Colorectal cancer: new drugs on the horizon

Michel Ducreux
Department of Medical Oncology
Disclosure

Participation to advisory boards:
- ROCHE
- MERCK SERONO
- AMGEN
- NOVARTIS
- SANOFI
- BAYER
- SIRTTEX
- LILLY
- SERVIER
- IPSEN

Speaker in symposiums:
- ROCHE
- MERCK SERONO
- NOVARTIS
- IPSEN
- LILLY
- AMGEN

Research funding:
- ROCHE
- MERCK SERONO
- PFIZER

My wife is Head of The Oncology Business Unit in Sandoz Company
Another disclosure...

- It is an arbitrary choice
- This is partially redundant with the great talk of Dr G Argiles....
PERSONALISED MEDICINE
Overall Fusion Prevalence in CRC with a ctDNA Assay

CRC patients with detectable alterations (N=3809)

No fusion detected (N=3768, 98.9%)

Fusion detected (N=41, 1.1%)

45 fusions detected

RET (N=16, 36%)

ALK (N=10, 22%)

FGFR3 (N=13, 29%)

NTRK1 (N=3, 7%)

ROS1 (N=2, 4%)

FGFR2 (N=1, 2%)
# Prevalence of Fusions by Rearrangement Partner

<table>
<thead>
<tr>
<th>Rearrangement Partner</th>
<th>Fusion Partner</th>
<th>Patients Tested</th>
<th>Patients with Fusion</th>
<th>Prevalence of Fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK</strong></td>
<td>EML4-ALK</td>
<td>4290</td>
<td>5</td>
<td>0.12%</td>
</tr>
<tr>
<td></td>
<td>STRN-ALK</td>
<td></td>
<td>5</td>
<td>0.12%</td>
</tr>
<tr>
<td><strong>FGFR2</strong></td>
<td>FGFR2-TACC2</td>
<td>3680</td>
<td>1</td>
<td>0.03%</td>
</tr>
<tr>
<td><strong>FGFR3</strong></td>
<td>FGFR3-TACC3</td>
<td>3680</td>
<td>13</td>
<td>0.35%</td>
</tr>
<tr>
<td><strong>NTRK1</strong></td>
<td>PLEKHA6-NTRK1</td>
<td>4290</td>
<td>1</td>
<td>0.02%</td>
</tr>
<tr>
<td></td>
<td>TPM3-NTRK1</td>
<td></td>
<td>2</td>
<td>0.05%</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>CCDC6-RET</td>
<td>4290</td>
<td>6</td>
<td>0.14%</td>
</tr>
<tr>
<td></td>
<td>NCOA4-RET</td>
<td></td>
<td>9</td>
<td>0.21%</td>
</tr>
<tr>
<td></td>
<td>TRIM24-RET</td>
<td></td>
<td>1</td>
<td>0.02%</td>
</tr>
<tr>
<td><strong>ROS1</strong></td>
<td>ERC1-ROS1</td>
<td>4290</td>
<td>1</td>
<td>0.02%</td>
</tr>
<tr>
<td></td>
<td>SLC34A2-ROS1</td>
<td></td>
<td>1</td>
<td>0.02%</td>
</tr>
</tbody>
</table>
Proff of concept: larotrectinib efficacy in patients with TRK fusions

Colon cancer: 7%
Entrectinib: inhibitor of TRKA/B/C, ROS1, ALK
IMMUNOTHERAPY AND COLON CANCER
Primary analysis of PFS: 1L BRAF\textsuperscript{wt}
Median follow-up 10.5 months

Median PFS, months
- FP + bev + atezo: 7.13
- FP + bev: 7.39

Stratified HR (95% CI)
- Total (N=445): 0.92 (0.72–1.17)
- Age <65 years (n=254): 0.89 (0.65–1.23)
- ≥65 years (n=191): 0.93 (0.64–1.35)
- Gender Male (n=271): 0.77 (0.56–1.04)
- Female (n=174): 1.21 (0.81–1.80)
- Region Europe (n=398): 0.92 (0.71–1.19)
- ROW (n=47): 0.81 (0.38–1.76)
- Tumour response at end of ITP CR/PR (n=275): 0.76 (0.55–1.05)
- SD (n=169): 1.23 (0.85–1.79)
- Baseline ECOG status 0 (n=266): 0.74 (0.54–1.01)
- 1/2 (n=179): 1.25 (0.85–1.84)
- AJCC/UICC stage at diagnosis Stage I/III (n=117): 1.25 (0.75–2.01)
- Stage IV (n=325): 0.83 (0.63–1.11)
- Prior systematic adjuvant therapy Yes (n=60): 1.41 (0.71–2.80)
- No (n=383): 0.85 (0.65–1.10)
- No. of metastatic sites at baseline <2 (n=203): 0.98 (0.68–1.41)
- ≥2 (n=242): 0.88 (0.63–1.22)
- Liver metastatic sites at baseline Yes (n=345): 0.91 (0.69–1.20)
- No (n=100): 0.87 (0.52–1.45)
- Cancer type Colon (n=269): 0.91 (0.66–1.26)
- Rectal (n=125): 1.09 (0.70–1.69)
- Tumour colon location Right (n=81): 0.92 (0.51–1.66)
- Left (n=313): 0.97 (0.73–1.30)
- Initial diagnosis Synchronous (n=336): 0.79 (0.60–1.05)
- Metachronous (n=100): 1.57 (0.90–2.74)

One MSI patient in the FP + bev + atezo arm had a complete response during the maintenance treatment phase.
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Atezo + cobi (n = 183)</th>
<th>Atezo (n = 90)</th>
<th>Rego (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>8.9 (7.00, 10.61)</td>
<td>7.1 (6.05, 10.05)</td>
<td>8.5 (6.41, 10.71)</td>
</tr>
<tr>
<td>HR vs rego (95% CI)</td>
<td>1.00 (0.73, 1.38)</td>
<td>1.19 (0.83, 1.71)</td>
<td>N/A</td>
</tr>
<tr>
<td>P value</td>
<td>0.9871</td>
<td>0.3360^a</td>
<td>N/A</td>
</tr>
<tr>
<td>12-mo OS, %</td>
<td>38.5%</td>
<td>27.2%</td>
<td>36.6%</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Atezo + cobi</th>
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<th>Rego</th>
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</table>

^a Significant at p < 0.05.
CCTG CO.26 Study Schema:

 Patients with advanced CRC refractory to all available therapy

 Stratify:
  - ECOG
  - Side of tumor

 Randomize

 2:1

 Durvalumab:
 1500 mg IV q 28 days
 Tremelimumab:
 75 mg IV q 28 days, cycles 1-4
 + Best Supportive Care

 Best Supportive Care

 Primary endpoint:
 - OS
 Secondary endpoints:
 - PFS
 - Safety and toxicity
 - ORR
 Tertiary endpoints:
 - QoL
 - Correlative studies

 Sample Size: 180

 Presented by: Eric X. Chen

 Presented at: 2019 Gastrointestinal Cancers Symposium | #GI19
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Results: overall survival

- Median BSC = 4.1 months; 90% CI (3.3-6.0)
- Median Durva+Treme = 6.6 months; 90% CI (6.0-7.4)

Stratified Hazard Ratio = 0.72; 90% CI (0.54-0.97); p=0.07
Unadjusted HR = 0.70; 90% CI (0.53-0.92); p=0.03

As of January 16, 2019
N=10 alive on D+T
N=1 alive on BSC

Best Supportive Care
Durvalumab+Tremelimunab

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>D+T</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>119</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Results: progression-free survival

Median BSC = 1.9 months; 90% CI (1.8-1.9)
Median Durva+Treme = 1.8 months; 90% CI (1.8-1.9)

Stratified Hazard Ratio = 1.01; 90% CI (0.76-1.34); p=0.97
Results: objective response rate

ITT DCR
Odds Ratio = 4.16
90%CI (1.40-12.3)
p=0.006
Study design and objectives

Dose escalation cohort: "3+3" design

- Regorafenib
  - Level 1: 80 mg/day
  - 21 on 7 days off
  - Nivolumab 3 mg/kg q2w
  - N = 3~6

- Regorafenib
  - Level 2: 120 mg/day
  - 21 on 7 days off
  - Nivolumab 3 mg/kg q2w

- Regorafenib
  - Level 3: 160 mg/day
  - 21 on 7 days off
  - Nivolumab 3 mg/kg q2w
  - N = 3~6

Expansion cohort

- Colorectal cancer
- Gastric cancer
- Total 36 cases

Primary objective: dose-limiting toxicity (DLT) during cycle one to investigate the maximum tolerated dose (MTD) and recommended dose (RD)

Secondary objective: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR)

Fukuoka S et al ASCO 2019 (abs 2522), Hara H et WCGIC 2019 (SO-008)
Responses and duration of treatment

- Colorectal cancer
  - ORR 36% (33% with MSS pts)
  - MSI-H (all other patients were MSS)

- Median duration of treatment was 6.1 months (range 0.7-14.9 months)
- Study treatment is ongoing in 21 patients

Fukuoka S et al ASCO 2019 (abs 2522), Hara H et WCGIC 2019 (SO-008)
Overall survival

Fukuoka S et al ASCO 2019 (abs 2522), Hara H et WCGIC 2019 (SO-008)
Bispecific antibodies

Active immunotherapy using Bispecific mAb

- Targeting 2 epitopes on a single target
- Targeting 2 antigens on the same tumor cell
- Targeting 2 antigens on different cells (example: tumor cell and T-cell)
→ Bispecific antibody: CEA-CD3 TCB

• Anti-CEA and CD3 antibody

- Advanced CEA+ solid tumours
  n=80 (mCRC n = 68)

- Advanced CEA+ solid tumours
  n=38 (mCRC n = 28)

- CEA-CDs TCB (0.05 mg-600 mg)

- CEA-CDs TCB (5mg-160 mg) + Atezolizumab

- Two ongoing phase I dose-escalation studies

- Objectives: preliminary efficacy and safety; PK and PD

J. Taberner, et al., ASCO® 2017, abs 3502
Bispecific antibody: CEA-CD3 TCB

CEA-TCB doses > 60 mg + atezolizumab: promising activity
3rd line MSS mCRC

J. Tabernero, et al., ASCO® 2017, abs 3502
A NEW STANDARD OF CARE!!!!
BEACON CRC:
A Randomized, 3-Arm, Phase 3 Study of Encorafenib, Cetuximab With or Without Binimetinib vs. Choice of Either Irinotecan or FOLFIRI, plus Cetuximab in BRAF-Mutant Metastatic Colorectal Cancer


BEACON CRC: Binimetinib, Encorafenib, And Cetuximab COMbined to Treat BRAF-mutant colorectal cancer
Original Study Design

Patients with \(BRAF^{V600E}\) 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.

**Safety Lead-in**

ENCO + BINI + CETUX  
\(N = 30\)

Encorafenib 300 mg PO daily  
Binimetinib 45 mg PO bid  
Cetuximab standard weekly dosing

**Phase 3**

**Triplet therapy**

\(ENCO + BINI + CETUX\)  
\(n = 205\)

**Doublet therapy**

\(ENCO + CETUX\)  
\(n = 205\)

**Control arm**

FOLFIRI + CETUX, or irinotecan + CETUX  
\(n = 205\)

**Primary Endpoint:**

Triplet vs Control

**Overall Survival**

OS

**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).
Primary Endpoint - Overall Survival: Triplet vs Control (all randomized patients)

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
# Overall Survival: Subgroup Analysis (all randomized patients)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>204/445</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS=0</td>
<td>85/227</td>
<td>0.52 (0.39, 0.70)</td>
</tr>
<tr>
<td>PS=1</td>
<td>119/218</td>
<td>0.63 (0.41, 0.96)</td>
</tr>
<tr>
<td><strong>Prior Irinotecan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99/219</td>
<td>0.48 (0.33, 0.70)</td>
</tr>
<tr>
<td>Yes</td>
<td>105/226</td>
<td>0.53 (0.35, 0.79)</td>
</tr>
<tr>
<td><strong>Number of Prior Regimens for Metastatic Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>123/291</td>
<td>0.55 (0.37, 0.80)</td>
</tr>
<tr>
<td>2+</td>
<td>81/154</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>130/290</td>
<td>0.54 (0.38, 0.77)</td>
</tr>
<tr>
<td>≥65</td>
<td>74/155</td>
<td>0.53 (0.41, 0.82)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>100/199</td>
<td>0.48 (0.30, 0.76)</td>
</tr>
<tr>
<td>Female</td>
<td>104/246</td>
<td>0.53 (0.36, 0.79)</td>
</tr>
<tr>
<td><strong>Number of Organs Involved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>104/237</td>
<td>0.54 (0.37, 0.80)</td>
</tr>
<tr>
<td>3+</td>
<td>100/208</td>
<td>0.50 (0.34, 0.75)</td>
</tr>
<tr>
<td><strong>MSI Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>18/34</td>
<td>0.67 (0.26, 1.76)</td>
</tr>
<tr>
<td>High</td>
<td>140/200</td>
<td>0.44 (0.31, 0.62)</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline CEA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Upper Limit of Normal</td>
<td>180/257</td>
<td>0.54 (0.40, 0.72)</td>
</tr>
<tr>
<td>≤ Upper Limit of Normal</td>
<td>23/67</td>
<td>0.42 (0.18, 0.99)</td>
</tr>
<tr>
<td><strong>Baseline CRP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Upper Limit of Normal</td>
<td>114/183</td>
<td>0.63 (0.43, 0.91)</td>
</tr>
<tr>
<td>≤ Upper Limit of Normal</td>
<td>83/247</td>
<td>0.46 (0.29, 0.71)</td>
</tr>
<tr>
<td><strong>Side of Tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Colon</td>
<td>53/147</td>
<td>0.43 (0.26, 0.72)</td>
</tr>
<tr>
<td>Right Colon</td>
<td>117/245</td>
<td>0.63 (0.44, 0.90)</td>
</tr>
</tbody>
</table>

*Note: The hazard ratio represents the relative risk of death compared to the control group.*
Waterfall Plots of Best Change in Sum of Diameters
(based on central review)

Control

N=73

Triplet

N=87

Doublet

N=98

Note: 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.
OLD TARGET NEW DRUG: KRAS MUTATION
AMG 510 First in Human Study Design

This is a multicenter, open-label, phase 1, first in human study (NCT 03600883) in adult patients with locally advanced or metastatic KRAS<sup>G12C</sup> mutant solid tumors.

**Key Eligibility Criteria**
- Documented locally-advanced or metastatic KRAS<sup>G12C</sup> measurable or evaluable solid tumors
- Received prior standard therapy appropriate for tumor type and stage of disease
- No active brain metastases

**Primary Endpoints**
- Safety and tolerability including the incidence of AEs and DLTs

**Key Secondary Endpoints**
- PK, best response
- Objective response rate, duration of response and duration of stable disease and PFS

---

**Treatment Period with Daily Oral Dose**
- Until disease progression, intolerance or consent withdrawal (radiographic scans every 6 weeks)
- ~30 Days After EOT
- Every 12 Weeks
NSCLC: Best Tumor Response* (n=10)

5 out of 10 patients had PR
- 4 are confirmed
- All 5 are still on treatment

* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 patient had clinical progression prior to week 6 and is not on this graph
☑ Confirmed response
☑ 2 additional patients had confirmed PR post data cutoff
$Patient had a CR of the target lesions at week 18, post data cutoff
CRC and Other Solid Tumors: Best Tumor Response* (n=19)

* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 CRC patient progressed prior to week 6 and is not on this graph
1 appendix patient had clinically stable disease but is not shown on this graph

% Change from Baseline in Sum of Longest Diameters

Patients Receiving AMG 510

Planned Dose: 180 mg, 360 mg, 720 mg, 960 mg
Duration of Treatment by Tumor Types and Responses (n=29)

Duration on Treatment (as of 4 April 2019)
- NSCLC Partial Response (n=5): 7.3 – 27.4 weeks
- Stable Disease (n=4): 8.4 – 25.1 weeks
- CRC/Other Stable Disease (n=14): 7.3 – 24.0 weeks

- First Response: 5
- Best Overall Response:
  - PR: 5
  - SD: 18
  - PD: 6
- Disease Progression: 9
- Ongoing on-study: 20

* Appendix adenocarcinoma patient
SD → PD: Patient with best response of SD but who later progressed

Tumor Type: CRC/Other(Appendix) NSCLC
Conclusion

• I am probably wrong… but
  – Encorafenib ± binimetinib will be used in the treatment of BRAF mutant mCRC
  – Personalised medicine of mCRC will continue to improve
  – We will find a way to use immunotherapy in mCRC
    • Combination
    • Bispecific antibodies
    • CAR-T cells??
  – New weapons on old targets…
    • Active anti-KRAS drug??