Advances in the management of metastatic colorectal cancer

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Colorectal Cancer: Background

- Second leading cause of cancer death worldwide after lung cancer.
- 1 in 3 people with CRC will die from their disease.
- ~105,000 cases of colon cancer and ~42,000 cases of rectal cancer yearly with ~60,000 deaths each year in USA
- Third most common cancer in South Africa in both men & women with ~3900 new cases/year (National Cancer Registry 2014)
- Highly curable if detected early.
Chemotherapy for mCRC

- Treatment of colorectal cancer is one of the most rapidly advancing areas of cancer research
- 5FU based chemotherapy has been the mainstay of colorectal cancer therapy since 1950s
- Addition of folinic acid in 1980s improved responses from ~10% to ~20%
- The addition of a number of new drugs since mid 1990s has dramatically changed the outlook of advanced colorectal cancer.
Modern therapies for mCRC

- Oxaliplatin
- Irinotecan
- Oral capecitabine (5FU prodrug)
- Monoclonal antibodies:
  - bevacizumab & ramucirumab (anti-VEGF)
  - cetuximab & panitumumab (anti-EGFR)
- VEGF trap - aflibercept
- Multi-kinase inhibitor – regorafenib
- Novel anti-folate - trifluridine/tipiracil
- Anti-PD-1 monoclonal antibody - pembrolizumab (MSI-H)
- Trastuzumab (HER2 enriched)
Angiogenesis inhibition
Angiogenesis is Required for Sustained Tumor Growth

Angiogenic Factors: VEGF

Tumor Cells

Ligand Receptor Interaction

Endothelial Proliferation

Invasion and Migration

Venules or Capillaries
Antiangiogenic agents

**MOA of Anti-Angiogenic Agents**

- **ZALTRAP** inhibits VEGF-B
- **AVASTIN** inhibits VEGF-A
- **CYRAMZA** inhibits VEGF-C
- **PGF** inhibits VEGF-D

**Endothelial Cell**

- Angiogenesis
- Lymphangiogenesis
- Role unclear

**MOA**:

- PGF = Placental Growth Factor
- VEGF = Vascular Endothelial Growth Factor
- VEGFR = Vascular Endothelial Growth Factor Receptor
Bevacizumab

- Recombinant humanized monoclonal antibody against VEGF-A.
- Binds directly to VEGF, inhibiting its activity and preventing angiogenesis.
- Prevents the interaction of VEGF with VEGFR-1 (flt-1), VEGFR-2 (KDR) and VEGFR-3 (flt-4) on endothelial cell surface.
- Reduces micro-vascular growth and inhibits progression of local and metastatic disease.
IFL +/- bevacizumab in mCRC

- Randomized study in mCRC compared irinotecan-based therapy (IFL) + placebo versus IFL + bevacizumab (Hurwitz et al; *N Engl J Med* 2004).
- Median PFS: 10.6 months versus 6.2 months (HR 0.54; p<0.001)
- Median OS: 20.3 versus 15.6 months, (HR 0.66; p<0.001)
- ORR: 44.8% vs. 34.8% (p=0.004)
- Grade 3 hypertension 11% versus 2.3%
- IFL is however suboptimal with more hematological and GI toxicity than infusional 5FU-based therapy eg. FOLFIRI
Bevacizumab beyond progression

- ML-18147: mCRC progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy (Bennouna et al. *Lancet Oncology* 2013)
- 1:1 randomization to 2nd line chemotherapy with or without bevacizumab 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks
- The choice of oxaliplatin or irinotecan-based 2nd line chemotherapy depended on the 1st line regimen
- Median OS: 11.2 months for bevacizumab plus chemotherapy vs. 9.8 months for chemotherapy alone (HR 0.81, 95% CI 0.69-0.94; p=0.0062).
- Grade 3-5 SAEs were neutropenia (16% vs 13%), diarrhoea (10% vs 8%) and asthenia (6% vs 4%)
Aflibercept

• Blocks all human VEGF-A isoforms, VEGF-B, and placental growth factor (PLGF)²†
• Binds VEGF-A more tightly than native receptors²†
• Inhibits VEGFR signaling more potently and blocks cell migration more effectively than bevacizumab in preclinical models³†

†Impact of preclinical activity on clinical efficacy is not known.

Afiberecept improves survival in a phase III randomized trial in metastatic colorectal cancer

**Overall Survival: ITT Population**

- **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**

Cut-off date: February 7, 2011

Median follow-up: 22.28 months

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<td>Number at Risk</td>
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<td>Survival Probability</td>
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Van Cutsem et al. J Clin Oncol 2012,
Aflibercept demonstrated statistically and clinically significant ongoing survival benefit in mCRC.

Survival Probability:
- Placebo/FOLFIRI: 79.1%, 50.3%, 30.9%, 18.7%, 12.0%, 7.7%
- Aflibercept/FOLFIRI: 81.9%, 56.1%, 38.5%, 28.0%, 22.3%

Median follow-up: 22.28 months.

Cut-off date: February 7, 2011.

Median survival:
- Placebo/FOLFIRI: 12.1 months
- Aflibercept/FOLFIRI: 13.5 months

Mean survival:
- Placebo/FOLFIRI: 20.3 months
- Aflibercept/FOLFIRI: 23.2 months

75% quartile:
- Placebo/FOLFIRI: 21.03 (18.92–22.80)
- Aflibercept/FOLFIRI: 25.59 (22.01–31.70)

Stratified HR = 0.817 [95.34% CI, 0.713–0.937]
Log-rank P = 0.0032

Hazard Ratios (Piecewise Cox Proportional Hazard Model):
- t ≤ 6: 0.860 (0.664–1.114)
- 6 < t ≤ 12: 0.8 (0.673–1.043)
- 12 < t ≤ 18: 0.782 (0.582–1.050)
- t > 18: 0.676 (0.463–0.988)

Mo = months.

Ramucirumab: Fully human anti-VEGFR-2 monoclonal antibody
Second line antiangiogenic therapy

• M18147 Study (bevacizumab beyond progression): median OS: 11.2 months vs 9.8 months (HR 0.81, 95% CI 0.69-0.94; p=0.0062).

• VELOUR Study (aflibercept): median OS: 13.50 vs 12.06 months (HR=0.817; 95.34%CI 0.713–0.937, p=0.0032)

• RAISE Study (ramucirumab): median OS: 13.3 months vs 11.7 months (HR 0.844, 95% CI 0.73-0.976, p=0.0219)
EGFR-1 signalling

**Cetuximab**

- Chimeric monoclonal antibody which binds to Epidermal Growth Factor Receptor (EGFR-1).
- Blocks binding of ligands including EGF to EGFR-1 thereby inhibiting intracellular tyrosine phosphorylation.
- Prevents signaling to nucleus via RAS-RAF-MEK-ERK-MAPK pathway.
- Inactive in all RAS mutant tumours.
Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer


Primary endpoint: PFS in KRAS wild-type patients

KRAS WT (n=348) HR=0.68; p=0.017
mPFS Cetuximab + FOLFIRI: 9.9 months
mPFS FOLFIRI: 8.7 months

1-year PFS rate: 25% vs 43%

van Cutsem E et al. NEJM 2009
Overall survival: KRAS WT

HR = 0.84 (95% CI: 0.64 – 1.11); p = 0.22

mOS Cetuximab + FOLFIRI (n=172): 24.9 months
mOS FOLFIRI (n=176): 21.0 months

2-year OS rate 51% vs 44%

van Cutsem E et al. NEJM 2009
CRystal: Efficacy analysis in patients by KRAS mutation status

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<th>KRAS wild-type</th>
<th>KRAS mutant</th>
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<tr>
<td>Cetuximab + FOLFI R (n=316)</td>
<td>Cetuximab + FOLFI R (n=214)</td>
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<td><strong>OS time</strong></td>
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<td>Median OS (months)</td>
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<tr>
<td>HR [95% CI]</td>
<td>0.796 [0.670-0.946]</td>
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<td>p-value*</td>
<td>0.0094</td>
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<td><strong>PFS time</strong></td>
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<td>Median PFS (months)</td>
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<tr>
<td>HR [95% CI]</td>
<td>0.696 [0.558-0.867]</td>
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<td>p-value*</td>
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<td><strong>Best overall response</strong></td>
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<td>OR rate (%)</td>
<td>57.3</td>
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<td>Odds ratio [95% CI]</td>
<td>2.0693 [1.5154-2.8258]</td>
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<tr>
<td>p-value**</td>
<td>&lt;0.0001</td>
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* log-rank p-value  **Cochran-Mantel-Haenszel test.
CI, confidence interval; HR, hazard ratio; OR, best overall response; OS, overall survival; PFS, progression-free survival.
Panitumumab

Fully human anti-EGFR-1 monoclonal antibody
PRIME Study: Schema and Stratification

Tx Arm 1:
Panitumumab 6.0 mg/kg Q2W + FOLFOX4 Q2W

Disease assessment every 8 weeks

Tx Arm 2:
FOLFOX4 Q2W

Target: 1150 patients

Randomization stratification:
- ECOG score: 0-1 vs. 2
- Geographic Region: Western Europe, Canada, and Australia vs. Rest of the World

NCT00364013; Amgen 20050203.
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer

Jean-Yves Douillard, Kelly Oliner, Salvatore Siena, Josep Tabernero, Ronald Burkes, Mario Barugel, Yves Humblet, Gyorgy Bodoky, David Cunningham, Jacek Jassem, Fernando Rivera, Ilona Kocáková, Paul Ruff, Maria Błasińska-Morawiec, Martin Šmakal, Jean Luc Canon, Mark Rother, Richard Williams, Alan Rong, Jeffrey Wiezorek, Roger Sidhu and Scott Patterson.

Prevalence of RAS and BRAF mutations*  

<table>
<thead>
<tr>
<th><strong>KRAS</strong></th>
<th>EXON 1</th>
<th>EXON 2</th>
<th>EXON 3</th>
<th>EXON 4</th>
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<td>12 13</td>
<td>59 61</td>
<td>117 146</td>
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<td>40.1% (440/1096)</td>
<td>4.5% (29/638)</td>
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<tr>
<th><strong>NRAS</strong></th>
<th>EXON 1</th>
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<td>3.5% (22/637)</td>
<td>4.4% (28/636)</td>
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<th><strong>BRAF</strong></th>
<th>EXON 1</th>
<th>EXON 15</th>
<th>EXON 18</th>
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<td>8.6% (53/619)</td>
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*The KRAS exon 2 data is from the overall population. The remaining data are within the wild-type KRAS exon 2 subset and based on samples that yielded a result.

PFS of original KRAS WT exon 2 & expanded RAS WT subgroups

Original WT KRAS Exon 2

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<tr>
<th>Events n (%)</th>
<th>Median months (95% CI)</th>
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<tr>
<td>Panitumumab + FOLFOX4</td>
<td>199 / 325 (61)</td>
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<tr>
<td>FOLFOX4 alone</td>
<td>215 / 331 (65)</td>
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Hazard Ratio = 0.80 (95% CI: 0.66 – 0.97)
Log-rank p-value = 0.023

Expanded WT RAS

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<th>Events n (%)</th>
<th>Median months (95% CI)</th>
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<tr>
<td>Panitumumab + FOLFOX4</td>
<td>156 / 259 (60)</td>
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<tr>
<td>FOLFOX4 alone</td>
<td>170 / 253 (67)</td>
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Hazard Ratio = 0.72 (95% CI: 0.58 – 0.90)
Log-rank p-value = 0.04

OS of original KRAS WT Exon 2 and expanded RAS WT

**Original WT KRAS Exon 2**

- Panitumumab + FOLFOX4: 165 / 325 (51) Events, Median 23.9 (20.3 – 28.3) months
- FOLFOX4 alone: 190 / 331 (57) Events, Median 19.7 (17.6 – 22.6) months

Hazard Ratio = 0.83 (95% CI: 0.67 – 1.02)
Log-rank p-value = 0.072

**Expanded WT RAS**

- Panitumumab + FOLFOX4: 128 / 259 (49) Events, Median 26.0 (21.7 – 30.4) months
- FOLFOX4 alone: 148 / 253 (58) Events, Median 20.2 (17.7 – 23.1) months

Hazard Ratio = 0.78 (95% CI: 0.62 – 0.99)
Log-rank p-value = 0.043

Panitumumab versus cetuximab in patients with metastatic colorectal cancer


Overall Survival

### Events

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<th>n/N (%)</th>
<th>Median (95% CI)</th>
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<tr>
<td>Panitumumab</td>
<td>383/499</td>
<td>10.4 (9.4, 11.6)</td>
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<td>Cetuximab</td>
<td>392/500</td>
<td>10.0 (9.3, 11.0)</td>
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### Hazard Ratio

Hazard Ratio: 0.97, 95% CI: (0.84, 1.11)

### P-value (non-inferiority)

P-value (non-inferiority): 0.0007

### Z-score

Z-score: -3.19

### Retention rate

Retention rate: 1.06, 95% CI: (0.82, 1.29)

### Patients at risk

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<th>Patients at risk:</th>
<th>Cetuximab</th>
<th>Panitumumab</th>
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### Months

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</table>
208 patients treated with panitumumab (had paired plasma samples at BL and SFU)

<table>
<thead>
<tr>
<th>Baseline Plasma (BL)</th>
<th>Posttreatment Plasma (SFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>113 wild-type</td>
<td>59 remained wild-type</td>
</tr>
<tr>
<td>65 single-gene mutations</td>
<td>54 Emergent mutations</td>
</tr>
<tr>
<td>30 multi-gene mutations</td>
<td>29: single-gene</td>
</tr>
<tr>
<td></td>
<td>25: multi-gene</td>
</tr>
</tbody>
</table>

Genes with predominant mutations identified at BL:
- *BRAF* (16.3%)
- *PI3KCA* (14.4%)
- *KRAS* (13.5%)

Genes with predominant emergent mutations at SFU:
- *KRAS* (23%)
- *BRAF* (19.5%)
- *MAP2K1* (15%)

SFU, safety follow-up; BL, baseline.
Emergent mutations in mCRC patients

- Patients on anti-EGFR monoclonal antibodies for mCRC develop new emergent mutations while on therapy.
- The most important gene products responsible for anti-EGFR resistance are those from:
  - RAS/RAF/MEK/MAPK pathway namely KRAS, NRAS, BRAF and MAP2K1
  - PI3K/AKT/mTOR pathway namely PTEN and PIK3CA
- Mutations in all these signalling pathway kinases correlate with poorer outcomes.
- Mutations are not mutually exclusive eg. RAS and RAF.
- Many other gene mutations are also seen by NGS.
- Further work is ongoing to assess the impact of emergent mutations at various time points and on different therapies while on treatment for mCRC.
Bevacizumab versus cetuximab in KRAS/RAS WT patients: FIRE-3 and CALGB/SWOG 80405
Overall survival
Final RAS* wild-type population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n/N (%)</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>107/199 (53.8%)</td>
<td>33.1</td>
<td>24.5 – 39.4</td>
</tr>
<tr>
<td>FOLFIRI + Bevacizumab</td>
<td>133/201 (66.2%)</td>
<td>25.0</td>
<td>23.0 – 28.1</td>
</tr>
</tbody>
</table>

HR 0.697 (95% CI: 0.54 – 0.90)

p (log-rank) = 0.0059

* KRAS and NRAS exon 2, 3 and 4 wild-type
Overall Survival By Arm
(All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>256</td>
<td>31.2</td>
<td>0.9</td>
<td>0.40</td>
</tr>
<tr>
<td>+ Bev</td>
<td>(178)</td>
<td>(26.9-34.3)</td>
<td>(0.7-1.1)</td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>270</td>
<td>32.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Cetux</td>
<td>(177)</td>
<td>(27.6-38.5)</td>
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</tr>
</tbody>
</table>
Left sided vs right sided CRC
FIRE-3: FOLFIRI + cetuximab or bevacizumab: Tumour location as a biomarker
Primary and secondary outcomes in RAS WT patients

<table>
<thead>
<tr>
<th></th>
<th>Left-sided (n=306)</th>
<th>Right-sided (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cet + CT (n=157)</td>
<td>Bev + CT (n=149)</td>
</tr>
<tr>
<td>ORR (1st endpoint)</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>68.8</td>
<td>61.7</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.37</td>
<td>1.11</td>
</tr>
<tr>
<td>p-value</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>Median, months</td>
<td></td>
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<tr>
<td></td>
<td>10.7</td>
<td>10.7</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>Median, months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.3</td>
<td>28.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Note: FIRE-3 did not meet its primary endpoint of significantly improving ORR in patients with KRAS (exon 2) WT mCRC based on investigators’ read

CALGB/SWOG 80405: Venook et al
Predictive value of primary tumour location (RAS WT)

<table>
<thead>
<tr>
<th>RAS WT</th>
<th>Left-sided</th>
<th>Right-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cet + CT</td>
<td>Bev + CT</td>
</tr>
<tr>
<td></td>
<td>(n=173)</td>
<td>(n=152)</td>
</tr>
</tbody>
</table>

### OS (1° end point)
- Median, months: 39.3, 32.6, 13.7, 29.2
- HR (95% CI): 0.77 (0.59–0.99), 1.36 (0.93–1.99)
- p-value: 0.04, 0.10
- Treatment × tumour location interaction (p-value): 0.009

### PFS
- HR (95% CI): 0.84 (0.66–1.06), 1.64 (1.15–2.36)
- p-value: 0.15, 0.006
- Treatment × tumour location interaction (p-value): 0.001

Note: CALGB/SWOG 80405 did not meet its primary endpoint of significantly improving OS in the cetuximab + FOLFOX/FOLFIRI vs bevacizumab + FOLFOX/FOLFIRI arm in patients with KRAS (exon 2) WT mCRC

Checkpoint inhibitors in MMR-D / MSI-H mCRC

Pembrolizumab was FDA approved in 2017 for MMR-D / MSI-H cancers agnostic of tumour site
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency (MMR-D).


PD-1 Blockade in Tumors with Mismatch-Repair Deficiency (MSI-H or MMR-D).

- Phase 2 study of pembrolizumab 10 mg/kg every 14 days in 41 patients with MMR-D CRCs, MMR-P CRCs and MMR-D non-CRC patients.
- The co-primary end points were the immune-related ORR and the 20-week immune-related PFS rate.
- The immune-related ORR and immune-related PFS rates were 40% (4 of 10) and 78% (7 of 9), respectively, for MMR-D CRC patients, and 0% (0 of 18) and 11% (2 of 18) for MMR-P CRC patients.
- The median PFS and OS were not reached in the MMR-D CRC patients but were 2.2 and 5.0 months, in MMR-P CRC patients (HR for death, 0.22 (p=0.05); HR for progression or death, 0.10 (p<0.001)
- Patients with MMR-D non-CRC had responses similar to MMR-D CRC (immune-related ORR, 71% (5 of 7); immune-related PFS rate, 67% (4 of 6).
- Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in MMR-D tumors, as compared with 73 in MMR-P tumors (p=0.007)
KRAS/RAS WT patients:
• FOLFIRI/FOLFOX + cetuximab (CRYSTAL; OPUS; FIRE-3)
• FOLFIRI + cetuximab better than FOLFIRI + bevacizumab (FIRE-3)
• FOLFOX + panitumumab (PRIME)

RAS WT patients with left sided tumours:
• FOLFIRI + cetuximab better than FOLFIRI + bevacizumab (FIRE-3)
• FOLFOX/FOLFIRI + cetuximab better than FOLFOX/FOLFIRI + bevacizumab (CALGB 80405)

RAS WT patients with right sided tumours:
• FOLFOX/FOLFIRI + bevacizumab may be better than FOLFOX/FOLFIRI + cetuximab (CALGB 80405)
Treatments in 1st line irresectable mCRC

KRAS/RAS MT patients:
- IFL/FOLFOX + bevacizumab (Hurwitz; Saltz)
- FOLFOXIRI may be an option if contraindications for bevacizumab and downsizing is desired
- FOLFOXIRI + bevacizumab (TRIBE)
- No benefit for cetuximab + FOLFIRI (CRYSTAL)
- Negative impact for panitumumab + FOLFOX (PRIME)

KRAS unknown:
- Negative impact of panitumumb + bevacizumab (PACCE) therefore treat as KRAS mutant type
Treatments in 2nd line irresectable mCRC

- **Chemotherapy:**
  - Change cytotoxic partner ie. oxaliplatin $\leftrightarrow$ irinotecan
- **Anti-VEGF:**
  - Bevacizumab beyond progression (TML: Bennouna et al. *Lancet Oncology* 2013)
  - Afiblercept + FOLFIRI including prior bevacizumab (VELOUR)
  - Ramucirumab + FOLFIRI (prior bevacizumab) (RAISE)
  - Bevacizumab, if no bevacizumab in first line (ECOG: Giantonio et al. *J Clin Oncol* 2007)
- **KRAS/RAS WT:**
  - Panitumumab + FOLFIRI (Peeters et al. *J Clin Oncol* 2010 & ASCO GI 2014)
Treatments in 3rd line irresectable mCRC

- **Antiangiogenic therapy:**
  - Regorafenib (Grothey et al. *Lancet* 2013)
  - Negative data for bevacizumab in third line (Chen et al. *J Clin Oncol* 2006)
  - No available data for aflibercept or ramucirumab in third line
  - KRAS WT not exposed to prior anti-EGFR antibody: