Explaining the “unexplainable” : CALGB and FIRE-3 “discrepant” data

Aderka D¹, Stintzing S², Kopetz S³, Heinemann V.², Venook A⁴.

Sheba Medical Center and Tel- Aviv Universisty Israel¹, Department of Medicine III,
University Hospital, LMU Munich, Munich, Germany², Dept. of
Gastrointestinal Medical Oncology, MD Anderson Medical Center³,
Helen Diller Family Comprehensive Cancer Center, Univ. of California
San Francisco⁴
Disclosures:

Honoraria, Advisory board – Merck, Bayer, Teva
Disagreement

The “discrepant” data

2014
CALGB conclusion: Bevacizumab=Cetuximab

2013
Fire 3 conclusion: Cetuximab is significantly better than Bevacizumab

Alan P. Venook, ASCO annual meeting 2014, abstr LBA3

Volker Heinemann, ASCO annual meeting 2013, abstr LBA3506
2016  Cetuximab > Bevacizumab for left sided colon cancers

Venook AP, et al. ASCO 2016 (Abstract No. 3504)

Cetuximab may potentiate the effectiveness of Oxaliplatin. Oxaliplatin antagonizes Cetuximab effects on the cancer stem cells in the CMS4 subgroup. Oxaliplatin antagonizes Cetuximab effects on the cancer stem cells in the presence of fibroblasts.

Bevacizumab

CALGB (FOLFOX 75%/FOLFIRI 25%)

CMS1

Disagreement

FIRE-3 (FOLFIRI 100%)

CMS2

Agreement

Heinz-Josef Lenz, ASCO Annual Meeting abstr 3511

Sebastian Stintzing ASCO Annual Meeting 2017 abstr 3510
CALGB (FOLFOX 75%/FOLFIRI 25%)

CMS3

Bevacizumab
Cetuximab
Disagreement

FIRE-3 (FOLFIRI 100%)

CMS4

Bevacizumab
Cetuximab
Disagreement

Heinz-Josef Lenz, ASCO Annual Meeting abstr 3511

Sebastian Stintzing  ASCO Annual Meeting 2017 abstr 3510
The data of the FIRE-3 and CALGB studies organized according to the median overall survival obtained for each CMS subtype.

<table>
<thead>
<tr>
<th>CMS Type</th>
<th>FIRE-3</th>
<th>CALGB/SWAG 80405</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan (100%)</td>
<td>Oxaliplatin (75%) / Irino (25%)</td>
</tr>
<tr>
<td>CMS1</td>
<td>17.9</td>
<td>11.7</td>
</tr>
<tr>
<td>CMS2</td>
<td>38.3</td>
<td>42.0</td>
</tr>
<tr>
<td>CMS3</td>
<td>16.6</td>
<td>26.8</td>
</tr>
<tr>
<td>CMS4</td>
<td>40.1</td>
<td>30.8</td>
</tr>
</tbody>
</table>

NO CONSISTENCY!

If the same **biological** in the same **microenvironment** has a different response, the **third** variable is probably responsible for his difference: the **chemotherapy**?
Let’s ignore for a moment the results generated by the two studies. There must be an interplay between -Biologics -Chemotherapy -Microenvironment

Can we deduce from the available scientific data the results of the interplay between these factors for each CMS subtype?
It suggests that the response to Bevacizumab is dependent on the specific tumor microenvironment!
It suggests that the response to Bevacizumab is dependent on the specific tumor microenvironment!

Can this excess of fibroblasts and monocytes explain the relative resistance to Bevacizumab in the CMS1 and CMS4 subgroups?
Cancer associated fibroblasts and tumor associated macrophages (TAM) mediate resistance to Bevacizumab by release of alternative pro-angiogenic factors!
Cancer associated fibroblasts and tumor associated macrophages (TAM) mediate resistance to Bevacizumab by release of alternative pro-angiogenic factors!

Thus, Bevacizumab is not enough to prevent angiogenesis in a fibroblast and monocyte rich microenvironment.
Molecular subtype assay reveals anti-EGFR response subclones in colorectal cancer (CRC)

Elisa Fontana¹, Gift Nyamundanda¹, David Cunningham², Chanthiraka Ragulan¹, Francesco Sclafani², Ines Vendrell³, Sing Yu Moorcraft², Maria Antonietta Balí³, Sanna Hulkk-Wilson², Katherine Eason¹, Yatish Patil¹, Ruwaida Begum³, Ian Chau², Naureen Starling³, and Anguraj Sadanandan¹.

Fontana E. et al. ASCO GI 2018 (abstract 658)
Despite the fact that all the tumors are Ras-WT, the response to Cetuximab is dependent on the tumor and its microenvironment!
Combination of the response to Cetuximab and Bevacizumab in the CMS microenvironments.

Venook AP, et al. ASCO 2016 (Abstract No. 3504)
Fontana E. et al. ASCO GI 2018 (abstract 658)
Mooi J. et al: ESMO 2017 (abstract 4790)
Combination of the response to Cetuximab and Bevacizumab in the CMS microenvironments.

On the left side, characterized by excess CMS2 and CMS4, Cetuximab is more effective than Bevacizumab.

Venook AP, et al. ASCO 2016 (Abstract No. 3504)
Fontana E. et al . ASCO GI 2018 (abstract 658)
Mooi J. et al: ESMO 2017 (abstract 4790)
Combination of the response to Cetuximab and Bevacizumab in the CMS microenvironments.

On the left side, characterized by excess CMS2 and CMS4, Cetuximab is more effective than Bevacizumab.

Venook AP, et al. ASCO 2016 (Abstract No. 3504)
Fontana E. et al. ASCO GI 2018 (abstract 658)
Mooi J. et al: ESMO 2017 (abstract 479O)
Bevacizumab seems equal to Cetuximab regarding response in the CMS1 group but is better than Cetuximab in the CMS3 group (rt. side).
Bevacizumab seems equal to Cetuximab regarding response in the CMS1 group but is better than Cetuximab in the CMS3 group (rt. side).

Presented By Alan Venook at 2016 ASCO Annual Meeting abstr 3504
Is there a difference in the response to \textit{chemotherapy} between the CMS subtypes?
For 15 years we consider that Oxaliplatin and Irinotecan have “identical” clinical effects.

FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study

Christophe Tournigand, Thierry André, Emmanuel Achille, Gérard Lledo, Michel Flesh, Dominique Mery-Mignard, Emmanuel Quinaux, Corinne Coutau, Marc Buyse, Gérard Ganem, Bruno Landi, Philippe Colin, Christophe Louvet, and Aimery de Gramont

*Fig 4. Overall survival curves. FOLFIRI, folic acid, fluorouracil, and irinotecan; FOLFOX6, folic acid, fluorouracil, and oxaliplatin.*
Clinical Outcome From Oxaliplatin Treatment in Stage II/III Colon Cancer According to Intrinsic Subtypes Secondary Analysis of NSABP C-07/NRG Oncology Randomized Clinical Trial

Song et al, JAMA Oncol. 2:1162-9, 2016

The response to oxaliplatin is dependent also on the tumor microenvironment!
Is the sensitivity to \textit{Irinotecan} also dependent the CMS subtypes?
A colorectal cancer classification system that associates cellular phenotype and responses to therapy


Irinotecan response by CMS subtypes

Irinotecan CMS4>CMS1>CMS2=CMS3

CMS2 is responsive to Oxaliplatin irrespective of the biologicals.

CMS4 is responsive to IRINOTECAN irrespective of the biologicals.

Some subtypes of CRC have primary resistance to Oxaliplatin or Irinotecan!

Assuming that Cetuximab synergism with the chemotherapy should be proportional to its activity in each microenvironment...

Biologicals synergize with Oxaliplatin and Irinotecan to overcome the tumor resistance and improve chemotherapy effectiveness.
Biologicals synergize with Oxaliplatin and Irinotecan to overcome the tumor resistance and improve chemotherapy effectiveness.
In a fibroblast and a monocyte-rich microenvironment Oxaliplatin may antagonize the Cetuximab effects!

Chemotherapy activates cancer-associated fibroblasts to maintain colorectal cancer-initiating cells by IL-17A

Fiorenza Lotti,1 Awad M. Jarrar,4 Rish K. Pai,5 Masahiro Hitomi,2,6 Justin Lathia,1,2,6,9 Adam Mace,4 Gerald A. Gantt Jr.,4 Kumar Sukhdeo,1 Jennifer DeVecchio,1 Amit Vasanji,7 Patrick Leahy,8 Anita B. Hjelmeland,1 Matthew F. Kalady,1,3,4,6 and Jeremy N. Rich1,6,9

Cancer cell
NK-cell
Dendritic cell
Cytotoxic T-cell
Oxaliplatin
AKT
TGF-β
Cancer Stem cell
Growth inhibition
Apoptosis
IL-17
Oxaliplatin
Cetuximab

Guo B. et al: Oncotarget 8:44465, 2017
In a fibroblast and a monocyte-rich Microenvironment (CMS1, CMS4?) Oxaliplatin may antagonize Cetuximab benefit by its off-target effects.

Guo B. et al: Oncotarget 8:44465, 2017

A fibroblast and monocyte rich microenvironment (such as CMS4 and CMS1), *antagonize* the Cetuximab effects in the presence of Oxaliplatin.
If this analysis is correct, can it explain the apparent contradictory and conflicting data of CALGB and FIRE-3?
b. Bevacizumab 1st line based treatment

Oxaliplatin or Irinotecan

Is Oxaliplatin a better partner for Bevacizumab than Irinotecan?

Oxaliplatin may reduce Cetuximab effects in CMS1 and CMS4.

Is Oxaliplatin a better partner for Bevacizumab than Irinotecan?

Cetuximab synergism

Oxaliplatin antagonism
Bevacizumab

Overall Survival By Arm (All RAS Wild Type Patients)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>258</td>
<td>31.2 (30.0-32.4)</td>
<td>0.94 (0.71-1.23)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>178</td>
<td>28.9-34.3 (27.6-38.5)</td>
<td>0.7 (0.54-0.90)</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Disagreement

Alan P. Venook, ASCO annual meeting 2014, abstr LBA3

Volker Heinemann, ASCO annual meeting 2013, abstr LBA3506
Bevacizumab

Cetuximab

Bevacizumab

Oxaliplatin

Irinotecan

**2014**

**CALGB:** Bevacizumab = Cetuximab

**2013**

**Fire 3:** Cetuximab is significantly better than Bevacizumab

**Disagreement**

**Alan P. Venook, ASCO annual meeting 2014, abstr LBA3**

**Volker Heinemann, ASCO annual meeting 2013, abstr LBA3506**

---

**Overall Survival By Arm (All RAS Wild Type Patients)**

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem Only</td>
<td>356</td>
<td>33.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem + Cet</td>
<td>270</td>
<td>32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem + Cet</td>
<td>177</td>
<td>27.6-38.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oxaliplatin may antagonize Cetuximab effects (in CMS1 and 4)

Oxaliplatin synergizes with Bevacizumab (?)
Conclusions:

1. The response to treatment is not dependent solely on a single variable such as a biological but on a complex synergistic-antagonistic interaction between the biologicals, the chemotherapy backbone and the specific tumor microenvironment.

- Oxaliplatin
- Irinotecan
- The chemotherapy backbone

- Bevacizumab
- Cetuximab
- The biological

- Synergism
- Antagonism

- The microenvironment

- Dendritic cell
- NK-cell
- Cytotoxic T-cell
- Tumor cell
- M2
- CAF
- Net cell
The original question of the studies was “What is the best biological to combine with the chemotherapy in 1st line CRC?” assuming that Oxaliplatin and Irinotecan have identical activity...

3. Correct question: What is the best chemotherapy + biological combination for each colon cancer subtype?

3. The two studies are not controversial or discrepant: they are complementary!
4. The best chemotherapy + biological combination for each colon cancer subtype:

- **CMS1**:
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 17.9 months
  - Oxaliplatin + Bevacizumab
  - Median Overall survival: 13.1 months

- **CMS2**:
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 38.3 months
  - Bevacizumab
  - Median Overall survival: 29.1 months
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 42.0 months
  - Bevacizumab
  - Median Overall survival: 36.0 months

- **CMS3**:
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 16.6 months
  - Oxaliplatin + Bevacizumab
  - Median Overall survival: 18.6 months
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 26.8 months
  - Bevacizumab
  - Median Overall survival: 15.1 months

- **CMS4**:
  - Oxaliplatin + Cetuximab
  - Median Overall survival: 40.1 months
  - Oxaliplatin + Bevacizumab
  - Median Overall survival: 21.1 months
  - Oxaliplatin + Bevacizumab
  - Median Overall survival: 30.8 months
  - Bevacizumab
  - Median Overall survival: 32.7 months

---

5. If the presented analysis will be extended to sidedness and further validated, it opens new avenues for optimization of the personalized treatment in the different metastatic colorectal cancer subtypes.
“The third wheel”

Chemotherapy | Biological | Microenvironment

Synergism | **Antagonism**

Thank you!