Systemic therapy selection in mCRC: Can we break the mold?

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Congratulations to the Presenters

- **O-025**: A randomized, multicenter, phase II trial comparing CAPTEM versus FOLFIRI as second-line treatment for MGMT methylated, RAS mutated metastatic colorectal cancer (mCRC) patients - *Filippo Pietrantonio, et al*

- **LBA-007**: Updated results of TRIBE2, a phase III, randomized strategy study by GONO in the 1st- and 2nd-line treatment of unresectable mCRC - *Chiara Cremolini, et al*

- **LBA-006**: BEACON CRC: A Randomized, 3-Arm, Phase-3 Study of Encorafenib and Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI plus Cetuximab in BRAF V600E–Mutant Metastatic Colorectal Cancer - *Scott Kopetz, et al*
A randomized, multicenter, phase II trial comparing CAPTEM versus FOLFIRI as second-line treatment for MGMT-methylated, RAS-mutated metastatic colorectal cancer patients

What we know about MGMT and CRC

- The predominant mechanism of resistance to temozolomide (TMZ) is the expression of O6-methyl- guanine-DNA-methyltransferase (MGMT)
- MGMT silencing is observed in 35-40% of CRC\(^1\)
  - higher prevalence in RAS mutated disease
- However, TMZ ORR is only \(\sim10\%\) in patients with refractory mCRC and \textit{MGMT} methylation detected by qualitative assays, e.g. methylation-specific PCR (MSP)

Can the efficacy of TMZ be improved by use in earlier line, in combination with capecitabine, and by refining the molecular selection beyond MSP?

CAPTEM Trial Design

Measurable mCRC, ECOG PS 0-1, failure of prior FOLFOX/CAPOX± bev
RAS mut, MGMT methylated*

R 1:1

ARM A: CAPTEM (N=42)

ARM B: FOLFIRI (N=41)

Primary Endpoint: PFS

Disease progression/unacceptable toxicity/consent withdrawal

Measurable mCRC, ECOG PS 0-1, failure of prior FOLFOX/CAPOX± bev
RAS mut, MGMT methylated*

*central assessment by qualitative assay (methylated vs non-methylated): methylation-specific

Stratification factors:
• 1L PFS: ≥ vs < 9 mos
• Prior Bev: yes vs no

Capecitabine 1500 mg/m2 d1-14 q 28
Temozolomide 150 mg/m2 d10-14 q 28

Irinotecan 180 mg/m2 d1 q14
LV 200 mg/m2 d1,2 q14
5FU bolus 400 mg/m2 d1,2 q14
5FU pvi 600 mg/m2 d1,2 q14

F. Pietroantonio WCGI 2019
Similar ORR – 12% CAPTEM vs 10% FOLFIRI
CAPTEM had a more favourable toxicity profile
CAPTEM Trial - my takeaways

• This study did not meet its primary endpoint of PFS superiority with CAPTEM over FOLFIRI in 2L RAS-mutated mCRC with MSP-confirmed MGMT methylation

• Use of IHC in addition to MSP may be a more sensitive predictive biomarker

• While the clinical activity seems modest, further study is warranted in an MGMT methylated and IHC negative population
  – CAPTEM is an oral regimen with a more favourable toxicity profile
  – We need more treatment options for RAS-mutated mCRC
FOLFOXIRI has demonstrated improved efficacy in 1L mCRC

- Median PFS 9.8 vs 6.9m
  - HR 0.63, p=0.0006

- Median PFS 12.1 vs 9.7m
  - HR 0.75, p=0.003

- Median OS 22.6 vs 16.7m
  - HR 0.70, p=0.032

- Median OS 31 vs 25.8m
  - HR 0.79, p=0.054

Falcone GONO JCO 2007
Loupakis TRIBE NEJM 2014
ESMO guidelines for 1L treatment of mCRC

Assessment of clinical condition of the patient
- Fit
- Unfit (but may be suitable)

GOAL
- FP+bevacizumab: reduced dose doublet; anti-EGFR
- BSC

Patients with clearly resectable metastases
- Surgery alone
- Surgery with perioperative postoperative CT

MOLECULAR PROFILE
- OMD
- See figure 2

Cytoreduction (Shrinkage)**
- RAS wt
- RAS mt
- BRAF mt

Disease control (control of progression)
- RAS wt
- RAS mt
- BRAF mt

CT doublet + anti-EGFR
Combination CT + bevacizumab
CT triplet + bevacizumab
CT doublet + biological agent
CT doublet + bevacizumab
CT triplet +/- bevacizumab

Re-evaluation/assessment of response every 2 months*
- GOAL
- Progressive disease
- Surgery

Disease control
- Continue
- Continue; maintenance; or pause

Second-line
- Progressive disease
- Continue; maintenance; or pause

Re-evaluation/assessment of response every 2-3 months*

Annals of Oncology, Volume 27, Issue 8, August 2016, Pages 1386–1422,
**TRIBE2: Study design and endpoints**

**Arm A**
- **FOLFOX + bev**
- PD1
- **FOLFOXIRI + bev**
- PD2

**Arm B**
- **FOLFOXIRI + bev**
- PD1
- **FOLFOXIRI + bev**
- PD2

- *R 1:1
- N = 679

**Primary Endpoint:** Progression Free Survival 2

**Secondary Endpoints:**
- 1st and 2nd Progression-Free Survival
- RECIST Response Rate in 1st and 2nd line
- Resection Rate
- Safety profile in 1st and 2nd line
- Overall Survival

- *Prior adjuvant oxaliplatin not permitted
- ** Up to 8 cycles (vs 12 cycles in TRIBE)**
Primary endpoint: Progression Free Survival 2

Median follow up = 30.6 mos

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events, N (%)</th>
<th>Median PFS2, mos</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>340</td>
<td>272 (80%)</td>
<td>17.5</td>
<td>0.74</td>
<td>0.62-0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arm B</td>
<td>339</td>
<td>242 (71%)</td>
<td>19.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cut-off date analyses: March 1st 2019
TRIBE2 - Summary of Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Doublet sequence + bevacizumab</th>
<th>FOLFOXIRI + bevacizumab</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (CR+PR)</strong></td>
<td>50% (1L FOLFOX-bev)</td>
<td>62%</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Secondary R0 Resection</strong></td>
<td>12%</td>
<td>17%</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>1st PFS (median)</strong></td>
<td>9.8 mos</td>
<td>12 mos</td>
<td>HR 0.75 (p&lt;0.001)</td>
</tr>
<tr>
<td><strong>2nd PFS (median)</strong>*</td>
<td>5.6 mos (2L FOLFIRI-bev)</td>
<td>6.2 mos</td>
<td>HR 0.87 (p=0.122)</td>
</tr>
<tr>
<td><strong>OS (median) prelim</strong></td>
<td>22.6 mos</td>
<td>27.6 mos</td>
<td>HR 0.81 (p=0.033)</td>
</tr>
</tbody>
</table>

*as presented at ASCO 2019

- 85% of enrolled subjects were PS 0
- 79% of enrolled subjects were right-sided primary and/or RAS/BRAF mutated.

C. Cremolini WCIG 2019
Right colon and/or RAS or BRAF mut and PS 0

Enhanced efficacy but interaction testing not significant

- mPFS2: arm A, n=231, 16.1 mos
- mPFS2: arm B, n=239, 19.8 mos
TRIBE2 – my takeaways

• Superior PFS2 demonstrated with a FOLFOXIRI/bev upfront and reintroduction strategy when compared with sequential doublets
  – PFS2 benefit primarily driven by difference in 1st-PFS
  – Would FOLFIRI-bevacizumab suffice for reintroduction?

• In whom?
  – Right-sided and/or RAS/BRAF mutated and ECOG PS 0
  – While interaction testing was not significant, this selection makes sense
    • *No prior adjuvant oxaliplatin*?

• For patients with left-sided disease and RAS/BRAF WT
  – Doublet plus EGFR remains a preferred 1L option
**BRAF**\(^{V600E}\) Mutation in mCRC - in need of better options

- **BRAF**\(^{V600E}\) mutation occurs in approximately 7-10% of patients of CRC
- Associated with hypermutated tumours, right-sided primary preponderance and increased risk of peritoneal and brain metastases\(^1\)
- Mutually exclusive of RAS mutations, unlikely to respond to EGFR\(^2\)
- **Poor prognosis**

<table>
<thead>
<tr>
<th>Study</th>
<th>BRAF WT Median OS (mos)</th>
<th>BRAF MT Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRE-3</td>
<td>20.1</td>
<td>13.7</td>
</tr>
<tr>
<td>CALGB 80405</td>
<td>35.1</td>
<td>17.4</td>
</tr>
<tr>
<td>TRIBE</td>
<td>33.5</td>
<td>10.7</td>
</tr>
<tr>
<td>TRIBE</td>
<td>41.7</td>
<td>19.0</td>
</tr>
</tbody>
</table>

- Lack of activity with single-agent vemurafenib (ph2 RR 5%)\(^6\)
  - BRAF inhibition results in rapid feedback activation of EGFR permitting sustained MAPK activation and continued cell proliferation\(^6\)
- Rationale to target multiple nodes in the MAPK pathway – BRAF, EGFR & MEK


Figure from Ursem C etal, Gastrointest Cancer. 2018; 8: 13–23.
SWOG 1406 – randomized phase II trial of simultaneous EGFR and BRAF inhibition in pretreated BRAF V600E

Study Schema

Cetuximab + Irinotecan (n= 52)

Vemurafenib + Cetuximab + Irinotecan (n=54)

End points
• Primary: PFS

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab + Irinotecan (n= 52)</th>
<th>Vemurafenib + Cetuximab + Irinotecan (n=54)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS (95%CI)</td>
<td>2.0m (1.8–2.1)</td>
<td>4.4m (3.6–5.7)</td>
<td>0.42 (0.26-0.66)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Response rate</td>
<td>4%</td>
<td>16%</td>
<td>-</td>
<td>0.09</td>
</tr>
<tr>
<td>DCR</td>
<td>22%</td>
<td>67%</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>mOS (95%CI)*</td>
<td>5.9m (3.0-9.9)</td>
<td>9.6m (7.5-13.1)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*with crossover

Kopetz S et al. JCO 2017;35: 520
Open-label, phase I/II study of trametinib and dabrafenib when administered in combination with panitumumab in BRAFV600E mutated mCRC

**ORR (n=91): 21%**

**mPFS D+T+P = 4.2m**

Corcoran R et al, Cancer Discov; 428-443, 2018
Patients with \textit{BRAF} V600E–mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor.

\textbf{Phase 3}

- Triplet therapy: \textit{ENCO} + \textit{BINI} + \textit{CETUX} \( n = 205 \)
- Doublet therapy: \textit{ENCO} + \textit{CETUX} \( n = 205 \)
- Control arm: FOLFIRI + CETUX, or irinotecan + CETUX \( n = 205 \)

\textbf{Primary Endpoints:}

- OS (Overall Survival)
- ORR (Blinded Central Review)

\textbf{Secondary Endpoints:}

- Doublet vs Control OS & ORR, PFS, Safety

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>Triplet N=224</th>
<th>Doublet N=220</th>
<th>Control N=221</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>53%</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>62 (26, 85)</td>
<td>61 (30, 91)</td>
<td>60 (27, 91)</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>52%</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Location of primary tumor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left colon (includes rectum)</td>
<td>35%</td>
<td>38%</td>
<td>31%</td>
</tr>
<tr>
<td>Right colon</td>
<td>56%</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>≥3 organs involved</td>
<td>49%</td>
<td>47%</td>
<td>44%</td>
</tr>
<tr>
<td>Presence of liver metastases</td>
<td>64%</td>
<td>61%</td>
<td>58%</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65%</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>&gt;1</td>
<td>35%</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>MSI-H†</strong></td>
<td><strong>10%</strong></td>
<td><strong>9%</strong></td>
<td><strong>5%</strong></td>
</tr>
<tr>
<td>CEA Baseline Value &gt; 5 ug/L</td>
<td>80%</td>
<td>70%</td>
<td>81%</td>
</tr>
<tr>
<td>CRP Baseline Value &gt; 10mg/L</td>
<td>42%</td>
<td>37%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen; CRP, c-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability high (abnormal high).

Baseline characteristics are summarized for all 665 randomized patients.

†Based on assessment by polymerase chain reaction. MSI status is missing in 16.8% of patients.

*Remaining patients had primary tumor in both left and right sides of colon and those with unknown location of primary tumor.
Overall Survival (all randomized patients)

**Triplet vs Control (primary endpoint)**

Median OS in months (95% CI)
- **Triplet**: 9.0 (8.0–11.4)
- **Control**: 5.4 (4.8–6.6)

HR (95% CI), 0.52 (0.39–0.70)
2-sided $P<0.0001^*$

**Doublet vs Control**

Median OS in months (95% CI)
- **Doublet**: 8.4 (7.5–11.0)
- **Control**: 5.4 (4.8–6.6)

HR (95% CI), 0.60 (0.45–0.79)
2-sided $P<0.0001$

OS benefit observed in all examined subgroups
Waterfall Plots of Best Change in Sum of Diameters (based on central review)

Control
- ORR: 2%
  - 1 prior line: 2%
  N=73

Triplet
- ORR: 26%
  - 1 prior line: 34%
  N=87

Doublet
- ORR: 20%
  - 1 prior line: 22%
  N=98

*Patients whose SoD was contraindicated by assessment of PD. SoD=sum of longest diameter. Includes patients with measurable disease with a baseline and at least one post-baseline scan

N=73

N=87

N=98

S. Kopetz WCGI 2019
Triplet vs Doublet

What is the value-add of a MEK inhibitor?

• Rationale: enhanced MAPK pathway inhibition
  – Improved clinical efficacy with combined BRAF and MEK inhibition\(^1\)
  – But what is the incremental improvement in efficacy when added to a doublet of BRAF and EGFR inhibition?

• Is the clinical efficacy superior?

Progression Free Survival (all randomized patients)

**Triplet vs Control**

- **Median PFS in months (95% CI)**
  - Triplet: 4.3 (3.7–5.4)
  - Control: 1.5 (1.5–1.7)
- **HR (95% CI)**, 0.38 (0.29–0.49)
- 2-sided $P<0.0001$

**Doublet vs Control**

- **Median PFS in months (95% CI)**
  - Doublet: 4.2 (3.7–5.4)
  - Control: 1.5 (1.5–1.7)
- **HR (95% CI)**, 0.40 (0.31–0.52)
- 2-sided $P<0.0001$

S. Kopetz WCGI 2019
Overall Survival: Triplet vs Doublet

**All Randomized Patients**

<table>
<thead>
<tr>
<th></th>
<th>Triplet</th>
<th>Doublet</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS in months (95% CI)</td>
<td>9.0 (8.0–11.4)</td>
<td>8.4 (7.5–11.0)</td>
<td>0.79 (0.59–1.06)</td>
</tr>
</tbody>
</table>

Study not powered to formally compare the results of the triplet to the doublet

Additional OS analyses are pending
Triplet vs Doublet

What is the value-add of a MEK inhibitor?

- Rationale of triplet vs doublet: *compelling*
- Superior clinical efficacy of triplet vs doublet: *less compelling at this time*
- Toxicity profile
  - Greater frequency of dermatitis acneiform, nausea, diarrhea, abdominal pain observed with triplet vs doublet
    - Increased risk of MEK inhibitor retinal toxicity
    - Lower frequency of malignant and hyperproliferative skin lesions
- Increased cost

BEACON - my takeaways

• Per ESMO guidelines, ‘Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment’¹
  – now also for predictive assessment

• For MSI-H mCRC with a BRAF^{V600E} mutation
  – Would favour checkpoint inhibitor prior to BRAF-targeted therapies (in the absence of direct comparative data)

• For MSS mCRC with a BRAF^{V600E} mutation
  – First-line FOLFOXIRI + bevacizumab in suitable patients
  – Second-line BRAF-targeted combination therapy
    • Based on the positive OS benefit demonstrated in BEACON, a triplet may be preferred but the doublet of encorafenib and cetuximab is also an option
    • Await mature survival analysis of triplet vs doublet OS analysis

• The phase 2 ANCHOR trial is enrolling patients in the first-line setting (NCT03693170)
  – encorAfenib, biNimetinib and Cetuximab in subjects with previously untreated BRAF-mutant mCRC

¹. Annals of Oncology, Vol 27, 8, August 2016, 1386–1422
Thank you for your attention