THE BEST OF ESMO 2016

Colorectal cancer

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DISCLOSURES

- JT has received research funding and/or acted in consultancy/advisory and/or participated in symposia roles for Roche, AMGEN, MERCK Serono, AMGEN, Lilly, Baxalta, Celgène received research funding from Roche and Merck Serono
NON METASTATIC DISEASE
Surgery for rectal cancer after radiochemoherapy, 6-7 or 11-12 weeks?

Does it increase the pCR rate?  
Sphincter preservation? Survival?
Prospective randomized controlled
6 vs 12 weeks trial

• Primary end point: to increase MRI downstaging from 40% (6w) to 60% (12w)

• Patients: 237 from 21 centres (37% of them included in one centre)

• MRI: at initial staging (pre CRT) and at 6 week +/- 12 week

• Work up then radiotherapy then surgery at 6-8 weeks or 14 weeks

Prospective randomized control 6 vs 12 trial

- 122 patients (6-week arm), 115 patients (12-week arm)
- **mrT down-staging**
  - 52 patients (43%) 6-week
  - 67 patients (58%) 12-week
  - \( p = 0.019 \)
- **mrN down-staging**
  - 54 patients (44%) 6 week
  - 61 patients (53%) 12 week
  - NS

_Hypothesis 40 \( => 60\% \)_
<table>
<thead>
<tr>
<th></th>
<th>6 week n=122</th>
<th>12 week n=115</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>mrTRG 1</td>
<td>6%</td>
<td>22%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRM involvement</td>
<td>68%</td>
<td>61%</td>
<td>NS</td>
</tr>
<tr>
<td>EMVI</td>
<td>50%</td>
<td>33%</td>
<td>0.001</td>
</tr>
<tr>
<td>ypT0</td>
<td><strong>7.4%</strong></td>
<td>20%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ypN0</td>
<td>42%</td>
<td>55%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>pTRG 1 = pCR</td>
<td><strong>9%</strong></td>
<td>20%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

- No significant differences between the 2 arms for surgical morbidity.
- 1% anastomotic leak???
Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6)

Jérémie H. Lefèvre, Laurent Mineur, Salma Kotti, Eric Rullier, Philippe Rouanet, Cécile de Chaisemartin, Bernard Meunier, Jafari Mehrdad, Eddy Cotte, Jérôme Desrane, Mehdi Karouï, Stéphane Benoist, Sylvain Kirzin, Anne Berger, Yves Panis, Guillaume Piessen, Alain Saudemont, Michel Prudhomme, Frédérique Peschard, Anne Dubois, Jérôme Loriau, Jean-Jacques Tuch, Guillaume Meurette, Renato Lupinacci, Nicolas Goasger, Yann Parc, Tabassome Simon, and Emmanuel Tiret

- 265 patients with T3-T4 and/or N+ rectal cancers from 24 centres
- randomized after the completion of CRT
- between 7-week and 11-week interval before surgery
pCR rate (ypT0N0): 15% (7w) vs 17.4% (11w) \( p=0.6 \)

Per protocol

Lefèvre J et al. JCO 2016
### Surgical morbidity

<table>
<thead>
<tr>
<th>Postoperative course</th>
<th>7 weeks</th>
<th>11 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall morbidity</strong></td>
<td>97 (38.3)</td>
<td>40 (32)</td>
</tr>
<tr>
<td><strong>Dindo classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>16 (16.7)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>II</td>
<td>44 (45.8)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>III</td>
<td>28 (29.2)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (8.3)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>V</td>
<td>2 (2.1)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>17 (6.7)</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td><strong>Mean units of packet blood</strong></td>
<td>2.6 ± 1.1</td>
<td>2.9 ± 1.4</td>
</tr>
<tr>
<td><strong>Anastomotic leakage</strong></td>
<td>34 of 227 (15.0)</td>
<td>18 of 113 (15.9)</td>
</tr>
<tr>
<td><strong>Management of anastomotic leakage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reintervention</td>
<td>17 (50)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Percutaneous drainage</td>
<td>6 (17.7)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>11 (32.4)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Perineal complications after APR</td>
<td>8 of 26 (30.8)</td>
<td>2 of 12 (16.7)</td>
</tr>
<tr>
<td><strong>Medical complications</strong></td>
<td>66 (26.1)</td>
<td>24 (19.2)</td>
</tr>
<tr>
<td>Urinary complications</td>
<td>33 (13.0)</td>
<td>12 (9.6)</td>
</tr>
<tr>
<td>Postoperative ileus</td>
<td>16 (6.3)</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>6 (2.4)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Dehydration/ionic disturbance</td>
<td>5 (2.0)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Vein thrombosis</td>
<td>4 (1.6)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Other medical complication</td>
<td>13 (5.1)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Reintervention rate</td>
<td>25 (9.9)</td>
<td>12 (9.6)</td>
</tr>
<tr>
<td><strong>Mean hospital stay, days</strong></td>
<td>12.5 ± 10.3</td>
<td>11.7 ± 8.9</td>
</tr>
</tbody>
</table>

Lefèvre J et al. JCO 2016
TO CONCLUDE

- Complete and detailed data needed
- 6 weeks may be too early
- 12 weeks may be too late
- 7 to 9 weeks seems enough to reach an optimal pCR without increasing morbidity
NGS ASSESSMENT OF CETUXIMAB ADJUVANT TRIAL

Is there a place?

- Better HR than MOSAIC (0.8)
- Clinically relevant
- Not significant
- Subgroup Analysis (unplanned)

=> New trial in hyper selected patients
RAS/BRAF WT may be of interest

HR = 0.77
P = 0.1

Taieb et al ESMO 2016
Does surveillance matters?

Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

R. Labianca1, B. Nordinger2, G. D. Beretta2, S. Mosconi2, M. Mandalà3, A. Cervantes4 & D. Arnold5 on behalf of the ESMO Guidelines Working Group

1Villega, Equipo de Oncologa del Culo, Valencia, Spain; 2Department of Medical Oncology, Ospedale di Venezia, Verona, Italy; 3Department of Oncology and Medical Oncology, A.O.U. La Sapienza, Rome, Italy; 4Department of Medicine of Cancer Care, Karolinska, Stockholm, Sweden; 5Department of Oncology and Medical Oncology, University of Southern California, Los Angeles, USA


Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

B. Gamelius1, E. Tirol1, A. Cervantes9 & D. Arnold5 on behalf of the ESMO Guidelines Working Group

1Department of Oncology, University of Malaga, Malaga, Spain; 2Department of Oncology, Niguarda hospital, Milan, Italy; 3Department of Medicine of Cancer Care, Karolinska, Stockholm, Sweden; 4Department of Medical Oncology, Ospedale di Venezia, Verona, Italy; 5Department of Oncology and Medical Oncology, University of Southern California, Los Angeles, USA


Jeffrey A. Meyerhardt, Pamela B. Magnus, Brett J. Fyfe, Larissa K. Kowde, Charles L. Layden, Bruce E. Marks, Nicholas J. Pirozzolo, Kim Ross, Deborah H. Schrag, Safiya L. Wong, and Ali H. Bening III

J Clin Oncol 31:4465-4470

Regular CEA monitoring
Colonoscopy at year 1 and every 3–5 years
Consider CT FU in patients at higher risk

Clinical assessment 6 monthly for 2 years
Hx and colonoscopy every 5 years (up to 75)
Additional FU for patients with symptoms

Regular CEA and CT FU for Stage II-III CRC
Insufficient evidence for stage I disease
Colonoscopy at 1 year and every 5 years
Does surveillance matter?

6-12 year results from the FACS trial

1211 patients

- 301 minimum follow-up
- 300 CEA follow-up
- 299 CT follow-up
- 302 CEA & CT follow-up

Pugh S et al. Abstract 4530. ESMO 2016
6-12 year results from the FACS trial

<table>
<thead>
<tr>
<th></th>
<th>Minimum follow-up</th>
<th>Intensive follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=301</td>
<td>n=300</td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td>38 (12.6%)</td>
<td>56 (18.7%)</td>
</tr>
<tr>
<td></td>
<td>61 (20.4%)</td>
<td>48 (15.9%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.06</td>
<td>0.008</td>
</tr>
<tr>
<td>Surgically treatable recurrence, n (%)</td>
<td>8 (2.7%)</td>
<td>19 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>28 (9.4%)</td>
<td>21 (7%)</td>
</tr>
<tr>
<td>Among recurrences, treatable (%)</td>
<td>21%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td><strong>46%</strong></td>
<td><strong>44%</strong></td>
</tr>
</tbody>
</table>

Intensive follow-up identified more recurrences surgically treatable with curative intent

Does it translate in improvement of survival?

Pugh S et al. Abstract 4530. ESMO 2016
Does surveillance matters?

- OF COURSE NOT in ITT or per-protocol
- But what is important is survival in patients that HAVE RELAPSED!!!
- <100 relapses out of 1200 pts

Yes surveillance matters especially CT-scan +++ and brings more patients to a curative strategy at relapse!
News from very rare mutations!

- Little is know about rare mutations in stage III colon cancer

- Their prognostic value may be important to stratify clinical trials or intensify adjuvant treatments in the future

- They may have predictive value as well !!!
News from very rare mutations/alterations!

Rare RAS and BRAF mutations are not prognostic (except codon 61)

Impact of rare individual mutations on TTR

- KRAS Exon 2 (n=785)
  - Codon 12 (n=594)
  - Codon 13 (n=171)
- KRAS Exon 3 (n=42)
  - Codon 61 (n=34)
- KRAS Exon 4 (n=9)
  - Codon 13 (n=6)
  - Codon 12 (n=3)
- NRAS Exon 2 (n=31)
  - Codon 12 (n=26)
- NRAS Exon 3 (n=31)
- BRAF V600E (n=192)
- BRAF non V600E (n=21)

Favors mutant Favors WT

10%

HER2/ERBB2 a bad prognostic factor (sensitive to anti-HER2?)

3.9%

PolE a good prognostic factor (Sensitive to anti-PD(L)-1?)

1%

Taieb et al. A; Puig et al. A; Domingo et al. ESMO 2016
METASTATIC DISEASE
What is the best maintenance?

- Capecitabine is better than chemotherapy stop \( (Luo\ Ann\ Oncol\ 2016) \)
- Bevacizumab alone = marginal benefit \( (SAKK, PRODIGE\ 9) \)
- Capecitabine + bevacizumab largely used and superior to bevacizumab alone or complete stop \( (CAIRO3, AIO0203) \)
- Added value of bevacizumab possible but still not proven?
- Maintenance with cetuximab suggested by a R ph II trial COIN.B
What is the best maintenance?

MACBETH: Study design

Phase II randomized non-comparative trial

mCRC pts:
✓ Unresectable disease
✓ Previously untreated for mts disease
✓ RAS and BRAF wt*

1:1

Arm A
mFOLFOXIRI + cetuximab§
up to 8 cycles

cetuximab§
until PD

Arm B
mFOLFOXIRI +
cetuximab§
up to 8 cycles

bevacizumab§
until PD

INDUCTION
MAINTENANCE

Cremolini et al. ESMO 2016
What is the best maintenance?

In RAS WT patients

Cetuximab seems to do better after cetuximab induction

In accordance with COIN B results

Still needs to be confirmed (insufficient number of patients)

Capecitabine+ ctx has now to be compared to capecitabine+ bev and to capecitabine alone!
Who side are you on?

- RAS WT subpopulation in all studies
- Tumor sidedness definition
- PEAK, FIRE.3 and CALGB
Who side are you on?

- RAS WT subpopulation in all studies
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- PEAK, FIRE.3 and CALGB

BRAF Mutants

Right colon

Left colorectum
Who side are you on?

- RAS WT subpopulation in all studies
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- BRAF Mutants
- Older patients
- Right colon
- MSI+
- CIMP+
- Left colorectum
- Transverse colon
- Rectosigmoid junction
- Sigmoid colon
- Rectum
- Hepatic flexure
- Splenic flexure
- Descending colon
Who side are you on?

- RAS WT subpopulation in all studies
- Tumor sidedness definition

BRAF Mutants

Older patients

Right colon

MSI+

CIMP+

Primary tumor not removed

Etc….
Who side are you on? (CALGB all RAS WT)

80405: Overall Survival by Biologic
(Right Sided Primary)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>Adjusted p</th>
</tr>
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<tbody>
<tr>
<td>Bev</td>
<td>78</td>
<td>29.2 (22.4-36.9)</td>
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80405: Overall Survival by Biologic
(Left Sided Primary)

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<tr>
<td>Bev</td>
<td>152</td>
<td>32.6 (28.3-36.2)</td>
<td>0.77 (0.59-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cetux</td>
<td>173</td>
<td>39.3 (32.9-42.9)</td>
<td></td>
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Venook et al. ESMO 2016
### 80405: Overall Survival by Biologic

#### Right Sided Primary

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#### Left Sided Primary

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Venook et al. ESMO 2016
Who side are you on? *(FIRE.3 and CRYSTAL all RAS WT)*

- Already presented before

- Cetuximab do better in **left sided** vs chemo alone or chemo + bevacizumab

- Still increased response rate in **right sided** induced by cetuximab

*Heinemann et al. and Van Cutsem et al. ESMO 2016*
Who side are you on: Conclusion (1)

Do we have to change our practice on unplanned subgroup analysis?

• Anti-EGFRs extremely efficient and > bevacizumab for LEFT SIDED

• Still increased response rate in RIGHT SIDED induced by cetuximab, how to identify them

• A trend to a better efficacy of bevacizumab in RIGHT SIDED but not significant yet
Who side are you on: Conclusion (2)

• LEFT SIDED: NO BEVACIZUMAB IN RAS WT (strong data)
  whatever my goal is (cytoreduction or stabilisation) as I target OS

• RIGHT SIDED: BOTH BEV OR ANTI-EGFRs REMAIN POSSIBLE but
  • Bad prognostic patients
  • Still more shrinkage with doublet anti-EGFRs
  • Better survival with bevacizumab

=> FOLFOXIRI+/- bevacizumab may be the good choice for patients able to receive it, clinical trials still needed
Last line treatments

• Sorafenib and irinotecan gives interesting results but what development in the future?

• TAS 102 confirms its efficacy and good tolerability in Asia

• FOLFIRI can combine with regorafenib and improves ORR and is tolerable with a modified regorafenib regimen

Samalin et al., Kim et al., O’Neil et al ESMO 2016
Phase II CCR m 2ème Ligne FOLFIRI +/- Regorafenib

- A multicenter, randomized, double-blind phase II trial of FOLFIRI + regorafenib or placebo

N = 240
Screening:
Obtain archival tissue for correlative studies in all patients, and fresh biopsy (optional) in subset²
mCRC following 1 prior oxaliplatin-containing regimen

Regorafenib 160 mg*
+ FOLFIRI
*Day 4–10, Day 18–24

FOLFIRI†
+ Placebo
†Day 1–2, Day 15–16

Repeat cycles² until documented tumor progression or unacceptable toxicity or study withdrawal or death


Obtain whole blood sample¹
Obtain blood samples on Day 21 cycle 2 and at end of treatment visit for correlative studies¹

Obtain blood samples on Day 21 cycle 2 and at end of treatment visit for correlative studies¹

Primary endpoint: PFS
Secondary endpoints: ORR, DCR, OS, PK, safety, and tolerability
Phase II CCR m 2ème Ligne FOLFIRI +/- Regorafenib

- Patients traités en 1L
  - Anti VEGF/ Anti EGFR / Aucune thérapie ciblée: 65.2% / 7.7% / 28.1%

- Bénéfice en survie sans progression (objectif principal)
  - 6.5 mois vs 5.3 mois, p=0.0473
  - B: Pas de bénéfice en survie globale (13.8 vs 11.7 mois NS)

Etude de phase II positive en PFS négative en OS
LUME: NINDETANIB IN LAST LINE

Negative for OS but positive for PFS???

PFS: 2.60 vs 1.41 mo
HR 0.57, P<0.0001

Investigator assessment

Van cutsem et al. ESMO 2016
CCTG CO.23: NAPABUCASIN IN LAST LINE

Negative for all comers but positive for Stat 3 + patients

Jonker et al. ESMO 2016
CCTG CO.23: NAPABUCASIN IN LAST LINE
Negative for all comers but positive for Stat 3 + patients

L2 Phase III ongoing...

Jonker et al. ESMO 2016
Acknowledgments

- For once I will not thank patients and their families
- I will thank my colleagues:

  - Chiara Cremolini
  - Florence Huguet
  - Marc Peeters
  - Heinz Joseph Lenz
  - Volker Heinemann
  - Eric Van Cutsem
  - Ramon Salazar
  - Per Pfeiffer
  - Jérémie Lefèvre
  - Ian Chau
  - Pierre Laurent Puig
  - Claus-Henning Khöne

For their excellent work and their slides ;}