The treatment of metastatic colorectal cancer in 2007

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CRC is a major health concern

- Life-time risk for CRC 4–6%\(^1\)
- Worldwide
  - Third most common cancer\(^2\)
  - > 1 000 000 new cases\(^2\)
  - Second leading cause of cancer death (~529 000)\(^2\)
- 400 000/year patients in Europe develop CRC\(^2\)
- 25% present with metastatic disease
- 40–50% eventually develop metastatic disease
- > 200 000 deaths/year in Europe\(^2\)

2. GLOBOCAN. http://www-dep.iarc.fr 2002
Maximising patient outcomes in CRC

- Colorectal cancer treatment in a context of Continuum of Care:
  - Treatment Plan throughout the continuum of care, based on best available evidence
  - More effective drugs now available and trend towards a targeted and possibly “tailored” therapy
  - Multi-Disciplinary Approach: i.e. resection of liver metastases

Colorectal liver metastases

• Disease is limited to the liver:
  - Unresectable liver metastases
    – Neoadjuvant or induction chemotherapy followed by resection if response
  – Resectable liver metastases
    • Neoadjuvant and/or adjuvant chemotherapy
The role of neo-adjuvant and adjuvant chemotherapy for liver metastases of colorectal cancer

Current Perspective

Towards a pan-European consensus on the treatment of patients with colorectal liver metastases

Eric Van Cutsem, Bernard Nordlinger, Rene Adam, Claus-Henning Köhne, Carmelo Pozzo, Graeme Poston, Marc Ychou, Philippe Rougier, on behalf of European Colorectal Metastases Treatment Group
Patterns of resectability in patients with CRC liver metastases

Metastatic CRC

85% unresectable

10-20% potentially resectable
80-90% never resectable

15% resectable

• Class I
• Class II

neoadjuvant chemotherapy to increase resectability?

neoadj. and/or adjuv. CT to increase cure rate?
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients</th>
<th>Op. Mort.</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Foster</td>
<td>1981</td>
<td>259</td>
<td>5%</td>
<td>22%</td>
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<tr>
<td>Iwatsuki</td>
<td>1986</td>
<td>60</td>
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<td>1987</td>
<td>80</td>
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<td>Adson</td>
<td>1987</td>
<td>141</td>
<td>3%</td>
<td>25%</td>
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<td>Hughes</td>
<td>1988</td>
<td>859</td>
<td>--</td>
<td>33%</td>
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<tr>
<td>Scheele</td>
<td>1991</td>
<td>219</td>
<td>5%</td>
<td>39%</td>
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<td>Rosen</td>
<td>1992</td>
<td>280</td>
<td>4%</td>
<td>25%</td>
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<td>AFC</td>
<td>1992</td>
<td>1818</td>
<td>2%</td>
<td>26%</td>
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<td>Gayowski</td>
<td>1994</td>
<td>204</td>
<td>0%</td>
<td>32%</td>
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<td>Fong</td>
<td>1999</td>
<td>1001</td>
<td>2.8%</td>
<td>37%</td>
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<td>Minigawa</td>
<td>2000</td>
<td>235</td>
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<td>38%</td>
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<td>Ercolani</td>
<td>2002</td>
<td>257</td>
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<td>34%</td>
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<tr>
<td>Choti</td>
<td>2002</td>
<td>133</td>
<td>-</td>
<td>58%</td>
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<tr>
<td>Adam</td>
<td>2003</td>
<td>615</td>
<td>1%</td>
<td>41%</td>
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<td>Abdalla</td>
<td>2004</td>
<td>190</td>
<td>-</td>
<td>58%</td>
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</table>
EORTC 40983: Study design

Randomize

FOLFOX4
6 cycles
(3 months)

Surgery

FOLFOX4
6 cycles
(3 months)

N=364 patients with ≤ 4 resectable liver metastases

Nordlinger B et al, Proc ASCO 2007
### EORTC 40983: Results

<table>
<thead>
<tr>
<th></th>
<th>N pts CT</th>
<th>N pts Surgery</th>
<th>% absolute difference in 3-year PFS</th>
<th>Hazard Ratio (Confidence Interval)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>182</td>
<td>182</td>
<td>+7.2% (28.1% to 35.4%)</td>
<td>0.79 (0.62-1.02)</td>
<td>P=0.058</td>
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<tr>
<td><strong>All eligible Patients</strong></td>
<td>171</td>
<td>171</td>
<td>+8.1% (28.1% to 36.2%)</td>
<td>0.77 (0.60-1.00)</td>
<td>P=0.041</td>
</tr>
<tr>
<td><strong>All resected Patients</strong></td>
<td>151</td>
<td>152</td>
<td>+9.2% (33.2% to 42.4%)</td>
<td>0.73 (0.55-0.97)</td>
<td>P=0.025</td>
</tr>
</tbody>
</table>

Nordlinger B et al, Proc ASCO 2007
Progression-free survival in eligible patients

HR = 0.77; CI: 0.60-1.00, p = 0.041

Periop CT

28.1%

36.2%

At 3 years

+8.1%

Nordlinger B et al, Proc ASCO 2007
# Cytotoxic chemotherapy for metastatic CRC

<table>
<thead>
<tr>
<th>Survival</th>
<th>Med (mo)</th>
<th>1 yr (%)</th>
<th>2 yr (%)</th>
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<tbody>
<tr>
<td>Best Supp. Care</td>
<td>6</td>
<td>&lt; 30</td>
<td>&lt; 10</td>
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<tr>
<td>5-FU + FA</td>
<td>11-12</td>
<td>45</td>
<td>20-30</td>
</tr>
<tr>
<td>- Capecitabine</td>
<td>12</td>
<td>50</td>
<td>20-30</td>
</tr>
<tr>
<td>- Irinotecan</td>
<td>18</td>
<td>60-70</td>
<td>30-40</td>
</tr>
<tr>
<td>- Oxaliplatin</td>
<td>18</td>
<td>60-70</td>
<td>30-40</td>
</tr>
</tbody>
</table>
The issues that face us to achieve a continuum of care

1st line chemo  2nd line chemo  3rd line chemo

How to start?

At progression change chemo, biologic or both?

Independent sequences?

1st biologic  2nd biologic

Van Cutsem E. Editorial J Clin Oncol. 2006
Sistin Chape: Universal Judgement of Michelangelo

The emerging Integrated Circuit of the Cell
J. FOLKMAN: 1971
The Angiogenic Switch and Antiangiogenic Therapy

- Somatic Mutation
- Small Avascular Tumor
- Tumor Secretion of Proangiogenic Factors Stimulates Angiogenesis
- Rapid Tumor Growth and Metastasis
- Angiogenic Inhibitors May Reverse this Process
Tumour vasculature resulting from VEGF-mediated angiogenesis is abnormal

Normal blood vessels

- Maturation/stabilisation factors present
- Less dependent on cell survival factors
- Basal integrin expression
- Less permeable
- Supporting cells present

Tumour blood vessels

- Growth and survival factors (e.g., VEGF) present
- Preferential expression of integrins $v_3$, $v_5$, and $\alpha_\beta_1$
- Leaky
- Fewer supporting cells

Jain, Semin Oncol 2002;29 (Suppl. 16):3–9; Carmeliet, Nat Med 2003;9:653–60; Lee et al., J Biol Chem 2003;278:5277–84
**Normal and Tumor Vasculature**

**Normal Blood Vessels**
- Maturation factors present
- Minimally dependent on cell survival factors
- Less permeable
- Supporting pericytes present
- Reduced integrin expression

**Tumor Blood Vessels**
- Growth and survival factors (e.g., VEGF) present
- Leaky
- Fewer pericytes
- Preferential expression of $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_5\beta_1$ integrins

Tumor Vasculature is Abnormal

Normal colon

Nearby colorectal cancer

Tumor vasculature is dilated, highly chaotic, and tortuous, with a lack of hierarchical vessel arrangement

Konerding et al; Microenvironment of Human Tumors 2002
Anti-VEGF antibody ‘normalises’ the tumour vasculature

Anti-VEGF

Reduces
interstitial fluid pressure
vessel density

Increases
drug delivery

Agents targeting the VEGF pathway

- Antibodies inhibiting VEGF receptors (e.g. bevacizumab)
- Soluble VEGF receptors (VEGF-TRAP)
- Small-molecules inhibiting VEGF receptors (TKIs) (e.g. PTK-787)
- Ribozymes (Angiozyme)

VEGF and VEGF receptors enhance migration, permeability, DNA synthesis, and survival. They also induce angiogenesis and lymphangiogenesis.
Clinical Results in Metastatic Colorectal Cancer

- **Bevacizumab** in combination with chemotherapy in metastatic CRC
  - pivotal trial: IFL: increased activity in first line
  - 5-FU/FA monotherapy: increased activity in first line
  - FOLFOX: increased activity in second line
  - Oxaliplatin based: increased activity in first line
  - Cetuximab +/- irinotecan: high activity in irinotecan refractory CRC
  - Bolus 5-FU/FA plus bevacizumab: not active in irinotecan and oxaliplatin refractory CRC
Superior PFS + OS with 1st line IFL + bevacizumab vs IFL

- Median progression-free survival:
  - IFL + bevacizumab: 6.2 months
  - IFL + placebo: 10.6 months
  - HR = 0.54, p < 0.0001

- Median survival:
  - IFL + bevacizumab: 15.6 months
  - IFL + placebo: 20.3 months
  - HR = 0.66, p < 0.001

Bevacizumab: Safety Overview

- Bevacizumab does not increase chemotherapy related toxicities.

- Bevacizumab has specific side effects:
  - Hypertension
  - Proteinuria
  - Thromboembolic events: arterial
  - Bleeding: minor mucosal (epistaxis) and major hemorrhage (non small cell lung cancer)
  - Gastrointestinal perforation
  - Wound healing/postoperative bleeding

Hurwitz H et al. NEJM 2004;350:2335–42
Arterial thromboembolic events*

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy alone</th>
<th>bevacizumab plus chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial TE events</td>
<td>2.0% (15/741)</td>
<td>4.5% (45/1004)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.4% (3/741)</td>
<td>0.8% (8/1004)</td>
</tr>
</tbody>
</table>

- Risk factors for arterial thromboembolic events included
  - history of prior arterial thromboembolic events such as stroke or heart attack
  - age of 65 years or older

- Arterial events included in analysis
  - CVA (stroke), transient ischemic attack, subarachnoid hemorrhage
  - myocardial infarction, angina (unstable angina), arterial thrombosis and other arterial thromboembolic events

*Pooled analysis of five randomised trials
EGFR pathway inhibition

Tabernero J et al 2003
Anti-EGF Receptor Therapies

**Monoclonal antibodies**
(cetuximab, panitumumab, matuzumab, ...)

**Tyrosine kinase inhibitors**
(gefitinib, erlotinib, CI-1033, EKB-569, ...)

Signal Transduction
Cetuximab +/- irinotecan in irinotecan refractory CRC: Response Ratio

Cetuximab + irinotecan (n=218)
- Response Rate: 23% (18-29%)
- Disease Control (CR+PR+SD): 56% (49-62%)

Cetuximab (n=111)
- Response Rate: 11% (6-18%)
- Disease Control (CR+PR+SD): 32% (24-42%)

* p=0.0074; ** p<0.001; [] = 95% CI

Cunningham D … Van Cutsem E. N Engl J Med 2004
Panitumumab in mCRC: phase 3 trial

**Randomize 1:1**

- Panitumumab 6.0 mg/kg Q2W + BSC → PD → Follow-up
- BSC → PD → Follow-up

**Optional Panitumumab Crossover Study**

**Key inclusion:**
- Disease progression on CT scan after fluoropyrimidine, irinotecan and oxaliplatin
- EGFr membrane staining on ≥ 1% tumor cells

**Stratification:**
- ECOG score: 0-1 vs. 2
- Geographic region

Progression-Free Survival

Hazard ratio = 0.54 (95% CI: 0.44, 0.66)
Stratified log-rank test
$p < 0.000000001$

Kaplan-Meier Progression-Free Survival Rates at Prespecified Time Points

Panitumumab (N=231) vs. BSC (N=232)

Wk 8: 49% vs. 30%
Wk 12: 30% vs. 35%
Wk 16: 26% vs. 14%
Wk 24: 18% vs. 9%
Wk 32: 10% vs. 5%
Wk 40: 4% vs. 1%
Wk 48: 1% vs. 1%

Patients at risk:
- Panitumumab: Wk 8 (118), Wk 12 (76), Wk 16 (49), Wk 24 (31), Wk 32 (13), Wk 40 (5), Wk 48 (1)
- BSC: Wk 8 (75), Wk 12 (31), Wk 16 (17), Wk 24 (7), Wk 32 (3), Wk 40 (1), Wk 48 (1)

Primary Analysis, All Randomized Analysis Set, Central Radiology

**EGFR-inhibitor induced skin reactions**

**Description of severe cases**

**Acne-like rash**
- Post inflammatory effects
  - dry skin
  - pruritus
  - fissura
  - paronychia

**THERAPY SUGGESTIONS**

- Topical anti-acne creams (drying effect)
- Pulse dye laser
- Emollients
- Hydrocolloid dressing
  - or
  - Propylene glycol +/- acetylsalicyl
- Anti-septic soaks
  - Silver nitrate (pyogenic granuloma)

+/− tetracyclines
+/− antihistamines

S Segaert & E Van Cutsem, Ann Oncology 2005
Correlation of rash and survival after treatment with cetuximab

Survival (months)


No reaction Grade 1 Grade 2 Grade 3

CRYSSTAL trial:
Study design

**Stratification factors:**
- Regions
- ECOG PS

**Populations**
- Randomized patients n=1217
- Safety population n=1202
- ITT population: n=1198

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**Cetuximab + FOLFIRI**

Cetuximab IV 400 mg/m² on day 1, then 250 mg/m² weekly
+ irinotecan (180 mg/m²)
+ 5-FU (400 mg/m² bolus + 2400 mg/m² as 46-hr continuous infusion)
+ FA every 2 weeks

---

**FOLFIRI**

irinotecan (180 mg/m²)
+ 5-FU 400 mg/m² bolus + 2400 mg/m² as 46-hr continuous infusion
+ FA every 2 weeks

---

Van Cutsem E et al, Proc ASCO 2007
CRYSTAL trial: Primary endpoint PFS met
ITT population independent review

Progression-free survival time (months)

PFS estimate

HR = 0.851; 95% CI = [0.726-0.998]
Stratified log-rank p-value = 0.0479

8.9 mo

1-year PFS rate
23% vs 34%

Van Cutsem E et al, Proc ASCO 2007
CRYSTAL trial: Surgery with curative intent

- Surgery with curative intent
  - ITT population (pre-planned)
  - FOLFIRI alone: 2.5%
  - Cetuximab + FOLFIRI: 6%
  - No residual tumor after resection
  - p=0.0034*
  - Odds ratio 3.0
  - [95% CI: 1.4 - 6.5]

- Liver metastases only population (exploratory)
  - No residual tumor in patients with liver metastases
  - FOLFIRI alone: 4.5%
  - Cetuximab + FOLFIRI: 9.8%

*CMH test

Van Cutsem E et al, Proc ASCO 2007
Challenges with EGFR inhibitors in CRC: determining the best treatment strategies

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Chemorefractory patients</td>
<td>Proven activity</td>
</tr>
<tr>
<td>First-line treatment</td>
<td>Promising activity in phase 2 studies</td>
</tr>
<tr>
<td>mCRC: liver metastases</td>
<td>Phase 2 studies show high resection rate of initially unresectable metastases</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>Studies ongoing / planned</td>
</tr>
<tr>
<td>Combination with radiotherapy in rectal cancer</td>
<td>Phase 1–2 studies ongoing / planned</td>
</tr>
</tbody>
</table>
Tailored Treatment
Can we find parameters to predict response to EGFR inhibitors?
Treatment Algorithm for Metastatic CRC

No prior adjuvant therapy

FOLFOX / Xelox + bevacizumab¹

FOLFIRI

FOLFIRI + bevacizumab¹

FOLFOX / Xelox

Irinotecan + cetuximab

Capecitabine (5-FU/FA) ± bevacizumab¹

FOLFOX / Xelox

FOLFIRI

Irinotecan + cetuximab

¹ if no cardiovascular contraindications
Individualisation of treatment in metastatic CRC with increasing number of active agents

Patient

Pharmacogenetic: cytotoxic metabolism

Tumor

Novel targets: EGFR, VEGF, Cox-2, IGF...

TS
TP

P53

MSI

Topo I

Individual personal treatment
Is progress made in chemotherapy and other treatments options of colon cancer? Yes

The dream ....

The reality ...