tr>
<tr>
<td>Rectum / rectosigmoid</td>
<td>166/170</td>
<td>177/182</td>
</tr>
<tr>
<td><strong>Number of metastatic sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>153/156</td>
<td>158/170</td>
</tr>
<tr>
<td>&gt;1</td>
<td>233/237</td>
<td>208/218</td>
</tr>
<tr>
<td><strong>Stage of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synchronous, resection</td>
<td>147/151</td>
<td>143/160</td>
</tr>
<tr>
<td>Synchronous, no resection</td>
<td>139/139</td>
<td>146/148</td>
</tr>
<tr>
<td>Metachronous</td>
<td>100/103</td>
<td>77/80</td>
</tr>
<tr>
<td><strong>LDH elevated at randomisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>189/194</td>
<td>166/176</td>
</tr>
<tr>
<td>Yes</td>
<td>197/199</td>
<td>200/212</td>
</tr>
<tr>
<td><strong>Platelets at start of induction treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400*10^9/L</td>
<td>233/236</td>
<td>242/256</td>
</tr>
<tr>
<td>≥400*10^9/L</td>
<td>131/135</td>
<td>101/109</td>
</tr>
<tr>
<td><strong>CEA at start of induction treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 ng/mL</td>
<td>103/106</td>
<td>116/126</td>
</tr>
<tr>
<td>&gt;20 ng/mL</td>
<td>119/122</td>
<td>178/184</td>
</tr>
<tr>
<td><strong>Mutation status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS / BRAF-wild-type</td>
<td>97/99</td>
<td>106/113</td>
</tr>
<tr>
<td>RAS mutant</td>
<td>174/176</td>
<td>144/153</td>
</tr>
<tr>
<td>BRAF V600 mutant</td>
<td>18/20</td>
<td>18/21</td>
</tr>
<tr>
<td>Overall</td>
<td>386/393</td>
<td>366/388</td>
</tr>
</tbody>
</table>

Goey, Arnold et al., Br J Cancer 2017
Who benefits from active maintenance?

RAS & BRAF wild-type

RAS or BRAF mutant

Hegewisch-Becker et al., Lancet Oncol 2015
Does sidedness predict benefit?

Figure 1
A) PFS left vs. right sided mCRCs in randomized patients.
B) PFS by maintenance arm in randomized patients with right sided tumors.
C) PFS by maintenance arm in randomized patients with left sided tumors.

FU=Fluoropyrimidine, Bev=Bevacizumab
Quality of life whilst maintenance

CAIRO-3

N=491

- QoL was maintained during maintenance treatment, and was clinically not inferior compared to QoL in observation arm

AIO 0207

N=427

Koopman et al, GI Cancer Symposium 2014; Quidde et al., DGHO 2014 (presentation)
AIO 0207: Quality of life analyses

@ wk 24:
% of patients with at least 10 IP „overall HRQoL“ improvement

@ wk 24:
% of patients with at least 10 IP „overall HRQoL“ deterioration

Quidde et al., Ann Oncol 2016
TRIBE2: a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable metastatic colorectal cancer (mCRC) patients (pts)


on behalf of the GONO Investigators
Intensive or sequential treatment?
Tribe-2 trial
Intensive or sequential treatment? Tribe-2 trial, PFS 2 (= sequence)

<table>
<thead>
<tr>
<th>Median follow up = 22.8 mos</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 340</td>
<td>N = 339</td>
</tr>
<tr>
<td>Events, N (%)</td>
<td>235 (69%)</td>
<td>188 (55%)</td>
</tr>
<tr>
<td>Median PFS2, mos</td>
<td>16.2</td>
<td>18.9</td>
</tr>
<tr>
<td>HR = 0.69 [95% CI: 0.57-0.83] p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intensive or sequential treatment?
Tribe-2 trial, PFS1 (= „1st line“)

<table>
<thead>
<tr>
<th>Median follow up</th>
<th>FOLFOX + bev N = 340</th>
<th>FOLFOXIRI + bev N = 339</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.8 mos</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events, N (%)</th>
<th>288 (85%)</th>
<th>261 (77%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Median PFS, mos</th>
<th>9.9</th>
<th>12.0</th>
</tr>
</thead>
</table>

HR = 0.73 [95% CI: 0.62-0.87] p<0.001
Intensive or sequential treatment? Tribe-2 trial

Arm A
- FOLFOX + bev*
- 5FU/bev

Arm B
- FOLFOXIRI + bev*
- 5FU/bev

Progression Free Survival 2

* Up to 8 cycles

R 1:1

Tribe-2 trial

FOLFOXIRI + bev*
Maintenance following FOLFOX/Cet´mab: The TTD MACRO2 trial
Maintenance following FOLFOX/Cet´mab: The TTD MACRO2 trial

Aranda et al., Eur J Cancer 2018
VALENTINO Trial: EGFR maintenance

Valentino study design

- RAS wt untreated unresectable mCRC pts N=224
- FOLFOX-4 up to 8 cycles
- 5-FU/LV
- Panitumumab

Arm A
- Disease progression/unacceptable toxicity/consent withdrawal

Arm B
- Induction therapy
- Maintenance therapy
- Panitumumab

Stratification Factors:
- Center
- Prior relevant (T/R)
- N. metastatic sites (≥1?1)

Pietrantonio et al., ASCO 2018
VALENTINO Trial: EGFR maintenance

HR = 1.55; 95% CI: 1.09-2.20; $P = 0.011$
Median PFS 10.2 vs. 13.0 months

Pietrantonio et al., ASCO 2018
VALENTINO Trial: EGFR maintenance

HR = 1.55; 95% CI: 1.09-2.20; $P = 0.011$
Median PFS 10.2 vs. 13.0 months

Pietrantonio et al., ASCO 2018
German AIO: PanaMa Trial

**PanaMa (AIO KRK 0212)**

- mKRK, Ras-Wildtyp
- Induktion: mFOLFOX + Panitumumab
- Erhaltung: PD → Re-Induktion
- 5-FU/FA + Panitumumab → mFOLFOX6 + Panitumumab
- 5-FU/FA → mFOLFOX6 + Panitumumab

Endpunkt: Progressionsfreies Überleben (PFS)
Auswertung ab 280 Patienten
Re-challenge of EGFR Inhibitors?

→ Detection?

→ Time interval?
Evaluation of response to treatment in mCRC

Evaluation of response to treatment in mCRC

The „again or still wildtype“ situation

Phase II, non comparative, study
Target accrual: 27 pts

- mCRC pts
- RAS and BRAF wt

FOLFIRI
- FOLFOXIRI
- Cetuximab

PD

\[ \rightarrow \text{ORR 22\%} \]
\[ \rightarrow \text{DCR 54\%} \]

≥ 6 Months

- At least a RECIST 1.1 partial response
- 1st-line PFS ≥ 6 months
- PD to 1st-line cetuximab within 4 weeks after the last cetuximab administration

≥ 4 Months

- Time between the end of 1st-line therapy and the start of 3rd-line ≥ 4 months

Study treatment:
- Irinotecan 180 mg/sqm iv
- Cetuximab 500 mg/sqm iv

ctDNA for RAS/BRAF mutations
(ddPCR+NGS)

Rossini et al., ASCO 2018
The „again or still wildtype“ situation

<table>
<thead>
<tr>
<th>Patients</th>
<th>RAS status on ctDNA</th>
<th>Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Wild-type</td>
<td>Confirmed PR</td>
</tr>
<tr>
<td>#2</td>
<td>KRAS G12D</td>
<td>PD</td>
</tr>
<tr>
<td>#3</td>
<td>Wild-type</td>
<td>Confirmed PR</td>
</tr>
<tr>
<td>#4</td>
<td>Wild-type</td>
<td>PD</td>
</tr>
<tr>
<td>#5</td>
<td>Wild-type</td>
<td>SD</td>
</tr>
<tr>
<td>#6</td>
<td>KRAS G12D</td>
<td>PD</td>
</tr>
<tr>
<td>#7</td>
<td>Wild-type</td>
<td>SD</td>
</tr>
<tr>
<td>#9</td>
<td>Wild-type</td>
<td>Confirmed PR</td>
</tr>
<tr>
<td>#10</td>
<td>Wild-type</td>
<td>Unconfirmed PR</td>
</tr>
<tr>
<td>#11</td>
<td>Wild-type</td>
<td>PD</td>
</tr>
<tr>
<td>#12</td>
<td>KRAS G12D</td>
<td>PD</td>
</tr>
<tr>
<td>#13</td>
<td>KRAS G12V</td>
<td>PD</td>
</tr>
<tr>
<td>#15</td>
<td>NRAS Q61L</td>
<td>SD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>RAS status on ctDNA</th>
<th>Objective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>#16</td>
<td>Wild-type</td>
<td>SD</td>
</tr>
<tr>
<td>#17</td>
<td>KRAS G12V/Q61H</td>
<td>PD</td>
</tr>
<tr>
<td>#18</td>
<td>KRAS G12V</td>
<td>PD</td>
</tr>
<tr>
<td>#19</td>
<td>Wild-type</td>
<td>Confirmed PR</td>
</tr>
<tr>
<td>#21</td>
<td>KRAS G12D</td>
<td>SD</td>
</tr>
<tr>
<td>#22</td>
<td>KRAS G12V</td>
<td>SD</td>
</tr>
<tr>
<td>#23</td>
<td>KRAS G12V</td>
<td>PD</td>
</tr>
<tr>
<td>#24</td>
<td>KRAS G12D</td>
<td>Unconfirmed PR</td>
</tr>
<tr>
<td>#25</td>
<td>KRAS G12D</td>
<td>SD</td>
</tr>
<tr>
<td>#26</td>
<td>Wild-type</td>
<td>SD</td>
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<tr>
<td>#27</td>
<td>Wild-type</td>
<td>PD</td>
</tr>
<tr>
<td>#28</td>
<td>Wild-type</td>
<td>SD</td>
</tr>
</tbody>
</table>

- Mutations in ctDNA in 48% (12/25)
- Confirmed response only in ctDNA RAS WT (before re-induction)

Rossini et al., ASCO 2018
CRICKET trial: Phase 2 single-arm study of re-challenge with cetuximab + irinotecan as 3rd-line therapy in RAS and BRAF WT pts with acquired resistance to 1st-line cetuximab- and irinotecan-containing therapy.

Contemporary mCRC algorithm

Induction

chemotherapy + antibody

where? response?

post induction

several manifestations, "palliative"

"best maintenance"
De-escalation? pause? other compound?

"best ablation"
resection "ablation toolbox"

Oligometastastatic disease "ablative"
Contemporary mCRC algorithm

Induction

- chemotherapy + antibody
  - where? response?
    - several manifestations, "palliative"
    - Oligometastastic disease "ablative"

post induction

- "best maintenance"
  - De-escalation? pause? other compound?

- "best ablation"
  - resection
  - "ablation toolbox"
New compounds in maintenance

Bev vs. Bev/Erlotinib following combination CT/Bev induction

PFS maintenance: HR 0.81; p=0.059
Median: 4.9 vs. 5.4 mos.

OS from maintenance: HR 0.79; p=0.036
Median: 22.1 vs. 24.9 mos.

Tournigand et al., Lancet Oncol 2015
FLUOROPYRIMIDINE (FP) AND BEVACIZUMAB ± ATEZOLIZUMAB AS FIRST-LINE TREATMENT FOR BRAF$^{\text{WT}}$ METASTATIC COLORECTAL CANCER: FINDINGS FROM THE MODUL TRIAL OF BIOMARKER-DRIVEN MAINTENANCE


¹West Cancer Center, Germantown, TN, USA; ²Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; ³Asklepios Clinic Altona, Hamburg, Germany; ⁴Franco-British Institute, Levallois-Perret, France; ⁵Gustave Roussy, Villejuif, Université Paris Saclay, France; ⁶Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; ⁷University Hospitals Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium; ⁸F. Hoffmann-La Roche Ltd, Basel, Switzerland; ⁹Martin-Luther-University, Halle, Germany
Primary objective: Progression-free survival (PFS; RECIST v1.1) measured from randomization in each maintenance treatment cohort

Secondary objectives: Overall survival (OS); overall response rate (ORR); disease control rate (DCR); time to treatment response (TTR); duration of response (DoR); change in ECOG performance status; safety

Grothey et al., ESMO 2018
**Primary objective:**
Progression-free survival (PFS; RECIST v1.1) measured from randomization in each maintenance treatment cohort

**Secondary objectives:**
Overall survival (OS); overall response rate (ORR); disease control rate (DCR); time to treatment response (TTR); duration of response (DoR); change in ECOG performance status; safety

---

**Induction treatment**
- FOLFOX + bevacizumab
  - 8 cycles (16w)
  - or
  - FOLFOX + bevacizumab
  - 6 cycles (12w)
  - then
  - 5-FU/LV + bevacizumab
  - 2 cycles (4w)

**Biomarker-driven maintenance treatment**
- Cohort 1
  - BRAF<sup>mut</sup>
  - 5-FU/LV + cetuximab + vemurafenib
  - FP + bevacizumab
- Cohort 2
  - BRAF<sup>wt</sup>
  - FP + bevacizumab + atezolizumab
  - FP + bevacizumab
- Cohort 3
  - HER2<sup>+</sup>
  - Capecitabine + trastuzumab + pertuzumab
  - FP + bevacizumab
- Cohort 4
  - HER2<sup>–</sup>
  - BRAF<sup>wt</sup>
  - Cobimetinib + atezolizumab
  - FP + bevacizumab

**Follow-up**
- Treatment until PD
Primary analysis of PFS: 1L BRAF$^{\text{wt}}$

Median follow-up 18.7 months

### PFS

- **FP + bev + atezo**
  - Median PFS, months: 7.20
  - Stratified HR (95% CI): 0.96 (0.77–1.20)
  - p=0.727

- **FP + bev**
  - Median PFS, months: 7.39

### OS

- **FP + bev + atezo**
  - Median OS, months: 22.05
  - Stratified HR (95% CI): 0.86 (0.66–1.13)
  - p=0.283

- **FP + bev**
  - Median OS, months: 21.91

Grothey et al., ESMO 2018
Immunotherapy as „switch maintenance“

N= > 580; primary endpoint: OS
PI: Dirk Arnold, DE & David Cunningham, UK
Treatment goals change with “line” of therapy

<table>
<thead>
<tr>
<th>Line of systemic treatment</th>
<th>Realistic treatment goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>‘Cure’ Reduce risk of recurrence</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>Deepest tumor response Long duration of low/no tumor burden</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Durable disease control Tumor response if needed</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>Durable disease control Maintenance of QoL and PS</td>
</tr>
<tr>
<td>Subsequent lines</td>
<td>Disease control and maintenance of QoL; palliation</td>
</tr>
</tbody>
</table>

Arnold D. Clin Colorect Cancer 2016
Factors That Impact on Treatment Decisions

<table>
<thead>
<tr>
<th>1st-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment goal</td>
</tr>
<tr>
<td>Disease-related factors</td>
</tr>
<tr>
<td>Patient-related factors</td>
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Factors That Impact on Treatment Decisions

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Arnold, WCGC 2016 (oral presentation)
Factors That Impact on Treatment Decisions

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ESMO 2014 Guidelines: Sequences

Figure 1. Strategic scenarios in the continuum of care of metastatic CRC

A: Scenario 1
- Cytotoxic doublet\(^1\) + bevacizumab
  - Cytotoxic doublet\(^2\) + bevacizumab or aflibercept
    - Irinotecan or FOLFIRI + anti-EGFR antibody\(^3\)
  - Irinotecan or FOLFIRI + anti-EGFR antibody\(^3\)
    - Regorafenib

B: Scenario 2
- Cytotoxic doublet\(^2\) + bevacizumab
  - Cytotoxic doublet\(^2\) + anti-EGFR antibody\(^2\)
    - Regorafenib

C: Scenario 3
- Cytotoxic doublet\(^1\) + anti-EGFR antibody\(^2\)
  - Cytotoxic doublet\(^2\) + bevacizumab or aflibercept
    - Regorafenib

\(^1\) cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; \(^2\) RAS wild type

Van Cutsem, Cervantes, Nordlinger & Arnold; Ann Oncol 2014
VEGF resistance occurs – but when?

Arnold et al., Clin Colorectal Cancer 2014
TML study: Results

Unstratified hazard ratio 0.81 (95% CI 0.69–0.94); p=0.0062 (log-rank test)
Stratified hazard ratio 0.83 (95% CI 0.71–0.97); p=0.0211 (log-rank test)

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<th>Bevacizumab and chemotherapy (n=409)</th>
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2L chemo alone or plus continued Bevacizumab after progression with chemo plus Bevacizumab

Arnold et al., J Clin Oncol Suppl. 2012
Benounna, Arnold et al., Lancet Oncol 2013
Bevacizumab Beyond Progression: 2 different trials, Overall Survival

**TML, Int’l phase III**
- Chemotherapy alone (n=410)
- Bevacizumab and chemotherapy (n=409)

Unstratified hazard ratio 0.81 (95% CI 0.69–0.94); p=0.0062 (log-rank test)
- Stratified hazard ratio 0.83 (95% CI 0.71–0.97); p=0.0211 (log-rank test)

**BEBYP, Italian phase II**
- Chemotherapy alone (n=92)
- Bevacizumab and chemotherapy (n=92)

adjusted HR 0.77, p=0.043 (strat. log-rank)

### TML trial: Subgroup analyses

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<th>HR</th>
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### PFS

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Vieitez de Prado, Borg, Arnold et al., ESMO 2012
Benounna, Arnold et al., Lancet Oncol 2013
Antiangiogenic treatment in mCRC

Arnold & Tabernero, J Oncopathol 2013
Antiangiogenic Treatment Options in mCRC

• When VEGF-A levels are reduced or activation of VEGFR-2 is reduced by an antagonist, there is evidence to suggest PlGF and VEGF-B ligands serve as an alternative angiogenic and/or metastatic pathway

• Targeting a broader set of pro-angiogenic growth factors could help in overcoming antiangiogenic resistance (e.g., PlGF and VEGF-B)
  – But, this hypothesis has yet to be confirmed in clinical studies
Van Cutsem et al., J Clin Oncol 2012

**Phase III VELOUR: 2nd line FOLFIRI +/- Aflibercept**

**Overall Survival (probability)**

- **OS Kaplan-Meier estimates, months**
  - Placebo/FOLFIRI: (95.34% CI) 12.06 (11.07 to 13.11)
  - Aflibercept/FOLFIRI: 13.50 (12.52 to 14.95)
- **HR (95% CI) = 0.821 (0.713 to 0.937); log-rank P = .0032**

**Progression-Free Survival (probability)**

- **PFS Kaplan-Meier estimates, months**
  - Placebo/FOLFIRI: 4.67 (4.21 to 5.36)
  - Aflibercept/FOLFIRI: 6.90 (6.51 to 7.20)
- **HR (95% CI) = 0.758 (0.661 to 0.889); log-rank P < .0001**

- **OS: HR 0.82, p<0.0032**
  - med. 12.06 vs. 13.5 mos.

- **PFS: HR 0.76, p<0.001**
  - med. 4.7 vs. 6.9 mos.
VELOUR trial: Stratified subgroups

Overall survival

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<th>N</th>
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<th>Interaction P</th>
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Progression free survival

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Van Cutsem et al., J Clin Oncol 2012
VELOUR trial: Stratified subgroups

Overall survival

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Progression free survival

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<table>
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<tr>
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Van Cutsem et al., J Clin Oncol 2012
Phase III RAISE: 2nd line FOLFIRI +/- Ramucirumab

**A**
- **Ramucirumab plus FOLFIRI**
- **Placebo plus FOLFIRI**

**Median (months)**
- Ramucirumab group 13.2 (95% CI 12.4-14.5)
- Placebo group 11.7 (95% CI 10.8-12.7)

**Hazard ratio 0.844 (95% CI 0.730-0.976)**
**Log-rank p=0.0219**

**Number at risk**
- Ramucirumab + FOLFIRI: 536
- Placebo + FOLFIRI: 536

**B**

**Median (months)**
- Ramucirumab group 5.7 (95% CI 5.5-6.2)
- Placebo group 4.5 (95% CI 4.2-5.4)

**Hazard ratio 0.793 (95% CI 0.657-0.930)**
**Log-rank p=0.0005**

**Number at risk**
- Ramucirumab + FOLFIRI: 536
- Placebo + FOLFIRI: 536

Tabernero et al., Lancet Oncol 2015
## 2nd line with anti-VEGF combinations

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<th>E3200</th>
<th>TML</th>
<th>VELOUR</th>
<th>RAISE</th>
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<tbody>
<tr>
<td>Bev + FOLFOX4</td>
<td>Bev + CT</td>
<td>Aflib + FOLFIRI</td>
<td>Ramu + FOLFIRI</td>
<td></td>
</tr>
<tr>
<td>(n=286)</td>
<td>(n=410)</td>
<td>(n=612)</td>
<td>(n=536)</td>
<td></td>
</tr>
<tr>
<td>Bev + CT</td>
<td>CT</td>
<td>Plac + FOLFIRI</td>
<td>Plac + FOLFIRI</td>
<td></td>
</tr>
<tr>
<td>(n=291)</td>
<td>(n=409)</td>
<td>(n=614)</td>
<td>(n=536)</td>
<td></td>
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<tr>
<td>Bev before?</td>
<td>none</td>
<td>all</td>
<td>30%</td>
<td>all</td>
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<tr>
<td>mOS, months</td>
<td>12.9</td>
<td>10.8</td>
<td>11.2</td>
<td>11.7</td>
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<tr>
<td>HR</td>
<td>0.75</td>
<td>0.81</td>
<td>0.82</td>
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<tr>
<td>p</td>
<td>0.0011</td>
<td>0.0062</td>
<td>0.0032</td>
<td>0.022</td>
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<td>mPFS, months</td>
<td>7.3</td>
<td>4.7</td>
<td>5.7</td>
<td>4.7</td>
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<tr>
<td>HR</td>
<td>0.61</td>
<td>0.68</td>
<td>0.76</td>
<td>0.79</td>
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<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0007</td>
<td>&lt;0.0005</td>
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<tr>
<td>ORR, %</td>
<td>22.7</td>
<td>8.6</td>
<td>5.4</td>
<td>19.8</td>
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<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>ns</td>
<td>ns</td>
<td>11.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.0001</td>
<td>13.4</td>
</tr>
<tr>
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<td></td>
<td>12.5</td>
</tr>
</tbody>
</table>

Treatment sequences: Strategies

Figure 1. Strategic scenarios in the continuum of care of metastatic CRC

A: Scenario 1
1. Cytotoxic doublet1 + bevacizumab
2. Cytotoxic doublet2 + bevacizumab or aflibercept
3. Irinotecan or FOLFIRI + anti-EGFR antibody3
4. Regorafenib

B: Scenario 2
1. Cytotoxic doublet1 + bevacizumab
2. Cytotoxic doublet2 + anti-EGFR antibody3
3. Regorafenib

C: Scenario 3
1. Cytotoxic doublet1 + anti-EGFR antibody3
2. Cytotoxic doublet2 + bevacizumab or aflibercept
3. Regorafenib

1 cytotoxic doublet: fluoropyrimidine + oxaliplatin or irinotecan
2 RAS wild type

Van Cutsem, Cervantes, Nordlinger & Arnold; Ann Oncol 2014
Case #1: 57y/o lawyer, ECOG PS 0, motivated

• C. transversum cancer, diagnosed and resected (19 mos. ago)
• Synchronous liver mets and retroperitoneal mets
• intraoperatively localized peritoneal carcinomatosis
  1st line FOLFOX/Bevacizumab for 5 months → PR
  FP/Bevacizumab maintenance for 8 more months
  at progression 2 months re-induction of oxaliplatin → neuropathy and increasing CEA
• RAS wild-type, BRAF wild-type
• What now?
Patients with wtKRAS exon 2 mCRC progressing after Bev plus chemotherapy doublet (fluoropyrimidine + oxaliplatin or irinotecan) 
(n = 133)

Primary endpoint • PFS rate at 4 months (a CT-scan was performed every 6 weeks)

Secondary endpoints • Objective Response Rate (RECIST 1.1)
• Overall survival (OS)
• PFS
• OS from the start of first-line therapy
• Safety (adverse events using the NCIC-CTCAE)
• Quality of life

Stratification factors • Type of first-line chemo. irinotecan vs oxaliplatin
• first-line PFS : ≥ 10 × > 9 months

Arm A 
mFOLFOX6 or FOLFIRI + bevacizumab

Arm B 
mFOLFOX6 or FOLFIRI + cetuximab

R 1:1

with a chemotherapy crossover from the first-line to second-line

PRODIGE 18 STUDY DESIGN

mFOLFOX6
Oxaliplatin: 85 mg/m², d1
Folinic acid: 400 mg/m², d1
5-FU bolus: 400 mg/m², d1
5-FU IV 46H: 2400 mg/m² d1-d14

FOLFIRI
Irinotecan: 180 mg/m², d1
Folinic acid: 400 mg/m², d1
5-FU bolus: 400 mg/m², d1
5-FU IV 46 h: 2400 mg/m² d1-d14

+ Bevacizumab: 5mg/kg, d1 or
+ Cetuximab: 500mg/m², d1 d1-d14
Progression-Free Survival

Bev (Arm A, n=65)
Median PFS 7.1 months
(95% CI: 5.7 – 8.2)
Cet (Arm B, n=67)
Median PFS 5.6 months
(95% CI: 4.2 – 6.5)

HR 0.710 (95% CI: 0.495–1.018)
p=0.0622

Overall Survival

Bev (Arm A, n=65)
Median OS 15.8 months
(95% CI: 9.5 – 22.3)
Cet (Arm B, n=67)
Median OS 10.4 months
(95% CI: 7.0 – 16.2)

HR 0.688 (95% CI: 0.456 – 1.038)
p=0.0750

Median follow-up was 37.4 months (95%CI: 25.1–39.6 months)
**MEDIAN PFS AND MEDIAN OS (WTKRAS, NRAS EXONS 2,3,4, WTBRAF)**

**Progression-Free Survival**
- **Bev (Arm A, n=36)**
  - Median PFS 8.2 months
  - (95% CI: 6.6 - 8.6)
- **Cet (Arm B, n=37)**
  - Median PFS 5.7 months
  - (95% CI: 4.1 – 7.1)

**Overall Survival**
- **Bev (Arm A, n=36)**
  - Median OS 21.1 months
  - (95% CI: 12.3 – 35.1)
- **Cet (Arm B, n=37)**
  - Median OS 12.6 months
  - (95% CI: 6.8 – 22.5)

**HR** 0.665 (95% CI: 0.407 – 1.087)  
**p**=0.1035

**HR** 0.758 (95 CI: 0.416 – 1.383)  
**p**=0.3669

Median follow-up was 29.2 months (CI95%: 19.7 – 41.4 months)
KRAS wild-type; N=182

2nd line, after FOLFOX/bev: FOLFIRI with bev or with p’mab? SPIRITT trial

ORR: 32% FOLFIRI/p’mab vs. 19% FOLFIRI/bev
**After 1st line bev combo:**

2nd line/bev versus 2nd line/egfr

**PRODIGE trial, KRAS wild-type; N=130**

**SPRITT trial, KRAS wild-type; N=182**

Prodige trial, Hiret et al., ASCO 2016

SPIRITT trial, Hecht et al., Clin Colorectal Cancer 2015
## Second-Line Treatment Options for wt KRAS/NRAS mCRC: Randomized Trials of Anti-EGFR Agents

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. Pts</th>
<th>ORR, %</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>181 (RAS WT subgp)</strong></td>
<td>FOLFIRI Panitumumab + FOLFIRI</td>
<td>294</td>
<td>10</td>
<td>6.7 (p=0.023)</td>
<td>14.5 (p=0.366)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>303</td>
<td>41</td>
<td>4.9</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>SPIRITT (KRAS WT)</strong></td>
<td>Panitumumab + FOLFIRI</td>
<td>91</td>
<td>32</td>
<td>7.7 (p=0.97)</td>
<td>18.0 (p=0.75)</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab + FOLFIRI</td>
<td>91</td>
<td>19</td>
<td>9.2</td>
<td>21.4</td>
</tr>
<tr>
<td><strong>PRODIGE-18 (KRAS WT)</strong></td>
<td>Cetuximab + chemo* Bevacizumab + chemo*</td>
<td>65</td>
<td>32</td>
<td>5.7 (p=0.07)</td>
<td>11.4 (p=0.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>25</td>
<td>7.5</td>
<td>19.3</td>
</tr>
</tbody>
</table>

* mFOLFOX6 or FOLFIRI

VEGF Resistance Occurs – But When?

Arnold et al., Clin Colorectal Cancer 2014
Potential biomarkers of Bevacizumab resistance and progression in mCRC

- Single arms trials showed an increase of PIGF at bevacizumab progression\textsuperscript{1,2}
- An increase in serum VEGF-A level during or before disease progression has been documented\textsuperscript{2}
- These increases may contribute to bevacizumab treatment resistance

PIGF expression correlates with progression and survival status

Distribution of Ratios Between Pretreatment Expression Levels of PIGF in Tumor and Non-tumor Tissues (UICC-TNM)

Survival Curves of Patients in Relation To Pretreatment PIGF Expression Levels in Tumors

Pretreatment Levels of PLGF-1 Transcript in CRC vs Normal Tissue

UICC-TNM classification stage I, n=14; stage II, n=27; stage III, n=22; stage IV, n=11

PIGF, placental growth factor; TNM, tumor node metastasis; VEGF, vascular endothelial growth factor

Results according to VEGF-D levels

High VEGF level (≥115 pg/mL, TR population)

Low VEGF level (<115 pg/mL, TR population)

Tabenero J et al., Ann Oncol 2018
PERMAD Trial: Determination of Markers for (Early) Angiogenic Switch

Biological | Bevacizumab | Afiblercept |
---|---|---|
Chemo | CHEMO A | CHEMO B |
N=60 | 1st-line | 2nd-line |

Conventional switch of Chemo and Biological at timepoint of PD

Chemo A/B = FP + Ox/Iri

Assessment of CAF every 2 weeks and RECIST every 8 weeks

PERMAD Trial: Randomized Part

**Patients with marker change and at least SD (RECIST)**

- **A** Conventional switch of chemo and biological at timepoint of PD
- **B** Marker-driven early switch of biological and conventional switch of chemo at timepoint of PD

**1st-line**
- Biological: Bevacizumab
- Chemo: CHEMO A

**2nd-line**
- Biological: Bevacizumab
- Chemo: CHEMO B

- n=120
- n=60

Treatment goals change with “line” of therapy

<table>
<thead>
<tr>
<th>Line of systemic treatment</th>
<th>Realistic treatment goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>‘Cure’ Reduce risk of recurrence</td>
</tr>
<tr>
<td>1(^{st}) line</td>
<td>Deepest tumor response Long duration of low/no tumor burden</td>
</tr>
<tr>
<td>2(^{nd}) line</td>
<td>Durable disease control Tumor response if needed</td>
</tr>
<tr>
<td>3(^{rd}) line</td>
<td>Durable disease control Maintenance of QoL and PS</td>
</tr>
<tr>
<td>Subsequent lines</td>
<td>Disease control and maintenance of QoL; palliation</td>
</tr>
</tbody>
</table>

Arnold D. Clin Colorect Cancer 2016
Evidence-based treatment beyond 2\textsuperscript{nd} line

Many patients are candidates for further treatment: After 2+ lines of treatment
a significant number of patients with mCRC are able and willing to receive more treatments

n=4877 patients with mCRC who received chemotherapy between Jan 2004 and March 2011 in oncology practices subscribing to a US-wide chemotherapy order entry system\textsuperscript{2}

“Snapshot” of 3\textsuperscript{rd} and 4\textsuperscript{th} line treatment for mCRC

- A significant number of patients progressing beyond the 2\textsuperscript{nd} line are still fit for further therapy.
- Italian study assessed oncologists’ clinical practice in the management of Italian mCRC patients, with a focus on the 3\textsuperscript{rd}, 4\textsuperscript{th}, and later lines of therapy.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{3L treatment ECOG PS (%) patients} & \textbf{4L treatment ECOG PS (%) patients} \\
\hline
ECOG 0 & 43\% & ECOG 0 & 43\% \\
ECOG 1 & 43\% & ECOG 1 & 52\% \\
ECOG 2 & 14\% & ECOG 2 & 19\% \\
ECOG 3 & 3\% & ECOG 3 & 3\% \\
\hline
\end{tabular}
\end{table}

Heiman F et al. Value in Health. 2015
Reasons for first-line discontinuation

- Tumour progression (clinical resistance)
  - Consider second-line CT (PS, organ function)
  - Progression

- Excessive toxicity (intolerance)
  - Early progression (during 1-2 months of discontinuation)
  - Late progression (occurring after at least 2 months of treatment)
  - Reintroduction of first-line CT

- Patient/doctor decision (stop CT) +/- maintenance

Van Cutsem E, Cervantes A, ......Arnold D. ESMO Consensus; Ann Oncol 2016
Regorafenib vs. placebo: Two phase III trials

- Overall'survival' (OS')

CORRECT & CONCUR &

Grothey et al., WCGC 2015 (oral presentation)
Trifluridine/Tipiracil mode of action

FTD  
Trifluridine

TPI  
Tipiracil hydrochloride

Inhibition
Thymidine phosphorylase

FTD degradation

Cancer cell

[References]
Tipiracil substantially increases bioavailability of trifluridine

Mean trifluridine plasma concentrations time profile after single dose of trifluridine/tipiracil (35 mg/m²) or trifluridine alone

Trifluridine/tipiracil dosing achieved:
- 37-fold greater trifluridine AUC concentration
- 22-fold greater trifluridine $C_{max}$
Trifluridine/Tipiracil mode of action

FTD
Trifluridine

TPI
Tipiracil hydrochloride

Inhibition
Thymidine phosphorylase degradation

FTD

Cancer cell
Trifluridine/Tipiracil mode of action

FTD
Trifluridine

TPI
Tipiracil hydrochloride

Inhibition
Thymidine phosphorylase

FTD degradation

DNA substrate

Phosphorylation steps

FTD
Thymidine
G Guanosine

Phosphate
A Adenosine
C Cytidine

Thymidine kinase

DNA replication

Cancer cell

87
Trifluridine/Tipiracil mode of action

FTD
Trifluridine

TPI
Tipiracil hydrochloride

Inhibition

Thymidine phosphorylase

FTD degradation

Phosphorylation steps

DNA substrate

DNA replication

FTD

DNA dysfunction

Prevention of cell proliferation

Antitumor activity

Cancer cell

FTD
Thymidine
Phosphate
Thymidine kinase

Guanosine
A Adenosine
C Cytidine

88
Cytotoxicity of trifluridine/tipiracil

Trifluridine/tipiracil efficacy in mCRC (RE COURSE)


**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>TFD/TPI (N=534)</th>
<th>Placebo (N=266)</th>
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<tbody>
<tr>
<td>Median OS, mo*</td>
<td>7.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Alive at 12 mo, %</td>
<td>27</td>
<td>18</td>
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<tr>
<td>Stratified log-rank test:</td>
<td>p&lt;0.001; HR 0.68</td>
<td>95% CI 0.58–0.81</td>
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</table>

**Progression-free survival**

<table>
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<th>TFD/TPI (N=534)</th>
<th>Placebo (N=266)</th>
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</thead>
<tbody>
<tr>
<td>Median PFS, mo*</td>
<td>2.0</td>
<td>1.7</td>
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</table>
| CT scans were performed every 8 weeks from month 2

No. at risk:

<table>
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<tr>
<th></th>
<th>TFD/TPI</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>534</td>
<td>266</td>
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<tr>
<td>TFD/TPI</td>
<td>459</td>
<td>198</td>
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<tr>
<td></td>
<td>294</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>137</td>
<td>47</td>
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<td></td>
<td>64</td>
<td>24</td>
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<td>7</td>
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No. at Risk:

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<th>Placebo</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>534</td>
<td>266</td>
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<tr>
<td>TFD/TPI</td>
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</table>
Trifluridine/tipiracil effectively prolongs time to deterioration (ECOG PS ≥2) (RE COURSE)

Longer median time to worsening ECOG PS from 0–1 to ≥2 (5.7 vs. 4.0)

84% of patients maintain ECOG PS

Trifluridine/tipiracil – haematological AEs (RE COURSE)

<table>
<thead>
<tr>
<th>Most common AEs*</th>
<th>Trifluridine/tipiracil (N=533)</th>
<th>Placebo (N=265)</th>
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<tbody>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td></td>
<td>Neutropenia, %</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Leukopenia, %</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Anaemia, %</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia, %</td>
<td>5</td>
</tr>
<tr>
<td>Non-haematological</td>
<td>Nausea,%</td>
<td>2</td>
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<tr>
<td></td>
<td>Vomiting,%</td>
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</tr>
<tr>
<td></td>
<td>Decreased appetite,%</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Fatigue,%</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea,%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain,%</td>
<td>2</td>
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<td></td>
<td>Fever,%</td>
<td>1</td>
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<tr>
<td></td>
<td>Asthenia,%</td>
<td>3</td>
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</table>

PRECONNECT (phase 3b EAP): Progression-free survival

Efficacy based on investigator assessment

- Median PFS: 2.8 months (95% CI 2.7–3.3), range (0.1–11.1);
- ORR: 2.4% (95% CI 1.2–4.2).
- DCR: 36.8% (95% CI 32.4–41.4).
- At cut-off, 40 deaths were reported in this population.
PRECONNECT (phase 3b EAP): Time to deterioration of PS

84% of patients are ECOG PS 0–1 at the end of FTD/TPI treatment

Time to first ECOG PS deterioration to PS ≥2
Median Range: 8.7 (0.2–11.0) months
Treatment decisions in metastatic colorectal cancer – Beyond first and second line combination therapies

A. Vogel\(^a\), R.D. Hofheinz\(^b\), S. Kubicka\(^c\), D. Arnold\(^d, *\)

\(^a\)Department of Gastroenterology, Hepatology and Endocrinology, Hanover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
\(^b\)Interdisciplinary Tumor Center Mannheim, University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany
\(^c\)Cancer Center Reutlingen, District Hospital Reutlingen, Steinernenstr. 31, 72764 Reutlingen, Germany
\(^d\)Instituto CUF de Oncologia, c/o Hospital Infante Santo, Tav. Castro 3, Lisboa, Portugal

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>n</th>
<th>Median OS, months</th>
<th>HR in OS (95% CI), (P) value</th>
<th>Median PFS, months</th>
<th>HR in PFS (95% CI), (P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECURSE Mayer, 2015</td>
<td>Trifluridine/tipiracil, Placebo</td>
<td>800</td>
<td>7.1 vs 5.3*</td>
<td>0.68 (0.58–0.81), (P &lt; .001)</td>
<td>2.0 vs 1.7</td>
<td>0.48 (0.41–0.57), (P &lt; .001)</td>
</tr>
<tr>
<td>CONCUR Li, 2015</td>
<td>Regorafenib, Placebo</td>
<td>204</td>
<td>8.8 vs 6.3*</td>
<td>0.55 (0.40–0.77), (P = .00016)</td>
<td>3.2 vs 1.7</td>
<td>0.31 (0.22–0.44), (P &lt; .0001)</td>
</tr>
<tr>
<td>ASPECTT Price, 2014</td>
<td>Panitumumab, Cetuximab</td>
<td>1010</td>
<td>10.4 vs 10.0</td>
<td>0.97 (0.84–1.11)</td>
<td>-</td>
<td>1.00 (0.88–1.14)</td>
</tr>
<tr>
<td>CORRECT Grothey, 2013</td>
<td>Regorafenib, Placebo</td>
<td>760</td>
<td>6.4 vs 5.0*</td>
<td>0.77 (0.64–0.94), (P = .0052)</td>
<td>1.9 vs 1.7</td>
<td>0.49 (0.42–0.58), (P &lt; .0001)</td>
</tr>
<tr>
<td>CO17 Jonker, 2007</td>
<td>Cetuximab + BSC, BSC</td>
<td>572</td>
<td>6.1 vs 4.6*</td>
<td>0.77 (0.64–0.92), (P = .005)</td>
<td>-</td>
<td>0.68 (0.57–0.80), (P &lt; .001)</td>
</tr>
<tr>
<td>Van Cutsem, 2007</td>
<td>Panitumumab + BSC, BSC</td>
<td>463</td>
<td>-</td>
<td>1.00 (0.82–1.22)</td>
<td>8.0 vs 7.3*</td>
<td>0.54 (0.44–0.66)</td>
</tr>
</tbody>
</table>
What to do after 1st line discontinuation?

- Reasons for first-line discontinuation
  - Tumour progression (clinical resistance)
  - Excessive toxicity (intolerance)
  - Patient/doctor decision (stop CT) +/- maintenance

- Consider second-line CT (PS, organ function)
- Early progression (during 1–2 months of discontinuation)
- Late progression (occurring after at least 2 months of treatment)

- Progression
- Reintroduction of first-line CT

Van Cutsem E, Cervantes A, ......Arnold D  ESMO Consensus; Ann Oncol 2016
Retreatment = Reintroduction or Rechallenge with a previously used regimen

Reintroduction

No progression of CRC while on therapy

Treatment was either of a set duration (eg, adjuvant) or was stopped for a planned break (eg, to reduce or manage AEs)

Rechallenge

Reintroduction, after an intervening treatment, of the same therapy to which tumor has already proved to be resistant

The disease is challenged with the same regimen/agent in later-line treatment

Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review

D. Arnold¹,²*, G. W. Prager³, A. Quintela¹, A. Stein⁴, S. Moreno Vera⁵, N. Mounedji⁵ & J. Taieb⁶

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Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review
Beyond second-line therapy in patients with metastatic colorectal cancer: a systematic review

With regard to approved third- and fourth-line treatments, both trifluridine/tipiracil and regorafenib were evaluated in large, well-conducted phase II and III trials [16, 17, 20, 21, 24]. On the basis of the efficacy findings, treatment with either trifluridine/tipiracil or regorafenib is an appropriate first choice beyond the second line; thus, performance status and the safety profiles of each are likely to be determinant in the choice of treatment.
Activation and priming of T cells
- mAb against PD-1, PD-L1, CTLA-4
- IL-2
- IL-12
- Agonists for CD137, OX40, CD27

Presentation of tumour associated antigens by APC
- Vaccines
- IFN-α
- GM-CSF

Release of tumour associated antigens
- Chemotherapy
- Radiotherapy
- Targeted therapy

Migration of activated T cells to the tumour via blood vessels

Infiltration of T cells into the tumour
- mAb against VEGF/VEGFR

Recognition and killing of tumour cells
- mAb against PD-1; PD-L1; IDO, LAG-3

Möhler et al., Eur J Cancer 2016
Sequences of „lines“ in 1L MCRC

- Induction
- post Induction
- 2nd line
- post 2nd line
- 3rd line
- Re-Induction
- 4th line
- bsc
Statine vor und während der Systemtherapie wirken protektiv! Seicean et al., JACC 2012.

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What to do after 1st line discontinuation?