The management of chemorefractory metastatic CRC

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Disclosures

- participation to advisory boards for Array, Astrazeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex

- research grants from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to institution.
A classical case of mCRC in 2019

CONTINUUM OF CARE

OS 30 months

Locoregional therapy: toolbox: surgery, HIPEC, RFA, Radioembolisation,…

1991: OS 6 months
A “snapshot” of third and fourth line treatment for mCRC in 2014: real world data for mCRC

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

Active treatment in later lines primarily reserved for “fit” (ECOG 0-1) patients

# Table 4: Drivers for first-line treatment

many are also valid in later line

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Patient characteristics</th>
<th>Treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour burden</td>
<td>Age</td>
<td>Toxicity profile</td>
</tr>
<tr>
<td>Tumour localisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour biology</td>
<td>Performance status</td>
<td>Flexibility of treatment administration</td>
</tr>
<tr>
<td>RAS mutation status</td>
<td>Organ function</td>
<td>Socio-economic factors</td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td>Comorbidities, patient attitude, expectation and preference</td>
<td>Quality of life</td>
</tr>
</tbody>
</table>

**Patient and treatment characteristics become even more relevant in later lines**

## 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><strong>Adjuvant</strong></td>
<td>&quot;Cure&quot;</td>
</tr>
<tr>
<td></td>
<td>Reduce risk of recurrence</td>
</tr>
<tr>
<td></td>
<td>Maximal tumor response</td>
</tr>
<tr>
<td></td>
<td>Enabling local ablation and/or long duration of low/no tumor burden</td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td>Durable disease control</td>
</tr>
<tr>
<td></td>
<td>Tumor response if needed</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td>Durable disease control</td>
</tr>
<tr>
<td></td>
<td>Maintenance of QOL and PS</td>
</tr>
<tr>
<td><strong>3rd line</strong></td>
<td>Disease control</td>
</tr>
<tr>
<td></td>
<td>and maintenance of QOL; palliation</td>
</tr>
<tr>
<td><strong>Subsequent lines</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)

<table>
<thead>
<tr>
<th>Category</th>
<th>Fit patients&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disease control (control of progression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment goal</td>
<td>Cytoreduction (tumour shrinkage)</td>
<td>Cytoreduction (tumour shrinkage)</td>
</tr>
<tr>
<td>Molecular profile</td>
<td>RAS wt</td>
<td>RAS mt</td>
</tr>
<tr>
<td>Third line</td>
<td>Preferred choice(s)</td>
<td>Regorafenib or trifluridine/tipiracil</td>
</tr>
<tr>
<td>Second choice</td>
<td>EGFR antibody monotherapy</td>
<td>EGFR antibody monotherapy</td>
</tr>
<tr>
<td>Third choice</td>
<td>Regorafenib or trifluridine/tipiracil</td>
<td>Regorafenib or trifluridine/tipiracil</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excluding those with oligometastatic disease. 

<sup>b</sup> Fit patients are defined as patients with good performance status (ECOG 0-1), adequate organ function, no previous prior treatment, and no extra-splanchnic metastases or metastases in the brain/leptomeninges or specific head and neck sites.
Regorafenib inhibits VEGFR1, VEGFR2, VEGFR3 AND other Pathways, including RET, KIT, PDGFRα, PDGFRβ, FGFR1, FGFR2, TIE2, BRAF, BRAFv600E.

FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TIE2, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2; VEGF, vascular endothelial growth factor.

Trifluridine/tipiracil
mechanism of action

F₃dThd (FTD)
Thymidine-based nucleoside analogue

Inhibition of tumor growth
DNA dysfunction
FTD incorporation into DNA
Trifluridine/tipiracil ≠ 5-FU rechallenge

dTMP, deoxythymidine diphosphate; dUMP, deoxyuridine diphosphate; dUTP, deoxyuridine triphosphate; FdUDP, fluorodeoxyuridine diphosphate; FdUMP, fluorodeoxyuridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; 5-FU, 5-fluorouridine; FUdR, fluorouridine; FUDP, fluorouridine diphosphate; FUMP, fluorouridine monophosphate; FUTP, fluorouridine triphosphate; FUR, fluorouridine; MoA, mechanism of action; TS, thymidylate synthase; UFT, tegafur-uracil.

Regorafenib phase III studies


**CORRECT**

Patients with mCRC who had progressed after standard therapy (N = 760)¹

- **Regorafenib + BSC**
- **Placebo + BSC**

**CONCUR**

Asian patients with mCRC who had progressed after standard therapy (N = 204)²

- **Regorafenib + BSC**
- **Placebo + BSC**

**CONSIGN**

Patients with mCRC who had progressed after standard therapy (N = 2872)³

- **Regorafenib**

**Primary endpoint**

<table>
<thead>
<tr>
<th>Regorafenib (n = 505)</th>
<th>Placebo (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>5.0</td>
</tr>
<tr>
<td>HR = 0.77; 95% CI (0.64–0.94)</td>
<td>P = .052</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regorafenib (n = 136)</th>
<th>Placebo (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.8</td>
<td>6.3</td>
</tr>
<tr>
<td>HR = 0.55; 95% CI (0.40–0.77)</td>
<td>P = .00016</td>
</tr>
</tbody>
</table>

**Safety**

Trifluridine/tipiracil randomised Phase II/III clinical development program

**JAPICCTI-090880**
- Phase 2 N=169
- mCRC patients refractory to ≥2 prior regimens
  - ECOG PS score 0–2
  - Adequate bone marrow and organ function
- R 2:1
- Trifluridine/tipiracil BID PO + BSC (N=112)
- Placebo + BSC (N=57)

**RE COURSE**
- Phase 3 (N=800)
- mCRC patients refractory to ≥2 prior regimens
  - ECOG PS score ≤1
  - Adequate bone marrow and organ function
  - Known KRAS status
- R 2:1
- Trifluridine/tipiracil BID PO + BSC (N=534)
- Placebo + BSC (N=266)

**TERRA**
- Phase 3 (N=406)
- East Asian mCRC patients refractory to ≥2 prior regimens
  - ECOG PS score ≤1
- R 2:1
- Trifluridine/tipiracil BID PO + BSC (N=271)
- Placebo + BSC (N=135)

**PRECONNECT**
- Phase 3 (N=300)
- Ongoing, planned for 1000 pts.
- mCRC patients ECOG Performance Status (PS) <2 and were refractory/intolerant to available therapies
- R 2:1
- Trifluridine/tipiracil BID PO + BSC (N=300)

*East Asian specific study
Trifluridine/tipiracil prescribing information is available at this meeting
BID, twice daily; BSC, best supportive care; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; PO, orally; q4w, every 4 weeks; RR, response rate; TTF, time to treatment failure
Regorafenib and trifluridine/tipiracil in refractory mCRC:

CORRECT: regorafenib

RECOURSE: trifluridine/tipiracil

Optimal Sequence in chemorefractory patients?

Regorafenib ➔ Trifluridine/tipiracil

or

Trifluridine/tipiracil ➔ Regorafenib

Considerations:
➢ Different safety pattern
  ✓ Trifluridine/tipiracil: more favourable safety patterns, but what if compared to lower starting dose of regorafenib
  ✓ No predictive markers for benefit, nor clearly differential patient characteristics
Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study


Dose escalation arm

Standard dose group
ReDOS study
QOL in ReDOS study

Bekaii-Saab T et al; The Lancet Oncology 2019: DOI: (10.1016/S1470-2045(19)30272-4)
Primary endpoint:
- **Safety**: % of patients having G3/G4 AEs during the entire course of the treatment

Secondary endpoints:
- OS
- PFS
- % of Patients starting C3 on each arm
- Dose intensity
- DCR

Argiles G et al, ESMO GI/WCGIC 2019
Primary Endpoint: Pts having G3/G4 AEs during treatment course

Threshold to reach positivity in the 2 experimental arms

Argiles G et al, ESMO GI/WCGIC 2019
Future: combination studies

- **Appealing combinations:**
  - Interesting phase 2 study: trifluridine/tipiracil + bevacizumab
  - Very interesting study, but preliminary data in Asian patients: regorafenib + nivolumab

Pfeiffer P et al, ESMO GI/WCGIC 2019; Hara H et al, ESMO GI/WCGIC 2019
Conclusions:

These findings support the introduction of an approved agent such as trifluridine/tipiracil or regorafenib beyond the second line before any rechallenge in patients with mCRC who have failed second-line treatment.
Figure 1: toolbox of ablative treatments

- Local treatments
  - Thermal devices
    - Radiofrequency ablation or cryoablation
    - Microwave ablation
  - Non-thermal devices
    - Brachytherapy electroporation
    - External Body radiotherapy with high-precision RT
- Locoregional treatments
  - Embolic devices
    - Radioembolisation SIRT
    - Chemoembolisation TACE/Beads
  - Local chemotherapy

Online Ann Oncol, July 2016
Integration of Y-90 resin radioembolisation into the mCRC treatment algorithm

Surgical resection

is tumour resectable?

Liver-only or liver-predominant mCRC

1\textsuperscript{st}-line CT + biologic

2\textsuperscript{nd}-line CT + biologic

Chemo-refractory

SIRT Y-90 resin

Published data of series and one randomized controlled trial
Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy

Alain Hendiissi, Marc Van den Eynde, Marc Peeters, Geert Maleux, Bieke Lambert, Jaakke Vanmoote, Katrien De Keukeleire, Chris Versype, Luc Dekeyne, Eric Van Cutsem, Philippe Delatte, Thierry Deaunois, Nicola Personeni, Marianne Paesmans, Jean-Luc Van Laethem, and Patrick Flamen

Fig 1. Study design. mCRC, metastatic colorectal cancer; 5FU, fluorouracil; IV, intravenous; D, day; q3w, every 3 weeks; ⁹⁰Y, yttrium-90.
Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy

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Fig 2. Time to progression in the liver (the primary end point) and at any site, taking all progressions into account. 5FU, fluorouracil; HR, hazard ratio.
Radioembolisation (1)

Radioembolisation (selective internal radiation therapy [SIRT]) typically involves a single delivery of yttrium-90 connected to either resin or glass particles into the hepatic artery with the therapeutic effect essentially limited to irradiation.

For patients with liver-limited metastases failing the available chemotherapeutic options, radioembolisation with yttrium-90 resin microspheres can prolong the time to tumour progression in the liver, based on a small randomised phase III study.

Van Cutsem E, Cervantes A… Arnold, ESMO Consensus, Ann Onc 2016
ESMO consensus guideline: Third-line choice

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

Ann Oncol, July 2016
Molecular subtypes in CRC

Can predict response to therapy

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

Trastuzumab + lapatinib

Larotrectinib

Sartore-Bianchi et al, Lancet Oncology 2016; Drilon et al, NEJM 2018
Genomic markers

- RAS mut +/- PIK3CA/PTEN mut: 45%
- PIK3CA/PTEN mut: 8%
- PIK3CA/PTEN: 26%
- Kinase inh: 2%
- Gene fusion: 1%
- MET inh: 2%
- MET ampl: 1%
- HER2 ampl: 2%
- POLE mut: 2%
- MSI: 2%
- MSI + other: 2%
- BRAF non-V600: 8%
- BRAF V600E: 8%
- BRF inh + anti-EGFR +/- MEK inh: 8%

Dienstmann et al, ASCO Ed Book 2018