INTEGRATING TARGETED THERAPIES INTO THE INDIVIDUALIZED MANAGEMENT OF METASTATIC COLORECTAL CANCER: A LOOK AT THE ROLE OF VEGF AND EGFR INHIBITORS

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November 10, 2016
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Disclosures:

- Research Grants:
  - Genentech/Roche
  - Forty-Seven, Inc
  - Sirtex
  - Bayer
- Speakers Bureau
  - Roche/Genentech
  - Lilly
- Consultant:
  - Eli Lilly
  - Bayer
  - Sirtex
  - Roche
  - Forty-Seven, Inc
Salient Discussion Points

- Focus will be on stage IV (metastatic) colorectal cancer
- Whenever possible surgically resect metastatic disease
  - 5-yr OS of 35%-65% vs. 13% (unresectable)
- For surgically unresectable stage IV patients, chemotherapy will be continued indefinitely to optimize overall survival.
  - Combination chemotherapy is commonly used.
- The conduct and completion of clinical trials is the way we can advance the field of colorectal cancer treatment.

Cancers of the Colon and Rectum
Global Statistics

Colorectal cancer is the 3rd most common cancer men and the 2nd in women.

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>USA (2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1.23 Million</td>
<td>134,490</td>
</tr>
<tr>
<td>Mortality</td>
<td>608,700 per annum</td>
<td>49,190</td>
</tr>
</tbody>
</table>

US Colon Cancer Facts

- **Number of New Cases and Deaths per 100,000:** The number of new cases of colon and rectum cancer was 41.0 per 100,000 men and women per year. The number of deaths was 15.1 per 100,000 men and women per year. These rates are age-adjusted and based on 2009-2013 cases and deaths.
- **Lifetime Risk of Developing Cancer:** Approximately 4.4 percent of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime, based on 2011-2013 data.
- **Prevalence of This Cancer:** In 2013, there were an estimated 1,177,556 people living with colon and rectum cancer in the United States.


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**Age distribution of colorectal cancer**

The chart shows the percent of new cases by age group for colon and rectum cancer. The median age at diagnosis is 68.

[SEER 18 2009-2013, All Races, Both Sexes](http://seer.gov)
Impact of Race and Ethnicity in the US

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colon and Rectal Cancer

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>47.1</td>
<td>36.0</td>
</tr>
<tr>
<td>White</td>
<td>46.0</td>
<td>35.2</td>
</tr>
<tr>
<td>Black</td>
<td>59.2</td>
<td>44.8</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>41.2</td>
<td>29.8</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>46.2</td>
<td>36.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>41.3</td>
<td>29.4</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>48.1</td>
<td>37.0</td>
</tr>
</tbody>
</table>

SEER 18 2000-2013, Age-Adjusted

The Problem: Underutilization of Screening

Colorectal Cancer Facts & Figures 2014-2016

Genetic Model of CRC Cancer

Risk factors for colorectal Development

http://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq
Colorectal CA: 5-Year Overall Survival


TREATMENT OF NEWLY DIAGNOSED METASTATIC COLORECTAL CANCER: PATHWAYS OF SIGNIFICANCE
Recent Advances in the Treatment of mCRC

Chemotherapies
- 5-FU
- Irinotecan
- Capecitabine
- Oxaliplatin

Targeted therapies
- Bevacizumab
- Cetuximab
- Panitumumab

KRAS testing
- Aflibercept
- Ramucirumab

RAS testing
- Regorafenib
- Extended

Extended

Recent Advances in the Treatment of mCRC

Chemotherapies
- 5-FU
- Irinotecan
- Capecitabine
- Oxaliplatin

Targeted therapies
- Bevacizumab
- Cetuximab
- Panitumumab

KRAS testing
- Aflibercept
- Ramucirumab

Extended

Extended

Median OS by First-line Therapy for mCRC

Best Supportive Care
- 4-6 mos

5-FU/LV
- 12-14 mos

IFL or FOLFIRI
- 15-16 mos

FOLFOX4 or CapeOx
- 19-20 mos

IFL + Bevacizumab
- 20.3 mos

FOLFOX6
- 21.5 mos

FOLFIRI + Bevacizumab
- 24-25.8 mos

2

FOLFOXIRI + Bevacizumab
- 29.8 mos

2

Median Overall Survival (Mos)

0 6 12 18 24 30

“Targeted” Therapies: Pertinent Pathways

Vasculature and Tumor Growth

Tumor is dormant  Angiogenic switch

- Neovascularization
  - Allows rapid tumor growth by providing oxygen, nutrients, and waste removal
  - Facilitates metastasis

Somatic mutation  Small avascular tumor  Tumor secretion of angiogenic factors stimulates angiogenesis  Rapid tumor growth and metastasis

The VEGF Family and Its Receptors

VEGF-A, VEGF-B, VEGF-C, VEGF-D, PlGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D, NRP-1, VEGFR-1, VEGFR-2, VEGFR-3

Angiogenesis, lymphangiogenesis, Lymphangiogenesis

PIGF = Placental growth factor; RTK = Receptor tyrosine kinase.

The Epidermal Growth Factor Receptor (EGFR) signal transduction pathway

EGFR ligand, Target for anti-EGFR (cetuximab and panitumumab)

RAS, BRAF, MEK, MAPK, AKT/PKB, PI3K, PTEN, mTOR

Proliferation/mature, Chemotherapy, radiotherapy resistance, Angiogenesis, Invasion and metastasis, Survival (anti-apoptosis)

Signaling to the nucleus
Pivotal Historical Trials

**BOND-1**

**Irinotecan + Cetuximab Second-Line: Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Irinotecan + Cetuximab (n = 218)</th>
<th>Cetuximab (n = 111)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>22.9%</td>
<td>10.8%</td>
<td>.0074</td>
</tr>
<tr>
<td>Disease control (CR + PR + SD)</td>
<td>55.5%</td>
<td>32.4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median TTP</td>
<td>4.1 mo</td>
<td>1.5 mo</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.6 mo</td>
<td>6.9 mo</td>
<td>.48</td>
</tr>
</tbody>
</table>

*Cetuximab appears to resensitize tumors to irinotecan*

TTP = time to progression.

QOL Limiting Factor with EGFR Targeted Therapy: Dermatologic Toxicity

- Acneform rash on chest
- Acneform rash on face
- Paronychial inflammation


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Cetuximab and K-ras modulate signaling through the epidermal growth factor receptor (EGFR) pathway

[Diagram of EGFR signaling pathway]
Phase III: Panitumumab vs. BSC: Impact of KRAS MT on PFS (WT vs. Mutant)

<table>
<thead>
<tr>
<th></th>
<th>Events/N (%)</th>
<th>Median In Weeks</th>
<th>Mean In Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmab + BSC (WT)</td>
<td>115/124 (93)</td>
<td>12.3</td>
<td>19.0</td>
</tr>
<tr>
<td>Pmab + BSC (MT)</td>
<td>76/84 (90)</td>
<td>7.4</td>
<td>9.9</td>
</tr>
<tr>
<td>BSC Alone (WT)</td>
<td>114/119 (96)</td>
<td>7.3</td>
<td>9.3</td>
</tr>
</tbody>
</table>

WT: HR = 0.45 (95% CI: 0.34–0.59)
Stratified log-rank test, p < 0.0001

Established Molecular Markers (anti-EGFR pathway)

- **KRAS**
  - Proto-oncogene
  - Predictive
  - 30%-50% of all patients
  - MT (exon 2): codons 12, 13, 61, and rarely 146

- **NRAS**
  - Mutations in codons 12, 13, 61, 117 and 146
    - Usually codon 61

- **BRAF**
  - Serine-threonine kinase belong to the RAF family
  - Mutation also leads to constitutive activation
  - V600E accounts for 90% of mutations
  - Found in < 10% of all CRC patients
  - Associated with hypermethylation of CpG island.
  - Poor prognosis: Median OS of 12-13M
Update on PRIME Study Phase III

Patients
- Previously untreated mCRC
- Fluorouracil-based adjuvant chemotherapy allowed if PD occurred ≥6 mo after completion; no oxaliplatin
- Tumor tissue from primary tumor or metastasis available for biomarker analysis
- ECOG PS 0-2
- N=1183

Panitumumab 6.0 mg/kg q 2 wk
FOLFOX4 q 2 wk

1:1 Randomization

FOLFOX4 q 2 wk

Primary endpoint: PFS


PRIME Biomarker Analysis: Analysis of KRAS/NRAS and BRAF Mutations

<table>
<thead>
<tr>
<th>RAS and BRAF Status</th>
<th>FOLFOX4 Alone</th>
<th>Panitumumab + FOLFOX4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS exon 2</strong> (codon 12/13), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>331</td>
<td>335</td>
</tr>
<tr>
<td>MT</td>
<td>219</td>
<td>221</td>
</tr>
<tr>
<td><strong>WT KRAS exon 2</strong> tumors tested for <strong>RAS</strong> and <strong>BRAF</strong> (n = 321) (n = 320)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>57 (18)</td>
<td>51 (16)</td>
</tr>
<tr>
<td>MT</td>
<td>306 (95)</td>
<td>308 (96)</td>
</tr>
<tr>
<td>Failure</td>
<td>1 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>WT</td>
<td>296 (92)</td>
<td>288 (90)</td>
</tr>
<tr>
<td>MT</td>
<td>15 (5)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Failure</td>
<td>10 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>WT</td>
<td>307 (96)</td>
<td>308 (96)</td>
</tr>
<tr>
<td>MT</td>
<td>14 (4)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Failure</td>
<td>0 (0)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>KRAS exon 3</strong> (codon 61), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>305 (95)</td>
<td>305 (95)</td>
</tr>
<tr>
<td>MT</td>
<td>14 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Failure</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>NRAS exon 2</strong> (codons 12/13), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>313 (98)</td>
<td>316 (99)</td>
</tr>
<tr>
<td>MT</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Failure</td>
<td>8 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>NRAS exon 3</strong> (codon 61), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>288 (87)</td>
<td>288 (89)</td>
</tr>
<tr>
<td>MT</td>
<td>23 (9)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Failure</td>
<td>12 (4)</td>
<td>10 (3)</td>
</tr>
</tbody>
</table>

Revised PRIME Consort Diagram

Douillard et al: NEJM, 2013

EGFR-Targeted Agents as First-line Therapy in RAS WT mCRC: Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparative Regimens</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>FOLFOX4/Pmab vs FOLFOX4</td>
<td>9.6 vs 8.0</td>
<td>23.8 vs 19.4</td>
</tr>
<tr>
<td></td>
<td>FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)</td>
<td>10.1 vs 7.9</td>
<td>26.0 vs 20.2</td>
</tr>
</tbody>
</table>

Physician Choice: Anti-EGFR Therapy or Anti-VEGF Therapy in an all RAS WT patient?

CALGB/SWOG 80405: Bevacizumab vs Cetuximab in First-line KRAS WT mCRC

- **Primary endpoint**: OS
  - Superiority trial with 90% power to detect an OS HR of 1.25 (2-sided $\alpha=0.05$)
- **Secondary endpoints**: ORR, PFS, TTF, DOR, and safety

- Untreated advanced or metastatic CRC (N=1142)
- Randomized patients with KRAS WT tumors
- Bevacizumab + FOLFOX or FOLFIRI q2w
- Cetuximab + FOLFOX or FOLFIRI q2w
- Approximately 70% FOLFOX, 30% FOLFIRI

FOLFIRI: leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride; FOLFOX: fluorouracil, leucovorin calcium (folinic acid), and oxaliplatin; TTF: time to treatment failure.

CALGB/SWOG 80405: Study Profile

11/14/2016

KRAS WT codons
12/13
(N=1137)

CT + Bev
(n=559)

Evaluable for RAS analysis
(n=324) (26 NA)

RAS WT
(n=256)

RAS mut
(n=42)

CT + Cetux
(n=270)

Evaluable for RAS analysis
(n=346) (23 NA)

RAS WT
(n=270)

RAS mut
(n=53)

Additional RAS MT: 18%

NA=not applicable.

CALGB/SWOG 80405: PFS and OS in All RAS WT Patients

Progression-Free Survival (All RAS WT Patients)

<table>
<thead>
<tr>
<th>N Events</th>
<th>mPFS, mos</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Bev (256)</td>
<td>221</td>
<td>11.3</td>
<td>(10.3-12.6)</td>
</tr>
<tr>
<td>CT + Cetux (270)</td>
<td>241</td>
<td>11.4</td>
<td>(9.6-12.9)</td>
</tr>
</tbody>
</table>

Overall Survival (All RAS WT Patients)

<table>
<thead>
<tr>
<th>N Events</th>
<th>mOS, mos</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Bev (256)</td>
<td>178</td>
<td>31.2</td>
<td>(26.9-34.3)</td>
</tr>
<tr>
<td>CT + Cetux (270)</td>
<td>177</td>
<td>32.0</td>
<td>(27.6-38.5)</td>
</tr>
</tbody>
</table>

Response Rate, %

<table>
<thead>
<tr>
<th></th>
<th>CT + Bev (n=256)</th>
<th>CT + Cetux (n=270)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53.8</td>
<td>68.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Does primary tumor location impact OS?

Embryology: The origin of the colon

CALGB 80405: Side of Primary Tumors

- LEFT: N = 732 (68%)
- RIGHT: N = 293 (27%)
- TRANSVERSE: N = 66
- COULD NOT DETERMINE: N = 46

Venook et al: ASCO 2016

CALGB 80405: Overall Survival by Sidedness

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>732 (550)</td>
<td>33.3 (31.4-35.7)</td>
<td>1.55 (1.32-1.82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>293 (242)</td>
<td>19.4 (16.7-23.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Venook et al: ASCO 2016
CALGB 80405: Sidedness is Prognostic

**KRAS wt N = 1025**

<table>
<thead>
<tr>
<th></th>
<th>Right 1*</th>
<th>Left 1*</th>
<th>Hazard Ratio 95% CI</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>8.9</td>
<td>11.7</td>
<td>1.03 (1.11, 1.50)</td>
<td>P = 0.0006</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>7.8</td>
<td>12.4</td>
<td>1.56 (1.26, 1.94)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>9.6</td>
<td>11.2</td>
<td>1.06 (0.86, 1.31)</td>
<td>P = 0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></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)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48, 2.32)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05, 1.65)</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

---

**Second Line Therapy**
Discussion Points

- To improve the OS of patients, we must continue treating the patients with chemotherapy
- Be cautious of prolonged toxicities of therapy
- Limitations of therapy for RAS MT patients

ML18147 (TML): Continuing Bevacizumab Beyond Progression

- A randomized, open-label phase III intergroup study

Stratified by first-line CT (oxaliplatin or irinotecan based), first-line PFS (≤ 9 or > 9 mos), time from last BEV dose (≤ 42 or > 42 days), ECOG PS at baseline (0/1 or 2)

- Progressive mCRC after BEV + standard first-line CT (either oxaliplatin or irinotecan based) (n = 820)

- Standard second-line CT (oxaliplatin or irinotecan based) until PD (n = 411)

- BEV 2.5 mg/kg/wk + standard second-line CT (oxaliplatin or irinotecan-based) until PD (n = 409)

Primary endpoint: OS

ML18147 (TML): Continuing Bevacizumab Beyond Progression Increases OS (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Unstratified* HR: 0.81 (95% CI: 0.69-0.94; log-rank ( P = .0062)</th>
<th>Stratified† HR: 0.83 (95% CI: 0.71-0.97; log-rank ( P = .0211)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS (%): 100</td>
<td>80</td>
</tr>
<tr>
<td>Mos</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>CT (n = 410)</td>
<td>9.8 mos</td>
<td>11.2 mos</td>
</tr>
<tr>
<td>BEV + CT (n = 409)</td>
<td>Unstratified* HR: 0.68 (95% CI: 0.59-0.78; log-rank ( P &lt; .0001)</td>
<td>Stratified† HR: 0.67 (95% CI: 0.58-0.78; log-rank ( P &lt; .0001)</td>
</tr>
<tr>
<td>MOS</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>PFS (%): 100</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Mos</td>
<td>4.1 mos</td>
<td>5.7 mos</td>
</tr>
</tbody>
</table>

*Primary analysis method. †Stratified by first-line CT (oxaliplatin based, irinotecan based), first-line PFS (≤ 9 mos, > 9 mos), time from last dose of BEV (≤ 42 days, > 42 days), ECOG PS at baseline (0, ≥ 1).


Second-line Therapy With Angiogenesis Inhibitors in mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparative Regimens</th>
<th>Median PFS, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML18147²</td>
<td>Bev + standard second-line chemotherapy (oxaliplatin- or irinotecan-based) vs standard second-line chemotherapy</td>
<td>5.7 vs 4.1*</td>
<td>11.2 vs 9.8*</td>
</tr>
<tr>
<td>Prior Bev (N = 820)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VELOUR³</td>
<td>Aflibercept/FOLFIRI vs Placebo/FOLFIRI</td>
<td>6.9 vs 4.7*</td>
<td>13.5 vs 12.1*</td>
</tr>
<tr>
<td>Previously treated with an oxaliplatin-based regimen (N = 1226)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAISE⁴</td>
<td>Ramucirumab/FOLFIRI vs Placebo/FOLFIRI</td>
<td>5.7 vs 4.5*</td>
<td>13.3 vs 11.7*</td>
</tr>
<tr>
<td>Progression during or after bevacizumab, oxaliplatin, and fluoropyrimidine (N = 1072)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant difference

Refractory MCRC

Regorafenib 160 mg daily
3 weeks on/1 week off
(4-week cycle)

Placebo

• All patients received BSC
• Treat until progression, death, unacceptable toxicity, or withdrawal
• Radiologic evaluation every 8 weeks

Treat until progression, death, unacceptable toxicity, or withdrawal

Patients with mCRC who progressed after standard therapies

Primary endpoint OS

Regorafenib Trials

<table>
<thead>
<tr>
<th></th>
<th>CORRECT¹</th>
<th>CONCUR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>N = 760</td>
<td>N = 204</td>
</tr>
<tr>
<td></td>
<td>16 countries in Europe, North America, Asia-Pacific region, rest of the world</td>
<td>China, Hong Kong, Taiwan, South Korea, Vietnam</td>
</tr>
<tr>
<td>Prior targeted biologic therapy: bevacizumab; cetuximab/panitumumab (KRAS wild-type)</td>
<td>Required</td>
<td>Allowed, but not required</td>
</tr>
<tr>
<td>Primary analysis of OS (assumed 33.3% improvement; HR 0.75 favoring regorafenib)</td>
<td>One-sided alpha 0.025 90% power</td>
<td>One-sided alpha 0.20 80% power</td>
</tr>
<tr>
<td>Stratification factors for randomization</td>
<td>Previous treatment with VEGF-targeting drugs; time from mCRC diagnosis (≥18 vs &lt;18 months); geographic region</td>
<td>Number of metastatic sites (single vs multiple); time from mCRC diagnosis (≥18 vs &lt;18 months)</td>
</tr>
</tbody>
</table>

11/14/2016

Regorafenib Efficacy


**Overall survival**

![Graph](https://www.nexavar-us.com/scripts/pages/en/patient/about-nexavar/possible-side-effects/skin-reactions/)

**Progression-free survival**

![Graph](https://www.nexavar-us.com/scripts/pages/en/patient/about-nexavar/possible-side-effects/skin-reactions/)

---

Hand-Foot Skin Reaction: Regorafenib

![Image](https://www.nexavar-us.com/scripts/pages/en/patient/about-nexavar/possible-side-effects/skin-reactions/)

TAS-102: Mechanism of Action

**TAS-102** (Oral Combination Drug)

Molar ratio = 1 : 0.5

**TF-Thy** (inactive form)

TPase

**TFT**

Inhibition of tumor growth

**TF-TMP**

**TPI**

TF-TDP

**TF-TTP** incorporation into DNA

DNA dysfunction

---

TFT, trifluridine; TPase, thymidine phosphorylase; TPI, thymidine phosphorylase inhibitor.

Yoshino et al., 2014.

---

TAS-102 Study Design

Patients with mCRC who progressed after standard therapies

R 2:1

TAS-102 35 mg/m² BID on days 1–5 and 8–12 every 28 days

- All patients received best supportive care
- Treat until progression, death, unacceptable toxicity, or withdrawal
- Radiologic evaluation every 8 weeks

Primary endpoint OS

Placebo

TAS-102 = trifluridine/tipiracil

Trifluridine is a nucleoside analog.

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, prevents rapid metabolism of trifluridine, increasing bioavailability

Overall Survival


![Overall Survival Graph]

<table>
<thead>
<tr>
<th>Months From Randomization</th>
<th>Survival Distribution Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

N at risk:
- **TAS-102** N = 534
  - 534
  - 459
  - 294
  - 137
  - 64
  - 23
  - 7
- **Placebo** N = 266
  - 266
  - 198
  - 107
  - 47
  - 24
  - 9
  - 3

Events # (%)
- **TAS-102**: 364 (68)
- **Placebo**: 210 (79)

HR (95% CI)
- 0.68 (0.58-0.81)

Stratified Log-rank test P = .0001

Median OS, months
- **TAS-102**: 7.1
- **Placebo**: 5.3

Median follow-up: 5.4 months

Alive at, %
- **6 months**: 58
  - **TAS-102**: 58
  - **Placebo**: 44
- **12 months**: 27
  - **TAS-102**: 27
  - **Placebo**: 18

TAS-102 Lab Toxicities

<table>
<thead>
<tr>
<th>Event</th>
<th>TAS-102 (N = 533)</th>
<th>Placebo (N = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Laboratory abnormalities—no./total no. (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>353/528 (67)</td>
<td>200/528 (38)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>467/528 (77)</td>
<td>113/528 (21)</td>
</tr>
<tr>
<td>Anemia</td>
<td>404/528 (77)</td>
<td>90/528 (18)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>223/528 (42)</td>
<td>27/528 (5)</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>126/526 (24)</td>
<td>10/526 (2)</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>155/524 (30)</td>
<td>23/524 (4)</td>
</tr>
<tr>
<td>Increase in total bilirubin</td>
<td>189/526 (36)</td>
<td>45/526 (9)</td>
</tr>
<tr>
<td>Increase in alkaline phosphatase level</td>
<td>205/526 (39)</td>
<td>42/526 (8)</td>
</tr>
<tr>
<td>Increase in creatinine level</td>
<td>71/527 (13)</td>
<td>5/527 (&lt;1)</td>
</tr>
</tbody>
</table>

*Denominator for percentage of patients is number of patients with at least one postbaseline measurement during treatment.

Potentially High Impact Rare Metastatic Colorectal Cancer Subsets

Established Molecular Markers (anti-EGFR pathway)

- **KRAS**
  - Proto-oncogene
  - Predictive
  - 30%-50% of all patients
  - MT (exon 2): codons 12, 13, 61, and rarely 146

- **NRAS**
  - Mutations in codons 12, 13, 61, 117 and 146
  - Usually codon 61

- **BRAF**
  - Serine-threonine kinase belong to the RAF family
  - Mutation also leads to constitutive activation
  - V600E accounts for 90% of mutations
  - Found in < 10% of all CRC patients
  - Associated with hypermethylation of CpG island.
  - Median OS is 12-13M
Modest activity in BRAF-mutant mCRC compared with BRAF mutant melanoma (Response rate of ~5% vs ~60%-80%)

Signaling in BRAF-mutated CRC
Reactivation of EGFR signaling upon BRAF inhibition
Robust inhibition of MAPK pathway signaling with inhibition of BRAF, MEK, EGFR

**New Therapeutic Strategies for BRAF Inhibitors in BRAFV600-mutant mCRC**

- Oncogenic BRAF mutations are found in ~10% of colorectal cancers and predict poor prognosis and limited activity with anti-EGFR therapy

**Recent and ongoing trials for BRAF-mutant CRC:**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Treatment</th>
<th>Response Rate, (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF monotherapy</td>
<td>Vemurafenib</td>
<td>1/21 (5%)</td>
</tr>
<tr>
<td>BRAF + MEK</td>
<td>Dabrafenib + trametinib</td>
<td>5/43 (12%)</td>
</tr>
<tr>
<td>BRAF + EGFR</td>
<td>Vemurafenib + cetuximab</td>
<td>2/27 (7%)</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib + panitumumab</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td></td>
<td>Encorafenib + cetuximab</td>
<td>6/26 (23%)</td>
</tr>
<tr>
<td></td>
<td>Dabrafenib + panitumumab</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>BRAF + EGFR + MEK</td>
<td>Dabrafenib + panitumumab + trametinib</td>
<td>6/15 (40%)</td>
</tr>
<tr>
<td>BRAF + EGFR + PI3Kα</td>
<td>Encorafenib + cetuximab + alpelisib</td>
<td>7/28 (25%)</td>
</tr>
<tr>
<td>BRAF + EGFR + cytotoxic</td>
<td>Vemurafenib + cetuximab + irinotecan</td>
<td>4/9 (44%)</td>
</tr>
</tbody>
</table>


---

**SWOG 1406: BRAF + EGFR+ Irinotecan**

- Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for BRAF MT

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 80%
HER2 amplification is a driver of resistance to cetuximab in mCRC patient-derived xenografts (xenopatients).

HER2+ mCRC xenopatients are sensitive to dual HER2 blockade with lapatinib and trastuzumab but not to either drug alone.
HERCALES Trial for Her2 + mCRC

849 patients with mCRC KRAS exon 2 WT

803 HER2-negative

46 HER2+ (5.4%)

22 not eligible because PS ≥2 or tumor-related comorbidities

24 enrolled

1 too early for safety & efficacy assessment

23 evaluable for response

Trastuzumab IV 4mg/kg load and then 2mg/kg/qw
Lapatinib po 1000 mg/qd

PD


Phase II HERACLES: Response Rate

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responses (PR+CR)</td>
<td>8</td>
<td>34.7</td>
</tr>
<tr>
<td>Complete Response</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>Partial Response</td>
<td>7</td>
<td>30.4</td>
</tr>
<tr>
<td>Stable Disease ≥4 mos</td>
<td>7</td>
<td>30.4</td>
</tr>
<tr>
<td>Stable Disease &lt;4 mos</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5</td>
<td>21.7</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>100</td>
</tr>
</tbody>
</table>

Presented By Salvatore Siena at 2015 ASCO Annual Meeting
SWOG 1613: Study Design

KRAS/NRAS/BRAF Wild Type Metastatic Colorectal Cancer
(Either newly diagnosed or treated cases prior to treatment with cetuximab/panitumumab)

Enroll on S1613 (Step 1) for HER2 testing

(If available) perform local HER2 testing: IHC/FISH or Sequencing

Any evidence of HER2 amplification: IHC 2+ or 3+ or FISH HER2/CEP17 ≥ 2.0 or HER2 amplification reported on sequencing

Enroll on S1613 (Step 1) for HER2 confirmation

HER2 Testing in Central lab

HER2 amplification +

Enroll on S1613 (Step 2) for randomization

Arm 1 (N=48)
Trastuzumab + Pertuzumab

Arm 2 (N=48)
Cetuximab + Irinotecan

After Progression

Arm 3
Trastuzumab + Pertuzumab

PI: K Raghav
Primary Endpoint: PFS

ASCO 2015

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


Published May 30, 2015
Table 2. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N = 10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N = 18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%) ‡</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — % §</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA ‡</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA ‡</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients who were not evaluable were censored at the time of transition to pembrolizumab.
§ Patients with mismatch repair–proficient colorectal cancer had a disease control rate of 90% (95% CI: 55–100) and patients with mismatch repair–deficient colorectal cancer had a disease control rate of 11% (95% CI: 1–35).

Pembro Response by RECIST

Figure 1. Clinical Responses to Pembrolizumab Treatment.
Phase III NRG/SWOG CR-1556/SWOG

MSI-high mCRC without prior systemic treatment for metastatic disease (N = 435)

Endpoints
• Primary: PFS
• Secondary: OS, ORR, duration of response, safety and tolerability

Randomization
• 1:1:1 randomization.
• Stratified according to BRAF mutation (WT, MT), metastatic disease: (liver-only, extra-hepatic), and prior adjuvant therapy for CRC (yes, no).

Specified crossover at the time of disease progression
• Arm 1: Atezolizumab +/- mFOLFOX6/Bevacizumab components at physician discretion
• Arm 2: mFOLFOX6/Bevacizumab plus Atezolizumab
• Arm 3: SOC chemotherapy at physician discretion

Can PD-1/PD-L1 be effective in MSI-S (pMMR) patients?
Cobimetinib: A Highly Selective MEK1/2 Inhibitor

- The MAP kinase pathway is one of the most frequently dysregulated pathways in cancer due to hyperactivation by growth factor receptors or activating mutations
  - Sustained inhibition of RAS, RAF, MEK and ERK signaling may decrease proliferation and induce apoptosis
- Cobimetinib is a reversible, potent and highly selective inhibitor of MEK1 and MEK2 that has been approved for melanoma
- Single agent MEK inhibition has shown little activity in mCRC
- MEK inhibition alone can result in intratumoral T-cell accumulation and MHC I upregulation, and synergizes with an anti-PDL1 agent to promote durable tumor regression


Atezolizumab: An Anti-PDL1 Antibody

- Atezolizumab is a humanized engineered mAb that inhibits binding of PD-L1 to its receptors PD-1 and B7.1
  - This inhibition can enhance T-cell priming and restore anti-tumor T-cell activity
- Atezolizumab has demonstrated activity in several tumor types including lung cancer, metastatic urothelial carcinoma, and renal cell carcinoma
  - Response to PD-L1/PD-1 targeting agents in mismatch-repair proficient CRC (ie MSS) has been lower than seen in other indications

Phase Ib Dose Escalation and Cohort Expansion Study (NCT01988896)

Dose-Escalation Stage

(3 + 3)

- 20 mg cobi PO QD*
  800 mg atezo IV q2w
- 40 mg cobi PO QD*
  800 mg atezo IV q2w
- 60 mg cobi PO QD*
  800 mg atezo IV q2w

Key eligibility Criteria

- ECOG PS of 0 or 1
- Measurable disease per RECIST v1.1

Primary Objectives

- Safety and clinical activity of cobimetinib + atezolizumab

Dose-Expansion Stage

- KRAS MT mCRC
- NSCLC
- Metastatic Melanoma
- Solid tumors serial biopsy

DLT window of 28 days until MTD for combination is defined

Efficacy: Confirmed Objective Response

<table>
<thead>
<tr>
<th>Confirmed Response per RECIST v1.1</th>
<th>KRAS mutant CRC Cohort (n = 20)</th>
<th>All CRC Patients (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>20% (5.7, 43.7)</td>
<td>17% (5.0, 38.8)</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>SD</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>PD</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>NE</td>
<td>10%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Response did not correlate with PD-L1 status: IC0 (n = 2), IC1 (n = 1) and IC3 (n = 1)

NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy-evaluable patients: Data cutoff, February 12, 2016.
Phase III International COTEZO Trial

Primary endpoint: OS

Stratified by tumor extended RAS status and time since diagnosis of first metastasis
MSI-H capped at approximately 5%
At least 180 patients with extended RAS-mutant tumors to be enrolled

mCRC = metastatic colorectal cancer; MSI-H = microsatellite high.

Colorectal Cancer Young Adult (YA) Patient Population
Rising Incidence of CRC in Young Patients
SEER (1975 through 2010)
Based on current trends, by 2030:

Colon Cancer

Rectal Cancer

Chang et al: JAMA Surgery, 2014

Effect of Age on OS and PFS

Lieu et al: JCO, 2013
Conclusions:

- Colorectal cancer once a common cancer is now being considered a rare cancer based on molecular subsets
  - RAS WT
  - BRAF MT
  - Her-2 neu
- Early onset colorectal cancer remains a small percentage of patients but may be rising in incidence.
- We need to continue to offer all available agents to optimize the overall survival of our patients.
- Clinical trial enrollment is *always* encouraged whenever possible