Update on Molecular Targeted Therapies for mCRC

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Brave-ish New World—What’s Needed to Make Precision Oncology a Practical Reality

Laura E. MacConaill, PhD1,2; Neal I. Lindeman, MD1,2; Barrett J. Rollins, MD, PhD2,3

Having a biomarker for a targeted therapy is associated with significantly better outcomes

Regardless of whether the therapy is on the market or in clinical trials

<table>
<thead>
<tr>
<th>Phase I Studies</th>
<th>n = 13,203</th>
<th>Increase in Overall Survival</th>
<th>Increase in Progression-Free Survival</th>
<th>Increase in Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.75 months from 2.95 to 5.7</td>
<td>25.7% from 4.9% to 30.6%</td>
<td></td>
</tr>
<tr>
<td>Phase II Studies</td>
<td>n = 32,149</td>
<td>4.8 months from 8.9 to 13.7</td>
<td>3.2 months from 2.7 to 5.9</td>
<td>20.5% from 10.5% to 31.0%</td>
</tr>
<tr>
<td>Phase III Studies</td>
<td>n = 38,104</td>
<td>5.8 months from 13.5 to 19.3</td>
<td>2.8 months from 5.5 to 8.3</td>
<td>25.0% from 23.0% to 48.0%</td>
</tr>
<tr>
<td>NSCLC – In Practice</td>
<td>n = 17,664</td>
<td>4.7 months from 11.8 to 16.5</td>
<td>2.9 months from 7.1 to 10.0</td>
<td>4.0% from 33.0% to 37.0%</td>
</tr>
</tbody>
</table>

Comparisons between traditional therapies or targeted therapies selected without biomarkers vs. biomarker selected targeted therapies

2. Schwaederle M et al. JCO. 2015;33(32):3817-3825
4. Barlesi F et al. The Lancet. 2016;387(10028):1415-26. All differences noted are statistically significant p<0.05.
Number of Targeted Therapeutics is Rising

Knowing Which Tests to Order is the Challenge

Extrapolated from BioCentury Online Intelligence Database

Target Markers

- ROS1
- FBXW7
- DDR2
- KRAS
- STK11
- VEGF/VEGFR
- BRAF
- CDK6
- FLT3
- AURKA
- BRCA1
- CDK4
- CCND1
- CDKN2A
- AKT1
- DNMT3A
- NOTCH1
- IDH1/2
- MET
- FGFR1
- HER2
- PIK3CA
- NF1
- PTEN
- GATA3
- TSC1/2
- TSC2
- ALK
- MAP2K1
- TNF
- IGF/IGFR
- KDR
- TNF
- IDH1/2

Year

- 2005
- 2012
- 2015
- 2020
- 2025

~15 approved drugs hitting ~10 targets

Today

~700 compounds targeting ~150 targets in development

2025

Extrapolated from BioCentury Online Intelligence Database
The Colorectal Cancer Subtyping Consortium (CRCSC) identifies a network of molecular subtypes
OS – All Patients by CMS Subtype

CM S  Events/Total Median (95% CI)

- CMS1  85/104  15.0 (11.7-22.4)
- CMS2  173/242  40.3 (36.1-43.1)
- CMS3  58/68  24.3 (16.4-29.0)
- CMS4  127/167  31.4 (26.3-36.9)

Logrank P-value: <.0001
OS – CMS1 Patients by Arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events/Total</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>36/49</td>
<td>22.5 (15.9-32.6)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>49/55</td>
<td>11.7 (10.9-18.0)</td>
</tr>
</tbody>
</table>

Logrank P-value: 0.0290
NEXT-GENERATION SEQUENCING (NGS) IN METASTATIC COLORECTAL CANCER (MCRC): NOVEL MUTATED GENES AND THEIR EFFECT ON RESPONSE TO THERAPY

Federico Innocenti, Naim Rashid, Mu Wancen, Fang-Shu Ou, Xueping Qu, Stefanie Denning, Monica Bertagnolli, Charles David Blanke, Alan P. Venook, Omar Kabbarah, Heinz-Josef Lenz

For the Alliance and SWOG
MUTATED GENES ASSOCIATED WITH OS IN THE BEVACIZUMAB ARM (N=216)

**GRM3, HR= 2.34 (1.09,5.02), p=0.028, Adj. p=0.451**

**LRP1B, HR= 0.55 (0.32,0.97), p=0.041, Adj. p=0.451**

\[ \text{HR}_{\text{adj}} 2.68 \ (95\% \ CI \ 1.242-5.781) \]

\[ \text{P-value } 0.012 \]

\[ \text{HR}_{\text{adj}} 0.59 \ (95\% \ CI \ 1.242-5.781) \]

\[ \text{P-value } 0.012 \]
NOVEL PREDICTIVE MARKER FOR ANTI EGFR AND ANTI VEGF THERAPIES IN 80405 USING NGS

ARID1A (8.1%)

WT HR_{adj} 0.97 (95% CI 0.77-1.22)
Mutated HR_{adj} 2.29 (95% CI 1.27-4.13)
Interaction p 0.014

RNF43 (5.6%)

WT HR_{adj} 0.97 (95% CI 0.78-1.22)
Mutated HR_{adj} 2.38 (95% CI 1.22-4.63)
Interaction p 0.0003
Heterogeneity also exists within individual tumors

- Ding et al., Nature 2010
  - Mutations present in 5–90% of sequencing reads from one tumor
- Navin et al., Nature 2011
  - Independent subclones coexisting in a single anatomic site in breast
- Gerlinger et al., NEJM 2012
  - Two-thirds of mutations in single biopsies were not uniformly detectable throughout all sampled regions
- Both sensitive and resistant RNA expression patterns
Intra-tumor copy number heterogeneity in CRC at the single gland level

C. Curtis & colleagues
Nature Genetics 2016
Validation of metastasis driver modules

Metastasis associated early driver modules

- APC, KRAS, TP53, PIK3CA, TCF7L2
- PTPRT

Phenotypes:
- Normal
- Metastasis
- Primary colon cancer
- Metastatic disease

Clinically annotated CRCs with targeted sequencing (n=2751)

Early stage Metastatic disease

Fraction of patients

Early stage colon cancer (n=1813) Metastatic colon cancer (n=938)

Hu...Curtis Nature Genetics 2019
Liquid Biopsies

Tumor specific change (e.g. Mutation)

Tumor cell release DNA and RNA

Circulating Tumor Cells (CTC)

Circulating tumor DNA

Circulating tumor RNA

CTC

Normal DNA

Blood Vessel

http://www.inostics.com/
KRAS mut/ampl under pressure

Initial response to cetuximab followed by PD

Quantitative analysis of KRAS(Q61H) mutant DNA in plasma, as assessed by BEAMing

Routine liquid biopsy assessment can effectively identify mechanisms of resistance across different tumor types and treatments.

In patients with matched tumor biopsies, ctDNA identified additional resistance mechanisms in 64%.

Mechanism of resistance identified in 80%

36% with multiple resistance mechanisms (range 2-12; median 3)
EGFR antibodies in RAS-WT CRC

- 10 distinct resistance alterations identified across 21 patients
  - KRAS mutations
  - KRAS amplification
  - EGFR ECD mutations
  - MET amplification
  - ERBB2 amplification
  - Novel MEK1 mutation
- Some patients with 5 or more alterations present in ctDNA
Interesting Findings

1. In a small series of 10 patients who all had mt ras in tissue and liquid biopsy treated with bev based chemotherapy. 5/10 changed to wt Ras under chemotherapy ) Gazzaniga et al Annals of Oncology (2017) 28 (suppl_5): v573-v594

2. Case report in JCO Precision Oncology from same group reported PR in one of this patient treated with cetuximab
Monitoring of Resistance during anti-EGFR treatment

Example for Monitoring for Response and Resistance
Change of ctDNA levels and Loss and Grain of new ctDNA

In 84 patients with metastatic CRC receiving serial monitoring, 87% had either gain (61%) or loss (63%) of clones over time.


Heinz-Josef Lenz
CALGB/SWOG 80405

1ST LINE MET / ADVANCED COLORECTAL

FOLFIRI or FOLFOX
MD choice

ESMO, 2016

Chemo + Cetuximab
OS = 32.5 mos

: NO DIFFERENCE

Chemo + Bevacizumab
OS = 31.2 mos

N = 474 *

All RAS wt

* Right or left-sided primary Included in sidedness analysis

N = 1137

OS = 29.9 mos
PFS = 10.4 mos

OS = 29.0 mos
PFS = 10.8 mos

ESMO, SEP, 2014

N = 526

ASCO, JUNE, 2014

* Right or left-sided primary Included in sidedness analysis
80405: Overall Survival by Sidedness (all RAS wt)

<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>325 (238)</td>
<td>35.2 (32.1-39.0)</td>
<td>0.72 (0.56-0.92)</td>
<td>0.009</td>
</tr>
<tr>
<td>Right</td>
<td>149 (114)</td>
<td>21.9 (16.3-29.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 80405: OS by Sidedness (Bevacizumab)

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>Adjusted p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>152 (119)</td>
<td>32.6 (28.3-36.2)</td>
<td>0.88 (0.62-1.25)</td>
<td>.50</td>
</tr>
<tr>
<td>Right</td>
<td>78 (58)</td>
<td>29.2 (22.4-36.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Kaplan-Meier curve illustrates the percentage of event-free survival over time for patients with left and right sidedness. The table shows that patients with left sidedness have a median survival of 32.6 months with a hazard ratio of 0.88, while patients with right sidedness have a median survival of 29.2 months with a hazard ratio of 0.88. The adjusted p-value is .50, indicating no significant difference in survival between the two groups.
## 80405: OS by Sidedness (Cetuximab)

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>173 (119)</td>
<td>39.3 (32.9-42.9)</td>
<td>0.55 (0.39-0.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>Right</td>
<td>71 (56)</td>
<td>13.6 (11.3-19.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **X-axis:** Months From Study Entry
- **Y-axis:** % Event Free
### 80405: Sidedness Predictive for Biologics

#### Biologic by 1° Side Interaction

<table>
<thead>
<tr>
<th>BIOLOGIC</th>
<th>SIDE OF PRIMARY</th>
<th>HAZARD RATIO 95% CI</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any biologic OS</td>
<td>Cetux v Bev; left</td>
<td>1.81 (1.15, 2.84)</td>
<td>P_{int} = 0.009</td>
</tr>
<tr>
<td>Cetux v Bev OS</td>
<td>Left</td>
<td>0.77 (0.59, 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cetux v Bev OS</td>
<td>Right</td>
<td>1.36 (0.93, 1.99)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cetux v Bev OS</td>
<td>Right</td>
<td>1.64 (1.15, 2.36)</td>
<td>0.006</td>
</tr>
<tr>
<td>PFS</td>
<td>1.94 (1.28, 2.95)</td>
<td>P_{int} = 0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases*
FIRE-3: Right-sided tumors

**Progression-free survival**

Right-sided mCRC

- Cetuximab + FOLFIRI (n=38)
- Bevacizumab + FOLFIRI (n=50)

**Overall survival**

Right-sided mCRC

- Cetuximab + FOLFIRI (n=38)
- Bevacizumab + FOLFIRI (n=50)

**Numbers at Risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>60</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + FOLFIRI</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bevacizumab + FOLFIRI</td>
<td>8</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cetuximab + FOLFIRI</td>
<td>5</td>
<td>50</td>
<td>37</td>
<td>16</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bevacizumab + FOLFIRI</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**FIRE-3: Left-sided tumors**

### Progression-free survival

- **A** Left-sided mCRC
  - Cetuximab + FOLFIRI (n=157)
  - Bevacizumab + FOLFIRI (n=149)

  - HR = 0.90 (95% CI: 0.71–1.14)
  - p = 0.38

### Overall survival

- **B** Left-sided mCRC
  - Cetuximab + FOLFIRI (n=157)
  - Bevacizumab + FOLFIRI (n=149)

  - HR = 0.63 (95% CI: 0.48–0.85)
  - p = 0.002
**Left versus right colon cancer story: My Take**

- **Right-sided**
  - **T + EGFR-i** if ORR is a primary goal
  - **D/T + Bev** if OS is a primary goal

- **Left-sided**
  - **D + EGFR-i** if OS is a primary goal
  - **D + Bev** if EGFR-i are not accepted/tolerated

**Default recommendation**

**Legend**
- D: chemo doublet
- T: chemo triplet
Distinct Biology of R v. L CRC

Analysis of PETACC-3 samples (n=2849)

- BRAF mut
- MSI
- KRAS
- PIK3CA
- Mucinous differentiation

Right

- EREG expression
- 18q loss
- 20q Gain
- EGFR gain
- HER2 gain

Left

High mutation Frequency

Poor Prognosis

Sensitive to Cetuximab

Good Prognosis

Missiaglia, ASCO 2013
Study Design

Phase II, non comparative, study
Target accrual: 27 pts

mCRC pts RAS and BRAF wt

FOLFIRI/ FOLFOXIRI + Cetuximab

PD

FOLFOX/XELOX/ FOLFOXIRI + Bevacizumab

PD

Irinotecan + Cetuximab

≥ 6 Months

• At least a RECIST 1.1 partial response
• 1st-line PFS ≥6 months
• PD to 1st-line cetuximab within 4 weeks after the last cetuximab administration

≥ 4 Months

• Time between the end of 1st-line therapy and the start of 3rd-line ≥4 months

Study treatment:
Irinotecan 180 mg/sqm iv
Cetuximab 500 mg/sqm iv

DOI: 10.1200/JCO.2018.36.15_suppl.12007 Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 12007-12007
# Best Response

<table>
<thead>
<tr>
<th>Study population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 28</td>
<td></td>
</tr>
<tr>
<td>No (%) [95% CI]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td></td>
</tr>
<tr>
<td>- Confirmed Partial Response</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>- Unconfirmed Partial Response</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>- Radiological PD</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>- Clinical PD</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Response Rate</td>
<td>6 (21.5%) [10-40%]</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>15 (53.6%) [36-70%]</td>
</tr>
</tbody>
</table>

DOI: 10.1200/JCO.2018.36.15_suppl.12007
*Journal of Clinical Oncology* 36, no. 15_suppl (May 2018) 12007-12007
The CRICKET trial further demonstrates the potential of cetuximab rechallenge in RAS wt/BRAF wt mCRC

Phase II, multicentre, single-arm study

- **RAS/BRAF wt mCRC n=28**
  - Cetuximab + FOLFIRI/FOLFOXIRI
  - Bevacizumab + FOLFOX/FOLFOXIRI/XELOX
  - Cetuximab + irinotecan

**Primary endpoint met:** ORR: 22% (PR n=6, SD n=9, DCR: 54%)

- **PFS by RAS status**
  - mPFS RAS wt ctDNA (n=13): 4.0 months
  - mPFS RAS mt* ctDNA (n=12): 1.9 months
  - p=0.026
  - HR: 0.44 [95% CI: 0.18-0.98]

- **OS by RAS status**
  - mOS RAS wt ctDNA (n=13): 12.5 months
  - mOS RAS mt* ctDNA (n=12): 5.2 months
  - p=0.24
  - HR: 0.58 [95% CI: 0.22-1.52]

**RAS mt and EGFR mt resistant clones decay with a half-life of 4.8 months**

*Cetuximab is approved in patients with RAS wt mCRC. Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown; †Prior 1st line irinotecan-based and cetuximab-containing regimen with at least RECIST partial response lasting at least 6 months, and progression within 4 weeks after the last administration of cetuximab, prior 2nd line oxaliplatin-based and bevacizumab-containing treatment; ‡2 patients had unconfirmed partial response.

1. Rossini D, et al. ASCO 2018 Abstract 12007;
2. Parseghian C, et al. ASCO 2018 (Abstract No. 3511);
3. Erbitux SmPC Dec 2016.
Microsatellite Instability
Pembrolizumab

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC, N=28</th>
<th>MMR-proficient CRC, N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>57%</td>
<td>0%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>89%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Le DT, et al. NEJM 2015 and ASCO 2016
MSI-high CRC: Nivolumab Monotherapy

RR 31%
SD 39%
PD 24%

Disease Control ≥12 weeks in 69%

Overman et al. Lancet Oncology 2017
Reduction in Target Lesions Regardless of PD-L1 Expression, BRAF or Lynch History

Investigator-Assessed Best Change in Target Lesion Size (%)

Tumor PD-L1 Expression

- ≥ 1%
- < 1%
- + Confirmed CR/PR

BRAF Mutation Status

- Mutant
- Wild type
- + Confirmed CR/PR

Clinical History of Lynch Syndrome

- Yes
- No
- + Confirmed CR/PR

Overman et al. Lancet Oncology 2017
Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Heinz-Josef Lenz,1 Eric Van Cutsem,2 Maria Luisa Limon,3 Ka Yeung Mark Wong,4 Alain Hendlisz,5 Massimo Aglietta,6 Pilar García-Alfonso,7 Bart Neyns,6 Gabriele Luppi,9 Dana B. Cardin,10 Tomislav Dragovich,11 Usman Shah,12 Ajlan Atasoy,13 Roelien Postema,13 Zachary Boyd,13 Jean-Marie Ledeine,13 Michael James Overman,14 Sara Lonardi15

1USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; 2University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; 3Hospital Universitario Virgen del Rocio, Sevilla, Spain; 4Westmead Hospital, Sydney, Australia; 5Institut Jules Bordet, Brussels, Belgium; 6Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; 7Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; 8University Hospital Brussels, Brussels, Belgium; 9University Hospital of Modena, Modena, Italy; 10Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; 11Banner MD Anderson Cancer Center, Gilbert, AZ, USA; 12Lehigh Valley Hospital, Allentown, PA, USA; 13Bristol-Myers Squibb, Princeton, NJ, USA; 14The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 15Istituto Oncologico Vento IOV-IRCSS, Padova, Italy
Best Change From Baseline in Target Lesions

84% of evaluable patients had a reduction in tumor burden from baseline.

*Confirmed response per investigator assessment.
*Evaluable patients per investigator assessment.
Progression-Free and Overall Survival

**Progression-free survival**\(^a\)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
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<td>15</td>
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<td>18</td>
<td>13</td>
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<tr>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
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</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
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<td>13</td>
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<tr>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

**Progression Free Survival**

- **All patients**
  - Median PFS (95% CI), months: NR (NE)
  - 12-month rate (95% CI), %: 77 (62–87)
  - 15-month rate (95% CI), %: 75 (59–85)

**Overall Survival**

- **All patients**
  - Median OS (95% CI), months: NR (NE)
  - 12-month rate (95% CI), %: 84 (70–92)
  - 15-month rate (95% CI), %: 84 (70–92)

\(^a\)Per investigator assessment.

NE, not estimable.
HER2 Overexpression
HER2/neu 3+ (2+)
HERACLES Trial

Trastuzumab + Lapatinib in HER2+ / KRAS-wt pts refractory to ani-EGFR AK

849 patients screened, 46 patients (5.4%) HER2+ (2+/3+); 23 patients evaluable for response
ORR 35%, DCR 78%

*Siena, et al. ASCO 2015
My Pathway: Trastuzumab + Pertuzumab in HER-2 Amplified CRC

N = 34 patients

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>ORR (n=34) n (%) [95% CI]</th>
<th>CBR (n=34) n (%) [95% CI]</th>
<th>Median duration of clinical benefit (n=17) Months (95% CI)</th>
<th>Median PFS (n=34) Months (95% CI)</th>
<th>Median OS (n=34) Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=34)</td>
<td>13 (38.2 [22.2–56.4])</td>
<td>17 (50.0 [32.4–67.6])</td>
<td>10.3 (4.3–NE)</td>
<td>4.6 (1.6–9.8)</td>
<td>10.3 (7.2–22.1)</td>
</tr>
<tr>
<td>KRAS status</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wild-type (n=25)</td>
<td>13 (52.0 [31.3–72.2])</td>
<td>17 (68.0 [46.5–85.1])</td>
<td>10.3 (4.3–NE)</td>
<td>5.7 (3.6–12.4)</td>
<td>14.0 (8.0–22.1)</td>
</tr>
<tr>
<td>Mutated (n=9)</td>
<td>0 (0 [NE–NE])</td>
<td>0 (0 [NE–NE])</td>
<td>NA</td>
<td>1.4 (1.1–2.8)</td>
<td>5.0 (1.2–10.3)</td>
</tr>
<tr>
<td>Number of prior regimens</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;4 (n=12)</td>
<td>4 (33.3 [9.9–65.1])</td>
<td>4 (33.3 [9.9–65.1])</td>
<td>2.8 (2.8–NE)</td>
<td>2.2 (1.3–5.6)</td>
<td>8.0 (1.8–NE)</td>
</tr>
<tr>
<td>≥4 (n=22)</td>
<td>9 (40.9 [20.7–63.6])</td>
<td>13 (59.1 [36.4–79.3])</td>
<td>10.3 (4.3–NE)</td>
<td>5.6 (2.7–12.4)</td>
<td>10.3 (7.2–22.1)</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon, left side (n=14)</td>
<td>6 (42.9 [17.7–71.1])</td>
<td>9 (64.3 [35.1–87.2])</td>
<td>10.4 (9.8–11.1)</td>
<td>9.8 (1.4–12.4)</td>
<td>11.5 (8.5–22.1)</td>
</tr>
<tr>
<td>Colon, right side (n=8)</td>
<td>1 (12.5 [0.3–52.7])</td>
<td>1 (12.5 [0.3–52.7])</td>
<td>10.3 (NE–NE)</td>
<td>1.4 (1.1–3.9)</td>
<td>4.5 (1.2–14.0)</td>
</tr>
<tr>
<td>Rectum (n=11)</td>
<td>5 (45.5 [16.7–76.6])</td>
<td>6 (54.5 [23.4–83.3])</td>
<td>5.0 (2.8–NE)</td>
<td>5.6 (1.3–11.1)</td>
<td>10.3 (1.8–NE)</td>
</tr>
</tbody>
</table>

Hurwitz, H. GI ASCO 2018
ZW25: Azymetric™ Bispecific HER2-Targeted Antibody

- Designed using the Azymetric bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding results in novel mechanisms of action
A first in human study evaluating single agent activity in heavily pretreated HER2-expressing cancers is ongoing (NCT02892123).
DS-8201a Structure and Mechanism of Action

- DS-8201a was designed with the goal of improving critical attributes of an ADC
Ant-Tumor Activity of DS-8201a

Consistent Tumor Shrinkage Across Tumor Types: (5.4 or 6.4 mg/kg)

Tumor Shrinkage Over Time by Tumor Type (5.4 or 6.4 mg/kg)

- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

*Includes subjects who had a postbaseline scan, had tumor decrease ≥20% from baseline and >50% reduction in tumor size, respectively.
Optimal treatment of mCRC in the presence of braf
BEACON CRC Phase 3 Study Design

Safety Lead-in Completed

ENCO 300 mg QD + BINI 45 mg BID + CETUX 400 mg/m² (initial), then 250 mg/m² QW

N=30

Phase 3 Currently Enrolling

Triple therapy
ENCO + BINI + CETUX
n=205

Doublet Therapy
ENCO + CETUX
n=205

Control Arm
FOLFIRI + CETUX, or IRI + CETUX
n=205

Disease progression
Disease progression
Disease progression

Continued follow-up for evaluation of OS


Van Cutsem et al., ESMO GI 2018
Best Percentage Change in Tumor Measurements from Baseline

*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.
†One patient had no baseline sum of longest diameters and is not presented.

Van Cutsem et al., ESMO GI 2018
BEACON SLI: Overall Survival

Overall survival (%)

Survival Rate | 1 Prior Regimen | 2 Prior Regimens
---|---|---
6 mo | 88% | 85%
12 mo | 63% | 62%

Data fully mature through 12.6 months

Median OS: Not reached

1-year OS rate: 62%

Van Cutsem et al., ESMO GI 2018
Upfront therapy to suppress resistant clones

In vivo tumor xenografts with resistant clones pooled at 1% each

Hazar-Rethinam et al, Cancer Discovery 2018
Ras and effector dependencies

- **KRAS subtype lines:**
  - depend on the canonical RAS-RAF-MAPK pathway
  - upregulate genes involved in the maintenance of the epithelial phenotype

- **RSK subtype lines:**
  - depend on the RSK-MTOR/PI3K axis to drive aerobic metabolism to supplement glycolysis
  - express mesenchymal markers ZEB1, TGFB, TWIST

Tina Yuan, Rachel Bagni, Cyril Benes, Arnaud Amzallag, Bob Stephens, Ming Yi, FNLCR
Cell Feb 2018
Could KRAS Mutation be a Biomarker for PCM-075 Sensitivity in CRC?

Sensitivity to PLK1 inhibition in the presence of KRAS mutations in vitro

- In a genome-wide RNAi screen aimed at the identification of synthetic lethal interactions with the RAS oncogene PLK1 was identified
- KRAS mutated NIH3T3 cells showed higher sensitivity to PCM-075 compare to WT KRAS cells

*Nerviano Medical Sciences (NMS)*
PCM-075 in Combination with Anticancer Agents in CRC

- In the HCT116 cell line, PCM-075 was found to be synergistic in vitro with different classes of drugs including:
  - the chemotherapeutic agent cisplatin
  - the active metabolite of the topoisomerase inhibitor irinotecan (SN-38)
  - the microtubule inhibitor paclitaxel

- In the HT29 xenograft model, PCM-075 was found to be:
  - Synergistic with the topoisomerase inhibitor irinotecan
  - Additive with the chemotherapeutic agent fluorouracil (5FU) or the angiogenesis inhibitor bevacizumab
Right Treatment at the Right Time

- Genetic Testing of Tumor at time of diagnosis and if possible again at time of growth (CARIS, FOUNDATION, ORIEN)
- Genetic Testing of patients if evidence of Predisposition
- Active Monitoring with Liquid Biopsies
- Accelerating Access to Clinical Trials
The one who knows more, may decide better