Systemic and targeted therapy in CRC - locally advanced and metastatic

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• Introduction
• Adjuvant
• Neoadjuvant
• Metastatic
• 43/ M, diagnosed to have bowel obstruction, after evaluation, underwent a emergency right hemicolecctiony and
• post op HPE – adenocarcinoma, pT3 N0,
• no. of nodes 0/6 nodes negative
Colon cancer

History

• Earliest clinical trials of adjuvant chemotherapy in colon cancer were conducted in the 1950s.

• In 1986, large meta-analysis of controlled randomized trials of adjuvant therapy.

• Nonsignificant trend toward an OS benefit, with a mortality OR of 0.83 in favor of therapy (95% CI = 0.70 to 0.98).
Adjuvant 5 FU

- **NSABP C 01 [1988]**
- Between 1977 and 1983,
- 1,166 patients with colon ca
- Randomized into the Observation, MOF and BCG
- MOF had a significantly **better DFS and OS** than the control group (P = .02 and P = .05, respectively)

Survival Results of NSABP C-07

Patients with stage II or III carcinoma of the colon stratified by number of positive lymph nodes

- FULV
  - 5-FU 500 m² IV bolus weekly x 6; LV 500 mg/m² IV weekly x 6, each 8-week cycle x 3
  - (N = 1,209)

- FLOX
  - FULV + oxaliplatin 85 mg/m² IV on Weeks 1, 3, and 5 of each 8-week cycle x 3
  - (N = 1,200)

- Primary endpoint: DFS

Eloxatin combinations: NSABP C-07 3-year DFS

21% risk reduction for FLOX

3-year DFS

- **FLOX**: 76.5%
- **FU/LV**: 71.6%

Hazard ratio: 0.79 (95% CI: 0.67–0.93)

p<0.004

P. Kuebler et al. JCO, June 2007, 2198-2204
X-Act Trial Design

Chemotherapy-naive patients with operable stage III colorectal cancer and resection ≤ 8 weeks

(N = 1987)

Bolus 5-FU/Leucovorin
5-FU 425 mg/m² + LV 20 mg/m² on Days 1-5, every 28 days (n = 983)

Median follow-up: 6.8 years

Capecitabine
1250 mg/m² twice daily on Days 1-14, every 21 days (n = 1004)

X-ACT Trial Key Findings

- Trend toward superior 5-year DFS and OS with capecitabine treatment
  - DFS: 60.8% vs 56.7% \((P = .0682)\)
  - OS: 68.4% vs 71.4% \((P = .06)\)

- Hand-foot syndrome common toxicity with capecitabine
  - Associated with higher DFS and OS
  - Possible clinical marker for optimal capecitabine exposure

Multicenter, randomized trial
1,886 patients.
57 months of follow-up,
RR 31.3% (XELOX) Vs 37.5% FU/FA
The 5-year OS for XELOX and FU/FA were 77.6% and 74.2%, respectively.
Addition of oxaliplatin to capecitabine improves DFS in patients with stage III colon cancer. XELOX is an additional adjuvant treatment option for these patients.
MOSAIC Phase III Trial

Schema

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
<th>FOLFOX4 X 12 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1100</td>
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</table>

LV5FU2

- 40% Stage II
- 60% Stage III

de Gramont A et al. Proc ASCO. 2003;23 (abstr 1015).
After a median follow-up of 9.5 years,

10-year OS among all 2,246 patients was 71.7% (FOLFOX4 group) vs 67.1% (5-FU/leucovorin group) (hazard ratio [HR] = 0.85, \( P = .043 \)),

78.4% vs 79.5% in those with stage II disease (HR = 1.00, \( P = .980 \)),

67.1% vs 59.0% in those with stage III disease (HR = 0.80, \( P = .016 \)).
• CAPEOX Vs FOLFOX
Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer

No significant difference in 3yr DFS and 3yr OS

Dimitrios Pectasides, *BMC Cancer* 2015 **15**:384
• 3 months or 6 months of adjuvant?
• Stage III - Low risk or high risk?
LBA1: Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration – Shi Q, et al

Key results

**Primary DFS analysis (mITT)**

![Graph showing DFS analysis](image)

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-year DFS</th>
</tr>
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<tbody>
<tr>
<td>3 months</td>
<td>74.6%</td>
</tr>
<tr>
<td>6 months</td>
<td>75.5%</td>
</tr>
</tbody>
</table>

3-year DFS difference: -0.9%, (95%CI -2.4, 0.6)

DFS HR 1.07, (95%CI 1.00, 1.15)

<table>
<thead>
<tr>
<th>Years from randomisation</th>
<th>No. at risk</th>
<th>No.</th>
<th>3-year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6424</td>
<td>6410</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5446</td>
<td>5530</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4464</td>
<td>4477</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3000</td>
<td>3065</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1609</td>
<td>1679</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>826</td>
<td>873</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>321</td>
<td>334</td>
<td></td>
</tr>
</tbody>
</table>

IDEA Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Risk group | Recommended duration of adjuvant therapy
---|---
T1-3 N1 (~60% of stage III) | 3 months
T4 and/or N2 (Or other high-risk factors) | 6 months

Duration of therapy determined by:
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)
• Timing of adjuvant chemotherapy?
• Each 4 week delay in chemotherapy after surgery resulted in 14% decrease in OS [Biagi JJ et al, JAMA 2011].
• > 6 weeks delay in adjuvant chemo resulted in reduced survival [Sun et al, Dis colon rectum 2016]
• Neoadjuvant?
Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial.

Locally advanced (T4 or T3 with extramural depth ≥5 mm) adenocarcinoma of the colon, with staging determined preoperatively by either spiral or multidetector CT and for whom a 24-week course of oxaliplatin and fluoropyrimidine-based adjuvant chemotherapy would be judged appropriate.

Primary outcome measures of the pilot phase were feasibility, safety, and tolerance of preoperative therapy, and accuracy of radiological staging.
## Pathologic Stage

<table>
<thead>
<tr>
<th>Tis; T1, N0, M0; T2, N0, M0; T3-4, N0, M0&lt;sup&gt;l&lt;/sup&gt; (MSI-H or dMMR)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3, N0, M0&lt;sup&gt;l,m&lt;/sup&gt; (MSS or pMMR and no high-risk features)</td>
<td>Observation or Consider capecitabine&lt;sup&gt;o&lt;/sup&gt; or 5-FU/leucovorin&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>or Capecitabine&lt;sup&gt;0,p&lt;/sup&gt; or 5-FU/leucovorin&lt;sup&gt;0,p&lt;/sup&gt; or FOLFOX&lt;sup&gt;0,p,q,r&lt;/sup&gt; or CAPEOX&lt;sup&gt;0,p,q,r&lt;/sup&gt; or Observation</td>
<td></td>
</tr>
<tr>
<td>T3, N0, M0 at high risk for systemic recurrence&lt;sup&gt;m,p&lt;/sup&gt; or T4, N0, M0 (MSS or pMMR)</td>
<td>Preferred: CAPEOX (3 mo)&lt;sup&gt;0,r&lt;/sup&gt; or FOLFOX (3–6 mo)&lt;sup&gt;0,r&lt;/sup&gt; (category 1 for 6 mo) or Other options include: Capecitabine (6 mo)&lt;sup&gt;0&lt;/sup&gt; or 5-FU (6 mo)&lt;sup&gt;0&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1-3, N1 (low-risk stage III)</td>
<td>Preferred: CAPEOX (3–6 mo)&lt;sup&gt;0,p,r&lt;/sup&gt; (category 1 for 6 mo) or FOLFOX (6 mo)&lt;sup&gt;0,p,r&lt;/sup&gt; (category 1) or Other options include: Capecitabine (6 mo)&lt;sup&gt;0,p&lt;/sup&gt; or 5-FU (6 mo)&lt;sup&gt;0,p&lt;/sup&gt;</td>
</tr>
<tr>
<td>T4, N1-2; T Any, N2 (high-risk stage III)</td>
<td></td>
</tr>
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</table>

<sup>b</sup>See Principles of Imaging (COL-A).
<sup>b</sup>See Principles of Pathologic Review (COL-B).
<sup>b</sup>See Principles of Risk Assessment for Stage II Disease (COL-F).

<sup>m</sup>High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

<sup>p</sup>There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

<sup>o</sup>See Principles of Adjuvant Therapy (COL-G).

<sup>q</sup>Consider RT for T4 with penetration to a fixed structure.

<sup>q</sup>See Principles of Radiation Therapy (COL-E).

<sup>q</sup>A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tourmigand C, et al. J Clin Oncol 2012; 30:3353–3360.

<sup>q</sup>A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

<sup>q</sup>In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs. 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 vs. 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs. 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX). Shi Q, et al. J Clin Oncol 2017;35 (suppl):LBA1.

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**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Rectum
Background

• Use of adjuvant radiation therapy is based on the substantial incidence of local-regional failure with surgical therapy alone.

• Local failure rates with surgery alone for up to 50% in patients with T3-4 or N+ disease\textsuperscript{1,2}

• Local-regional failure is decreased by the use of radiation therapy and is further decreased by the use of concurrent 5-FU-based chemotherapy

• Use of adjuvant chemotherapy has centered on the use of 5-FU chemotherapy.
• Initial trials – bolus 5 FU during weeks 1 and 5 of the RT.
• NCCTG- use of long-term continuous infusion 5-Fu¹.

Neoadjuvant Vs Adjuvant?
Neoadjuvant Chemoradiotherapy for Rectal Cancer: CAO/ARO/AIO-94

Randomize

Control Arm

Surgery

Primary endpoint: DFS

Sauer et al. NEJM, 2004:
## German Trial – CAO/ARO/AIO-94

### 800+ pts – T3/T4, N+ rectal cancer (CI 5-FU + 50.4 Gy)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Op</th>
<th>Post-Op</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-yr Local Recurrence</strong></td>
<td>6%</td>
<td>12%</td>
<td>p=.02</td>
</tr>
<tr>
<td><strong>5-yr Distant Relapse</strong></td>
<td>35%</td>
<td>39%</td>
<td>p=.52</td>
</tr>
<tr>
<td><strong>5-yr DFS</strong></td>
<td>59%</td>
<td>55%</td>
<td>p=.23</td>
</tr>
<tr>
<td><strong>5-yr Overall Survival</strong></td>
<td>78%</td>
<td>73%</td>
<td>p=.38</td>
</tr>
<tr>
<td><strong>Acute Grade 3/4 Tox</strong></td>
<td>30%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Anastomotic Stenosis</strong></td>
<td>2.7%</td>
<td>8.5%</td>
<td>p=.001</td>
</tr>
<tr>
<td><strong>Sphincter preserved</strong></td>
<td>39% (pCR 8%)</td>
<td>19%</td>
<td>p=.004</td>
</tr>
</tbody>
</table>
The 10-year cumulative incidence of local relapse was 7.1% and 10.1% in the pre- and postoperative arms, respectively (P = .048).

No significant differences were detected for 10-year cumulative incidence of distant metastases (29.8% and 29.6%; P = 0.9) and disease-free survival

Study objective
- To determine whether perioperative mFOLFOX6 CT improves DFS in locally advanced rectal cancer

Key patient inclusion criteria
- Rectal cancer ≤12 cm from the anal verge
- T3/4 and/or N+; R0/1
- Staged by MRI
- ECOG PS 0–1 (n=495)

Primary endpoint
- DFS

Secondary endpoints
- pCR, R0 resection, sphincter preservation, local recurrence, OS, QoL, toxicity (follow-up ongoing for recurrence/OS)

Leucovorin 0.4 mg/m² D1, 5FU 0.4 mg/m² bolus IV then 2.4 mg/m² continuous IV 48 h; †As above but with initial oxaliplatin 85 mg/m² 2 h IV infusion. ‡Postoperative radiation permitted (physician’s decision)


### Key results

<table>
<thead>
<tr>
<th></th>
<th>5FU + RT (n=133)</th>
<th>mFOLFOX6 + RT (n=143)</th>
<th>mFOLFOX6 alone (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>120 (90.2)</td>
<td>128 (89.5)</td>
<td>132 (91.2)</td>
</tr>
<tr>
<td>pCR*</td>
<td>19 (14.3)</td>
<td>40 (28.0)</td>
<td>9 (6.1)</td>
</tr>
<tr>
<td>Anastomotic leakage†</td>
<td>28 (21.1)</td>
<td>26 (18.2)</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Infection of incision‡</td>
<td>30 (22.6)</td>
<td>24 (16.8)</td>
<td>9 (6.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3/4 AEs, n (%)</th>
<th>5FU + RT (n=155)</th>
<th>mFOLFOX6 + RT (n=158)</th>
<th>mFOLFOX6 alone (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>19 (12.9)</td>
<td>29 (19.0)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4 (2.6)</td>
<td>9 (5.7)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (7.7)</td>
<td>23 (14.5)</td>
<td>12 (7.3)</td>
</tr>
<tr>
<td>Radiodermatitis</td>
<td>22 (14.1)</td>
<td>32 (20.3)</td>
<td>-</td>
</tr>
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### Conclusions

- mFOLFOX + RT as a neoadjuvant treatment had a higher pCR rate, increased response and slightly increased toxicity vs. 5FU in patients with locally advanced rectal cancer
- mFOLFOX alone had a similar R0 resection rate, similar good response rate and fewer surgical complications vs. 5FU
- mFOLFOX6 + RT may replace 5FU as a standard treatment in this setting
- ~35% of the patients may not need RT to create a good excision plane for surgery

*p=0.001; †p=0.02; ‡p=0.009

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Inclusion Criteria</th>
<th>Chemotherapy</th>
<th>pCR</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uehara et al (2013)[51]</td>
<td>32</td>
<td>MRI-defined poor risk</td>
<td>Oxaliplatin + capecitabine + bevacizumab × 12 wks</td>
<td>13%</td>
<td>R0 resection rate = 90% Postoperative complication rate = 43%</td>
</tr>
<tr>
<td>Hasegawa et al (2014)[48]</td>
<td>25</td>
<td>T4 or lymph node-positive</td>
<td>XELOX (4 cycles) plus bevacizumab (3 cycles)</td>
<td>4%</td>
<td>R0 resection rate = 92% Postoperative complication rate = 26%</td>
</tr>
<tr>
<td>Ishii et al (2010)[49]</td>
<td>26</td>
<td>T3 or T4 and N0–2</td>
<td>IFL (2 cycles)</td>
<td>3.8%</td>
<td>5-yr DFS = 74% 5-yr OS = 84% LR = 11%</td>
</tr>
<tr>
<td>Schrag et al (2014)[50]</td>
<td>32</td>
<td>Clinical stages II to III</td>
<td>FOLFOX (6 cycles) + bevacizumab (cycles 1–4)</td>
<td>25%</td>
<td>R0 resection rate = 100% 4-yr LR = 0% 4-yr DFS = 84%</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; FOLFOX = leucovorin + fluorouracil + oxaliplatin; IFL = irinotecan + fluorouracil + leucovorin; LR = local recurrence; MRI = magnetic resonance imaging; OS = overall survival; pCR = pathologic complete response; XELOX = capecitabine + oxaliplatin.
NCCN Guidelines Version 1.2019
Rectal Cancer

CLINICAL STAGE
NEOADJUVANT THERAPY
- Chemo/RT
  - Capcitabine/long-course RT\(^{9}\) or infusional 5-FU/long-course RT\(^{9}\) (category 1 and preferred for both) or bolus 5-FU/leucovorin/long-course RT\(^{0,9}\)
  - or
  - Short-course RT\(^{9}\,\text{t}\) followed by 12–16 weeks of chemotherapy
    - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine

PRIMARY TREATMENT
- Involved CRM or bulky residual disease
- Restaging at 6 weeks post completion of RT
- Chemotherapy (12–16 weeks)
  - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine

ADJUVANT TREATMENT\(^{6,8}\) (6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)
- Transabdominal resection\(^{6}\)
  - Restaging\(^{6}\)
  - Resection contraindicated
  - Systemic therapy\(^{w}\)
    (See REC-F)

Surveillance (See REC-11)
- OBSERVE
- Transabdominal resection\(^{6,8}\)
  - Restaging\(^{6}\)
  - Resection contraindicated
  - Systemic therapy\(^{w}\)
    (See REC-F)

Notes:
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^{9}\) See Principles of Imaging (REC-A).
\(^{9,9}\) See Principles of Surgery (REC-C).
\(^{9}\) CRM measured at the closest distance of the tumor to the mesorectal fascia.

\(^{0}\) Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

\(^{9}\) Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capcitabine or infusional 5-FU.

\(^{9}\) See Principles of Adjuvant Therapy (REC-D).
\(^{9}\) See Principles of Radiation Therapy (REC-E).

\(^{1}\) Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.

\(^{2}\) In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance.

\(^{w}\) FOLFOXIRI is not recommended in this setting.
**NCCN Guidelines Version 1.2019**  
**Rectal Cancer**

**Pathologic Findings After Transanal Local Excision for T1, N0**

- **pT1, NX, without high-risk features**
  - Observe

- **pT1, NX with high-risk features or pT2, NX**
  - Chemo/RT
    - Capcitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT
  - Transabdominal resection (preferred for pT2 lesions)

**Adjuvant Treatment**

- **pT1-2, N0, M0**
  - Observe

- **pT3, N0, M0**
  - Infusional 5-FU/RT (preferred) or capecitabine/RT (preferred) or bolus 5-FU/leucovorin/RT followed by 5-FU/leucovorin (infusional preferred) or capecitabine or Observation

- **pT4, N0, M0 or pT1-4, N1-2**
  - Consider observation (if no evidence of disease)
  - Transabdominal resection (if evidence of disease)
  - Consider FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine

**Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in upper rectum. Willett CG, Badizadegan K, Anucikiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173.**

**FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine**

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

**RT 50.4 Gy + 5-FU**
1000 mg/m² days 1-5 + 29-33

**5-FU**
500 mg/m² d 1-5, q29
4 cycles (4 months)

Based on phase I/II trials:

**RT 50.4 Gy + 5-FU/OX**
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

**Note:** Chemo gap 3rd week of RT!

**mFOLFOX6**
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)
The use of adjuvant chemotherapy was associated with a significant reduction in the risk of disease relapse (hazard ratio [HR] for relapse 0.75, 95% CI 0.68-0.83) and death (HR for death 0.83, 95% CI 0.76-0.91).

A survival benefit for the addition of adjuvant chemotherapy after potentially curative resection of rectal cancer was shown in a 2012 meta-analysis of 21 trials.

Infusional versus bolus fluorouracil?

• Both bolus and infusional FU alone represent appropriate choices.

• PVI FU was associated with a significant reduction in distant metastases (31 Vs 40 %) and improvements in 4yr RFS as well as OS (70 Vs 60 %), but there was no difference in LR, higher risk of severe diarrhea.

• Int 0144 revealed no diff in 3yr DFS or OS or side effects except that the PVI FU arm had less hematologic toxicity
Capecitabine Vs 5 FU?

• Thymidine phosphorylase is present in higher concentrations in tumors (particularly colorectal cancers) than in normal tissue

• Higher tumor to plasma ratios of FU are achievable with capecitabine than with intravenous FU

• 5-yr OS in the capecitabine group was non-inferior to that in the fluorouracil group (76% vs 67%; \( p=0.0004 \)). [Hofheinz RD, Lancet Oncol. 2012]
• Postresection use of adjuvant chemotherapy based on the results in colon cancer.

• Use of FOLFOX is reasonable, albeit unproven, extrapolation from
Adenocarcinoma of rectum amenable to surgical resection located < 12 cm from anal verge

**STRATIFICATION**
- Gender
- Clinical Tumor Stage II or III
- Intent for Type of Surgery (sphincter saving; non-sphincter saving)

**RANDOMIZATION**
- No Oxaliplatin
- Oxaliplatin

**GROUPS**
1. **Group 1**
   - 5FU (CVI 225mg/m² 5d/week)
   - 4600cGy + 540-1080cGy

2. **Group 2**
   - 5FU (CVI 225mg/m² 5d/week) + Oxaliplatin 50 mg/m²/week X 5
   - 4600cGy + 540-1080cGy

3. **Group 3**
   - Capecitabine 825 mg/m² PO BID + 4600cGy + 540-1080cGy

4. **Group 4**
   - Capecitabine 825 mg/m² PO BID + Oxaliplatin 50 mg/m²/week X 5
   - 4600cGy + 540-1080cGy

**SURGERY**

1200 pts

***Capecitabine is 825 mg/m² bid for 5/7 (Rad days)***

Roh et al ASCO 2011
NSABP-R04 results

<table>
<thead>
<tr>
<th></th>
<th>5-FU (± Oxaliplatin)</th>
<th>Capecitabine (± Oxaliplatin)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate, (n=719, 707)</td>
<td>18.8%</td>
<td>22.2%</td>
<td>0.12</td>
</tr>
<tr>
<td>SSS, (n=727, 710)</td>
<td>61.2%</td>
<td>62.7%</td>
<td>0.59</td>
</tr>
<tr>
<td>SD, (n=188, 187)</td>
<td>20.7%</td>
<td>23.0%</td>
<td>0.62</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>(5-FU or Capecitabine) Oxaliplatin</th>
<th>(5-FU or Capecitabine) No Oxaliplatin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate, (n=578, 580)</td>
<td>20.9%</td>
<td>19.1%</td>
<td>0.46</td>
</tr>
<tr>
<td>SSS, (n=584, 582)</td>
<td>60.4%</td>
<td>63.6%</td>
<td>0.28</td>
</tr>
<tr>
<td>SD, (n=151, 152)</td>
<td>19.2%</td>
<td>23.0%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

• **Oxaliplatin** — Given the lack of benefit and the enhanced toxicity when oxaliplatin is added as a component of neoadjuvant concomitant chemoradiotherapy, it should not be used concurrently with RT in the adjuvant setting.
• Addition of irinotecan, but because of the overlapping toxicity of diarrhea with radiation therapy, 5-FU and irinotecan, this has not been heavily pursued\(^1\).

Metastatic disease

• Cure?
• Prolong overall survival and maintain quality of life (QOL) for as long as possible.
• For decades, fluorouracil (FU) was the sole active agent for advanced colorectal cancer (CRC).
The Luxury of So Many Options: How Do We Personalize Therapy?

- Patient X
- Patient Y
- Patient Z

- Oxaliplatin
- Irinotecan
- Bevacizumab
- 5-FU

- Oxaliplatin
- Bevacizumab
- Cetuximab

- Regorafenib
- Aflibercept
- Panitumumab

- TAS-102
- Ramucirumab
- BSC

- 5-FU
- Irinotecan

- Oxaliplatin
- Bevacizumab

- Cetuximab

- Capecitabine

- Oxaliplatin
- Bevacizumab
Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy

1. FOLFIRI ± cetuximab\(^1\)
2. FOLFOX4 ± panitumumab\(^2\)
3. FOLFOX/XELOX ± bevacizumab\(^3\)
4. FOLFOX ± bevacizumab\(^4\)
5. FOLFIRI ± panitumumab\(^5\)
6. FOLFIRI ± ramucirumab\(^6\)
7. CT ± continued bevacizumab\(^7\)
8. FOLFIRI ± aflibercept\(^8\)
9. Regorafenib vs placebo\(^9\)
10. TAS-102 vs placebo\(^10\)

\(^*\)KRAS WT subset; \(P = \text{significant.}\)
\(^†\)KRAS WT subset; \(P = \text{not significant.}\)

Median OS Improvement, Mos

---

References in slidenotes.

• Accumulating data suggest that long-term survival may also be improving.\textsuperscript{1-2}

• North Center Cancer Treatment Group (NCCTG) trials conducted in the FU plus leucovorin (LV) era, 5 yr survival rate 1.1\% \textsuperscript{3}.

• Phase III FIRE-3 trial (first-line irinotecan with short-term infusional FU plus LV [FOLFIRI] plus either bevacizumab or cetuximab), the 5yr SR for patients with RAS wild-type tumors treated with FOLFIRI plus cetuximab was \textasciitilde 20 \%. \textsuperscript{4}

CALGB/SWOG 80405: FINAL DESIGN

mCRC 1st-line
KRAS wild type
(codons 12, 13)

STRATA:
FOLFOX/FOLFIRI
Prior adjuvant
Prior XRT

FOLFIRI or FOLFOX
MD choice

Chemo + Cetuximab
Chemo + Bevacizumab

N = 1140
1° Endpoint: Overall Survival

Presented By Alan Venook at 2014 ASCO Annual Meeting
Three Takeaways in Colorectal Cancer From ASCO 2014

- For first-line therapy, either cetuximab or bevacizumab offer improved median survival and long-term responses in patients with KRAS wild-type metastatic disease.
- For maintenance therapy, switching to either 5-FU with or without bevacizumab, or bevacizumab alone—but not to a treatment holiday—appears appropriate.
- Extended RAS analysis—not just KRAS screening—should be performed for all patients.
80405: Overall Survival by Sidedness and Biologic

- **Left/Bev**
  - Median (95% CI): 31.4 (28.3-33.6)

- **Left/Cet**
  - Median (95% CI): 36.0 (32.6-40.3)

- **Right/Bev**
  - Median (95% CI): 24.2 (17.9-30.3)

- **Right/Cet**
  - Median (95% CI): 16.7 (13.1-19.4)

% Event Free
CALGB/SWOG 80405 Substudy: Tumor Sidedness Prognostic for OS by Therapy

- OS for pts with left-sided tumors is 19.3 mos longer than for right-sided tumors treated with cetuximab\(^1\)

<table>
<thead>
<tr>
<th>Median OS, Mos (N = 1025)</th>
<th>Primary Tumor Side</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right (n = 293) Left (n = 732)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55 (1.32-1.82) &lt; .0001</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48-2.32) &lt; .0001</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05-1.65) .01</td>
</tr>
</tbody>
</table>

*Adjusted for biologic, protocol chemotherapy, previous adjuvant therapy, previous radiotherapy, age, sex, synchronous disease, in place primary, liver metastases.

- Findings consistent with FIRE-3 trial in pts with all RAS wt\(^2,3\)

Conclusions

- **OS and PFS** were superior in patients with KRAS WT mCRC with left- vs right-sided 1° tumours
- **Efficacy with 1L cetuximab vs bevacizumab** differ according to 1° tumour location
- More precise biomarkers are needed to replace left- or right-sided tumour location in order to individualise patient care
  - However, for now mCRC studies should stratify patients by tumour sidedness
- These data support 1L bevacizumab in patients with mCRC and right-sided 1° tumours

*Corresponds to a 19.3-month increase in mOS when the primary is on the left.

Venook et al. J Clin Oncol 2016; 34 (suppl): abstr 3504
Consistent OS Benefit of Attaining ETS in More Recent Phase 3 Studies With Targeted Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No ETS</th>
<th>ETS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRYSTAL</strong></td>
<td>Cet + FOLFIRI (n = 299)</td>
<td>18.6</td>
<td>30.0</td>
</tr>
<tr>
<td>(KRAS wt*)</td>
<td>FOLFIRI (n = 332)</td>
<td>18.6</td>
<td>24.1</td>
</tr>
<tr>
<td><strong>FIRE-3</strong></td>
<td>Cet + FOLFIRI (n = 157)</td>
<td>20.5</td>
<td>38.3</td>
</tr>
<tr>
<td>(RAS wt)</td>
<td>Bev + FOLFIRI (n = 173)</td>
<td>21.2</td>
<td>31.9</td>
</tr>
<tr>
<td><strong>PRIME</strong></td>
<td>Pan + FOLFOX4 (n = 219)</td>
<td>12.6</td>
<td>32.5</td>
</tr>
<tr>
<td>(RAS wt)</td>
<td>FOLFOX4 (n = 221)</td>
<td>15.2</td>
<td>26.0</td>
</tr>
<tr>
<td><strong>TRIBE</strong></td>
<td>Bev + FOLFOXIRI/ FOLFIRI (n = 407)</td>
<td>21.9</td>
<td>31.9</td>
</tr>
</tbody>
</table>

* KRAS wt: KRAS wild-type

References:

Evidenced-Based First-Line Options Today

• FOLFOX, XELOX, or FOLFIRI + bevacizumab or anti-EGFR therapy
• FOLFOXIRI + bevacizumab
• 5-FU or capecitabine + bevacizumab
FIRE-3 Phase III Study Design

- Primary objective: ORR (investigator assessed)
  - Designed to detect a difference of 12% in ORR induced by FOLFIRI + cetuximab (62%) as compared to FOLFIRI + bevacizumab (50%)
  - 284 evaluable patients per arm needed to achieve 80% power for an one-sided Fisher’s exact test at an alpha level of 2.5%

FIRE-3 (FOLFIRI + Bevacizumab or Cetuximab): PFS and OS by Tumor Location

**PFS**
- **Left-sided mCRC**
  - Cetuximab + FOLFIRI (n = 157)
  - Bevacizumab + FOLFIRI (n = 149)
  - HR: 0.90 (95% CI: 0.71-1.14; P = .38)

- **Right-sided mCRC**
  - Cetuximab + FOLFIRI (n = 38)
  - Bevacizumab + FOLFIRI (n = 50)
  - HR: 1.44 (95% CI: 0.92-2.26; P = .11)

**OS**
- **Left-sided mCRC**
  - Cetuximab + FOLFIRI (n = 157)
  - Bevacizumab + FOLFIRI (n = 149)
  - HR: 0.63 (95% CI: 0.48-0.85; P = .002)

- **Right-sided mCRC**
  - Cetuximab + FOLFIRI (n = 38)
  - Bevacizumab + FOLFIRI (n = 50)
  - HR: 1.44 (95% CI: 0.81-2.11; P = .28)

PRIME (FOLFOX +/- Panitumumab) PFS by KRAS Mutation Status

**WT KRAS**

- Median, months (95% CI)
  - Panitumumab + FOLFOX4: 10.0 (9.3–11.4)
  - FOLFOX4: 8.6 (7.5–9.5)

\[ \text{HR} = 0.80 \ (95\% \ CI: 0.67 – 0.95) \]
\[ \text{Log-rank } P\text{-value} = .01 \]

**MT KRAS**

- Median, months (95% CI)
  - Panitumumab + FOLFOX4: 7.4 (6.9–8.1)
  - FOLFOX4: 9.2 (8.1–9.9)

\[ \text{HR} = 1.27 \ (95\% \ CI: 1.04 – 1.55) \]
\[ \text{Log-rank } P\text{-value} = .02 \]

Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer; A JSMO - ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS

T Yoshino, D Arnold, H Taniguchi, G Pentheroudakis, K Yamazaki, R-H Xu, T W Kim, F Ismail, I B Tan, K-H Yeh ...


Published: 16 November 2017
The European Perspective on the ESMO Position Paper on Tumor Sidedness

• European guidelines and practices have been traditionally more focused on treatment goal
• By comparison, Asian guidelines have perhaps been more based on molecular markers
• Both viewpoints recommend that anti-EGFR antibodies be used in RASwt and BRAFwt left-sided primary tumors
• Benefit of anti-EGFR antibodies not clear in right-sided tumors even when RASwt and BRAFwt
• In first-line combination approaches, both FOLFOX and FOLFIRI provide similar benefit
First-Line Treatment Choice for RAS and BRAF Wild-Type Right-Sided Tumors

- Selection of first-line therapy for right-sided tumors is very challenging
- Prognosis of right-sided tumors is very poor
- Selection of standard therapy depends on treatment goal:

**Tumor shrinkage not required**
- Doublet or triplet chemo + bevacizumab

**Tumor shrinkage required**
- Triplet chemo + bevacizumab
  - or
  - Chemo + cetuximab/panitumumab
Discussion Summary: Key Points

- Left and right-sided primary tumors differ in terms of biology, pathophysiology, the development of cancer, and the genes involved
  - This information is important in guiding selection of the best treatment for the individual patient in terms of the chemotherapy backbone and molecularly targeted agent
- Chemotherapy + anti-EGFR antibody is the most appropriate treatment choice for the patient with a RASwt and BRAFwt left-sided tumor
The CRYSTAL trial

Cetuximab + FOLFIRI vs FOLFIRI in first line mCRC

HR 0.85; p = 0.048

HR 0.93; p = NS


The addition of cetuximab improved response rate and PFS.

Despite the statistically significant decrease in the risk of disease progression (HR, 0.85), the absolute benefit was modest (8.9 mo vs 8).
## Mutant RAS and Outcome With EGFR Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>PRIME[1,2]</th>
<th>OPUS[3,4]</th>
<th>CRYSTAL[5,6]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td><strong>KRAS Ex2 WT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab + FOLFOX4 (n = 325)</td>
<td></td>
<td>10.0</td>
<td>23.9</td>
</tr>
<tr>
<td>FOLFOX4 (n = 331)</td>
<td></td>
<td>8.6</td>
<td>19.7</td>
</tr>
<tr>
<td>HR 0.80*</td>
<td>HR 0.88</td>
<td>HR 0.57*</td>
<td>HR 0.86*</td>
</tr>
<tr>
<td><strong>KRAS Ex2 MT</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Panitumumab + FOLFOX4 (n = 221)</td>
<td></td>
<td>7.4</td>
<td>15.5</td>
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<tr>
<td>FOLFOX4 (n = 219)</td>
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<td>9.2</td>
<td>19.2</td>
</tr>
<tr>
<td>HR 1.27*</td>
<td>HR 1.17</td>
<td>HR 1.72*</td>
<td>HR 1.29</td>
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<tr>
<td><strong>No RAS MT</strong></td>
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<td></td>
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<tr>
<td>Panitumumab + FOLFOX4 (n = 250)</td>
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<td>10.1</td>
<td>25.8</td>
</tr>
<tr>
<td>FOLFOX4 (n = 253)</td>
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<td>7.9</td>
<td>20.2</td>
</tr>
<tr>
<td>HR 0.72*</td>
<td>HR 0.77*</td>
<td>HR 0.53*</td>
<td>HR 0.94*</td>
</tr>
<tr>
<td><strong>Any RAS MT</strong></td>
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<td></td>
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<tr>
<td>Panitumumab + FOLFOX4 (n = 272)</td>
<td></td>
<td>7.3</td>
<td>15.5</td>
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<tr>
<td>FOLFOX4 (n = 276)</td>
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<td>8.7</td>
<td>18.7</td>
</tr>
<tr>
<td>HR 1.31*</td>
<td>HR 1.21*</td>
<td>HR 1.54*</td>
<td>HR 1.29</td>
</tr>
</tbody>
</table>

*Statistically significant.
References in slide notes.
mCRC Treatment Decision Recommendations: First Line

1L
- RAS mutation
  - Chemo + anti-VEGF
- RAS wild type
  - Chemo + anti-VEGF

2L
- RAS wild type
  - Chemo + anti-VEGF

3L
- Regorafenib or TAS-102

4L
- Other anticancer therapy, BSC, or clinical trial

Anti-VEGF: Bevacizumab
Anti-EGFR: Cetuximab, Panitumumab

Left-sided cancers only
- RAS wild type
  - Chemo + anti-VEGF


Slide credit: clinicaloptions.com
Second-line RAS-Mutated mCRC
Factors in Choosing Second-line Treatment

- Prior treatment with VEGF or EGFR inhibitor
- Progression within 6 months on prior VEGF inhibitor
- If received prior VEGF, > 3 months after maintenance
- Molecular and genetic phenotype of tumor (including MSI, BRAF, HER2 status)
- Toxicity considerations
VEGF Inhibition After Progression on Bevacizumab

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bevacizumab</th>
<th>Ziv-aflibercept</th>
<th>Ramucirumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>TML¹</td>
<td>VELOUR²</td>
<td>RAISE³</td>
</tr>
<tr>
<td>1st Line</td>
<td>Chemo + BEV</td>
<td>FP + Oxali ± BEV</td>
<td>FP + Oxali + BEV</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Chemo + BEV</td>
<td>FOLFIRI + AFL</td>
<td>FOLFIRI + RAM</td>
</tr>
<tr>
<td></td>
<td>(n = 409)</td>
<td>(n = 612)</td>
<td>(n = 536)</td>
</tr>
<tr>
<td></td>
<td>Chemo</td>
<td>FOLFIRI + PL</td>
<td>FOLFIRI + PL</td>
</tr>
<tr>
<td></td>
<td>(n = 410)</td>
<td>(n = 614)</td>
<td>(n = 536)</td>
</tr>
<tr>
<td>mOS, mo</td>
<td>11.2</td>
<td>13.5</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>9.8</td>
<td>12.1</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>HR 0.81</td>
<td>HR 0.82</td>
<td>HR 0.84</td>
</tr>
<tr>
<td></td>
<td><em>P = .0062</em></td>
<td><em>P = .0032</em></td>
<td><em>P = .022</em></td>
</tr>
<tr>
<td>mPFS, mo</td>
<td>5.7</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>4.1</td>
<td>4.7</td>
<td>4.5</td>
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<tr>
<td></td>
<td>HR 0.68</td>
<td>HR 0.76</td>
<td>HR 0.79</td>
</tr>
<tr>
<td></td>
<td><em>P &lt; .0001</em></td>
<td><em>P &lt; .0001</em></td>
<td><em>P = .0005</em></td>
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<tr>
<td>RR, %</td>
<td>5.4</td>
<td>19.8</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>11.1</td>
<td>12.5</td>
</tr>
</tbody>
</table>

# HER2 Amplification as a Negative Predictive Biomarker for EGFR Targeting: Outcomes

<table>
<thead>
<tr>
<th>Cohort</th>
<th>HER2 Amplified</th>
<th>HER2 Not Amplified</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-EGFR in 2L/3L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Testing cohort 1</td>
<td>2.9</td>
<td>8.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>- Validation cohort 2</td>
<td>2.9</td>
<td>9.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No anti-EGFR in 1L</td>
<td></td>
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<td></td>
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<tr>
<td>Median PFS, mo</td>
<td></td>
<td></td>
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<tr>
<td>- Testing cohort 1</td>
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<td>10.1</td>
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<tr>
<td>- Validation cohort 2</td>
<td>13.7</td>
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<td>OS, HR (95% CI)</td>
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</tr>
<tr>
<td>- Testing cohort 1</td>
<td>1.13 (0.5-2.3)</td>
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<td>.78</td>
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<tr>
<td>- Validation cohort 2</td>
<td>1.09 (0.4-2.7)</td>
<td></td>
<td>.86</td>
</tr>
</tbody>
</table>

EGFR Targeting: Key Points

- Cetuximab and panitumumab may be interchangeable\textsuperscript{[1]}
- Molecular markers identify patients unlikely to benefit from EGFR therapy\textsuperscript{[2,3]}
  - \textit{RAS (KRAS/NRAS)} mutations
  - \textit{BRAF} mutation (likely)
  - \textit{HER2} amplification (needs to be validated)
- Tumor location may affect chance of benefit\textsuperscript{[4,5]}
  - No benefit from EGFR mAbs in right-sided cancers (at least in first-line)
- Patient subset considered candidates for EGFR antibody therapy becoming more refined

VEGF-Targeted Therapies: Key Points

- Duration of VEGF inhibition matters
  - Treatment to progression
  - Maintenance strategies
  - Treatment beyond progression

- Clinical synergism between fluoropyrimidine and bevacizumab\(^1,2\)

- Prolonged VEGF inhibition beyond progression supported by 3 positive phase III trials\(^1-3\)
  - No compelling arguments for aflibercept or ramucirumab over bevacizumab

- Bevacizumab can be combined with FOLFOXIRI (phase III TRIBE)\(^4\)

Salvage Therapy
# Comparison of Regorafenib, TAS-102 After mCRC Progression

<table>
<thead>
<tr>
<th>Agent</th>
<th>Regorafenib</th>
<th>TAS-102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>CORRECT(^1)</td>
<td>RECURSE(^3)</td>
</tr>
<tr>
<td>Prior biologics</td>
<td>100% BEV</td>
<td>100% BEV</td>
</tr>
<tr>
<td></td>
<td>100% EGFR mAbs</td>
<td>53% EGFR mAbs</td>
</tr>
<tr>
<td></td>
<td>18% Prior Rego</td>
<td>18% EGFR mAbs</td>
</tr>
<tr>
<td>Rego (n = 505)</td>
<td>6.4</td>
<td>7.1</td>
</tr>
<tr>
<td>BSC+PL (n = 255)</td>
<td>5.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Rego (n = 136)</td>
<td>8.8</td>
<td>7.8</td>
</tr>
<tr>
<td>BSC+PL (n = 68)</td>
<td>6.3</td>
<td>7.1</td>
</tr>
<tr>
<td>mOS, mo</td>
<td>HR 0.77</td>
<td>HR 0.68</td>
</tr>
<tr>
<td></td>
<td>(P = .0052)</td>
<td>(P &lt; .0001)</td>
</tr>
<tr>
<td>mPFS, mo</td>
<td>HR 0.49</td>
<td>HR 0.48</td>
</tr>
<tr>
<td></td>
<td>(P &lt; .0001)</td>
<td>(P &lt; .0001)</td>
</tr>
<tr>
<td>RR, %</td>
<td>1.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- **Main adverse events:** hand-foot skin reaction, fatigue (regorafenib); neutropenia, GI toxicities, fatigue (TAS-102)

mCRC Treatment Decision Recommendations: Third Line

RAS mutation

1L: Chemo + anti-VEGF
2L: Chemo + anti-VEGF
3L: Regorafenib or TAS-102
4L: Other anticancer therapy, BSC, or clinical trial

Anti-VEGF: Bevacizumab, Ramucirumab, Ziv-aflibercept
Anti-EGFR: Cetuximab, Panitumumab

RAS wild type

1L: Chemo + anti-VEGF
2L: Chemo + anti-EGFR
3L: Regorafenib or TAS-102
4L: Other anticancer therapy, BSC, or clinical trial

RAS wild type

1L: Chemo + anti-VEGF
2L: Chemo + anti-VEGF
3L: Regorafenib or TAS-102
4L: Other anticancer therapy, BSC, or clinical trial

Left-sided cancers only

1L: Chemo + anti-EGFR
2L: Chemo + anti-VEGF
3L: Chemo + anti-EGFR
4L: Regorafenib or TAS-102

## BRAF V600E Mutation: Treatment Outcomes

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR, %</th>
<th>mPFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/Doublet BRAF/MEK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Dabrafenib + Trametinib</td>
<td>12</td>
<td>3.5</td>
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<tr>
<td>Doublet with EGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib + Panitumumab</td>
<td>13</td>
<td>3.2</td>
</tr>
<tr>
<td>Vemurafenib + Cetuximab</td>
<td>20</td>
<td>3.2</td>
</tr>
<tr>
<td>Encorafenib + Cetuximab</td>
<td>19</td>
<td>3.7</td>
</tr>
<tr>
<td>Dabrafenib + Panitumumab</td>
<td>10</td>
<td>3.4</td>
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<tr>
<td>Triplet with EGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib + Cetuximab + Irinotecan</td>
<td>35</td>
<td>7.7</td>
</tr>
<tr>
<td>Dabrafenib + Trametinib + Panitumumab</td>
<td>26</td>
<td>4.1</td>
</tr>
<tr>
<td>Encorafenib + Cetuximab + Alpelisib</td>
<td>18</td>
<td>4.2</td>
</tr>
</tbody>
</table>

References in slide notes.
Treatment Paradigm for mCRC

R Side: Chemo + Bev
L Side: Chemo + Bev or Anti-EGFR

MSI-high:
Pembrolizumab
Nivolumab
IO Trial
BRAFm:
FOLFOXIRI + Bev

If BBP then:
FOLFIRI + Anti-EGFR

BRAFm: VICTOR Test HER2

HER2 overexpressed
⇒ Trial[2,3]

TAS-102
(TFT + TPI)

MEKi plus anti-PD1? [4]

Phase I
Other actionable mutation

Regorafenib

References:
2. ClinicalTrials.gov. NCT03225937.
Conclusions

- Survival of patients with mCRC has significantly improved in the last decade
- Survival gains are not driven by advances in first-line therapy, but by incremental additional effects of subsequent treatment lines
- To maximize outcomes, patients should receive all active agents
- Identification of patient subgroups is increasing individualization of treatment
- Promising immunotherapeutic strategies include development of improved methods to deliver key antigens to make the tumor environment more receptive to immune infiltration of effector T-cells
KEEP LEARNING

New ideas make work INTERESTING!

thank u
Thank you!

Questions
Comments