How to deal with elderly patients or individuals with co-morbidities

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ESMO Preceptorship Programme – Colorectal Cancer

Metastatic Colorectal Cancer – Special Clinical Situations

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Disclosures

- Ad Boards: Roche, Novartis, Merck
- Speaker at sponsored meetings / satellite symposia: Roche, Amgen, Merck
- Financial support to attend conferences: Roche, Merck, MSD
Outline

- Introduction
- Geriatric Assessment
- Trials
- Conclusions
Outline

- Introduction
- Geriatric Assessment
- Trials
- Conclusions
Introduction

- CRC is predominantly a disease of the elderly
- Treatment guidelines are largely based on randomised trials involving only small numbers of fit older patients
- It is unclear whether treatment regimens that are beneficial for younger patients are also the best choice for the older population given their heterogeneity in physiological reserves, co-morbidities, functional status, and cognition.
Association of Age With Survival in Patients With Metastatic Colorectal Cancer: Analysis From the ARCAD Clinical Trials Program


ABSTRACT

Purpose
This study addressed whether age is prognostic for overall survival (OS) or progression-free survival (PFS) in patients with metastatic colorectal cancer (mCRC).

Patients and Methods
A total of 20,023 patients from 24 first-line clinical trials in the ARCAD (Aide et Recherche en Cancerologie Digestive) database were analyzed. Primary age effects and interactions with age, sex, performance status (PS), and metastatic site were modeled using Cox proportional hazards stratified by treatment arm within study.

Results
Of total patients, 3,051 (15%) were age \( \leq 50 \) years. Age was prognostic for both OS (\( P < .001 \)) and PFS (\( P < .001 \)), with U-shaped risk (ie, highest risk was evident in youngest and oldest patients). Relative to patients of middle age, the youngest patients experienced 19% (95% CI, 7% to 33%) increased risk of death and 22% (95% CI, 10% to 35%) increased risk of progression. The oldest patients experienced 42% (95% CI, 31% to 54%) increased risk of death and 15% (95% CI, 7% to 24%) increased risk of progression or death. This relationship was more pronounced in the first year of follow-up. Age remained marginally significant for OS (\( P = .08 \)) when adjusted for PS, sex, and presence of liver, lung, or peritoneal metastases, and age was significant in an adjusted model for PFS (\( P = .005 \)). The age effect did not differ by site of metastatic disease, year of enrollment, type of therapy received, or biomarker mutational status.

Conclusion
Younger and older age are associated with poorer OS and PFS among treated patients with mCRC. Younger and older patients may represent higher-risk populations, and additional studies are warranted.

J Clin Oncol 32:2975-2982. © 2014 by American Society of Clinical Oncology
Association of Age With Survival in Patients With Metastatic Colorectal Cancer: Analysis From the ARCAD Clinical Trials Program

Christopher H. Lieu, Lindsay A. Renfro, Aimery de Gramont, Jeffrey P. Meyers, Timothy S. Maughan, Matthew T. Seymour, Leonard Saltz, Richard M. Goldberg, Daniel J. Sargent, S. Gail Eckhardt, and Cathy Eng

Fig 2. Risk of (A) death and (B) progression or death as nonlinear function of age, with highest risk at young and old extremes; risk of (C) death and (D) progression or death as function of age according to performance status (PS); risk of (E) death and (F) progression or death as function of age according to sex; (G) risk of death and (H) progression or death as function of targeted or nontargeted therapy. Figures based on all available follow-up. Age-by-sex interaction was not significant.
Outline

• Introduction
• Geriatric Assessment
• Trials
• Conclusions
Geriatric assessment (1)

- Functional status
- Psychological health
- Polypharmacy
- Co-morbidities
- Nutrition
- Social support
- Cognition
Geriatric assessment (2)

Why bother in cancer patients?

- Can identify areas of vulnerability even in patients with ECOG PS (0,1)
- Can predict survival and adverse events during treatment (retrospective data)
- Can identify areas where interventions can be performed, such as dietary advice, physical therapy, and social support
**Proposed Approach**

Geriatric assessment in all patients age 70 years and older are considered for any cancer treatment and younger patients with age-related health concerns in high-resource settings.

**Self-administered portion**

- Functional evaluation—for example, ADL and IADL
- Depression—for example, GDS-5
- Medications are generally evaluated at clinic visits; for older individuals, greater emphasis is needed to minimize potential drug–drug interactions and de-prescribe unnecessary medications
- Comorbidity is often assessed at clinic visits, but oncologists may consider using a validated comorbidity index to quantify comorbidity
- Nutritional evaluation—for example, weight loss and MNA
- Social support; living situation and need for additional home support for older individuals—a social worker or other allied health care professional will often inquire about these circumstances

**Health care professional portion**

- Cognitive screening—for example, Mini-Cog or MMSE
- Physical performance—for example, TUG
- Chemotherapy toxicity risk calculation—for example, CARG or CRASH toxicity scores

**Geriatric screening tool** (one of the following) if at risk, followed by geriatric assessment described above—this may spare the efforts of full geriatric assessment in 20%-40% of patients:

- Geriatric 8
- Vulnerable Elders Survey-13
- Triage Risk Screening Tool
- Groningen Frailty Index
- Senior Adult Oncology Program 2
- Abbreviated Geriatric Assessment
- Fried frailty criteria

**Low-resource setting or if time is limited (one or more of the following):**

- One of the geriatric screening tools described above and chemotherapy toxicity risk calculation—for example, CARG or CRASH toxicity scores
- Referral to geriatrician if screened positive for impairment on geriatric screening tools
- If a geriatrician is not available, consider other tests on the basis of clinical impression and health areas at risk—for example, as indicated by screening tool; may consider ADL, IADL, and Mini-Cog in addition to the geriatric screening tool

Abbreviations: ADL, activity of daily living; CARG, Cancer and Aging Research Group; CRASH, Chemotherapy Risk Assessment Scale for High-Age Patients; GDS-5, Geriatric Depression Scale-5; IADL, instrumental activity of daily living; MMSE, Mini-Mental State Examination; MNA, Mini-Nutritional Assessment; TUG, Timed Get Up and Go.

*The self-administered portion can be done at home before the clinic visit or at the waiting area before physician encounter.
†The health care professional portion can be done while patients are waiting to be seen. Geriatric assessment can also be done over multiple visits.
### G8 Geriatric Assessment Tool - EORTC

<table>
<thead>
<tr>
<th>Items</th>
<th>Possible responses (score)</th>
</tr>
</thead>
</table>
| Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties? | 0 = Severe decrease in food intake  
1 = Moderate decrease in food intake  
2 = No decrease in food intake |
| Weight loss during the last 3 months?                                | 0 = Weight loss >3 kg  
1 = Does not know  
2 = Weight loss between 1 and 3 kg  
3 = No weight loss |
| Mobility?                                                             | 0 = Bed or chair bound  
1 = Able to get out of bed/chair but does not go out  
2 = Goes out |
| Neuropsychological problems?                                         | 0 = Severe dementia or depression  
1 = Mild dementia  
2 = No psychological problems |
| Body mass index (BMI)? (weight in kilograms) / (height in square metres) | 0 = BMI <19  
1 = BMI 19 to <21  
2 = BMI 21 to <23  
3 = BMI ≥23 |
| Takes more than three prescription drugs per day?                    | 0 = Yes  
1 = No |
| In comparison with other people of the same age, how does the patient consider his/her health status? | 0.0 = Not as good  
0.5 = Does not know  
1.0 = As good  
2.0 = Better |
| Age                                                                  | 0 = >85  
1 = 80–85  
2 = <80 |
| Total score 0–17                                                     | Cut-off ≤ 14 |
International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer


ABSTRACT

Purpose
To update the International Society of Geriatric Oncology (SIOG) 2005 recommendations on geriatric assessment (GA) in older patients with cancer.

Methods
SIOG composed a panel with expertise in geriatric oncology to develop consensus statements after literature review of key evidence on the following topics: rationale for performing GA; findings from a GA performed in geriatric oncology patients; ability of GA to predict oncology treatment-related complications; association between GA findings and overall survival (OS); impact of GA findings on oncology treatment decisions; composition of a GA, including domains and tools; and methods for implementing GA in clinical care.

Results
GA can be valuable in oncology practice for following reasons: detection of impairment not identified in routine history or physical examination, ability to predict severe treatment-related toxicity, ability to predict OS in a variety of tumors and treatment settings, and ability to influence treatment choice and intensity. The panel recommended that the following domains be evaluated in a GA: functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes. Although several combinations of tools and various models are available for implementation of GA in oncology practice, the expert panel could not endorse one over another.

Conclusion
There is mounting data regarding the utility of GA in oncology practice; however, additional research is needed to continue to strengthen the evidence base.

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Comprehensive Geriatric Assessment

**Group 1**: fit patients
- functionally independent
- no comorbidities

**Group 2**: ‘in-between’
- dependence in one activity
- 1-2 comorbidities

**Group 3**: frail patients
- dependence for daily activities
- ≥ 3 comorbidities

Cancer < Life Expectancy < Cancer

- Life-prolonging Treatment
- Adapted Treatment Only
- Palliation

Treatment of mCRC: ESMO Guidelines

Assessment of clinical condition of the patient

Fit

Untit* (but may be suitable)

FP+bevacizumab: reduced dose doublet; anti-EGFR

Untit*

GOAL

Patients with clearly resectable metastases

Surgery alone

Surgery with preoperative postoperative CT

MOLECULAR PROFILE

Cytoreduction (Shrinkage)**

OMD

See figure 2

RAS wt

RAS mt

BRAF mt

CT doublet + anti-EGFR

Combination CT + bevacizumab

CT triplet + bevacizumab

CT doublet + biological agent

CT doublet + bevacizumab

CT triplet +/- bevacizumab

Re-evaluation/assessment of response every 2 months*

GOAL

Progressive disease

Cytoreduction (Shrinkage)**

Disease control

Continue

Continue; maintenance; or pause

Second-line

Progressive disease

Second-line

Disease control (control of progression)

MOLECULAR PROFILE

RAS wt

RAS mt

BRAF mt

Re-evaluation/assessment of response every 2–3 months*

GOAL

Progressive disease

Continue; maintenance; or pause

Second-line

Integrating geriatric assessment in the first line chemotherapy treatment in older patients with metastatic colorectal cancer: Results of a prospective observational cohort study (AVAPLUS)

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f Department of Gastroenterology, AZ Diamant, Gasthuisstraat 100, 8400 Oostende, Belgium
g Department of Gastroenterology, AZ Maria Middelaars, Brusselsesteenweg 30, 9000 Gent, Belgium
h Department of Gastroenterology, Imelda Ziekenhuis, Imeldaak 9, 2820 Bornem, Belgium
i Department of Gastroenterology, AZ Groeninge, President Kennedylaan 4, 8500 Kortrijk, Belgium
j Department of Gastroenterology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium
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Metastatic colorectal cancer
Chemotherapy
Bevacizumab geriatric assessment

Abstract

Objectives: This study aims to investigate the use of chemotherapy with or without bevacizumab in older patients with metastatic colorectal cancer (mCRC) in current daily practice and to identify predictive parameters for treatment-related outcomes.

Patients and Methods: This is a Belgian multi-centre, observational cohort study. Patients ≥ 70 years old with mCRC considered suitable for first-line chemotherapy were eligible for inclusion. At baseline geriatric screening and assessment was performed. Treatment choice was at the discretion of the investigator. Treatment duration, Progression Free Survival (PFS) and safety were recorded.

Results: Between August 2011 and July 2013, 252 patients with mCRC were included of which 50.8% were treated with bevacizumab. Median treatment duration was 5.5 months and median PFS was 8.9 months. Approximately 50% of patients experienced severe adverse events, most frequently diarrhea. In multivariate analysis, baseline Eastern Cooperative Oncology Group (ECOG)-performance status (PS) was predictive for treatment duration (p = 0.0047), PFS (p < 0.0001) and severe toxicity and baseline nutritional status for PFS (p = 0.0007). In patients with a good ECOG-PS, nutritional status was predictive for PFS.

Conclusions: In current daily practice in Belgium, half of older patients with colorectal cancer treated with chemotherapy also receive bevacizumab. Nearly half of older patients presented with severe toxicity during treatment. Baseline nutritional status is a predictive marker for PFS. Patients with a baseline ECOG-PS ≥ 2 have shorter PFS and higher risk of severe toxicity and should therefore be treated with caution.
Table 4
Associations between geriatric assessment at baseline in univariate analysis – safety and reference population.

<table>
<thead>
<tr>
<th>GA score</th>
<th>Chemotherapy with or without bevacizumab</th>
<th>Chemotherapy backbone</th>
<th>Treatment duration</th>
<th>PFS</th>
<th>Severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-PS</td>
<td>p = 0.278</td>
<td>p = 0.385</td>
<td>p = 0.0006</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>G8</td>
<td>p = 0.305</td>
<td>p = 0.758</td>
<td>p = 0.0607</td>
<td>p = 0.0208</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>fTTRST</td>
<td>p = 0.003</td>
<td>p = 0.025</td>
<td>p = 0.2880</td>
<td>p = 0.4193</td>
<td>p = 0.081</td>
</tr>
<tr>
<td>MNA</td>
<td>p = 0.706</td>
<td>p = 0.657</td>
<td>p = 0.0162</td>
<td>p = 0.0001</td>
<td>p = 0.120</td>
</tr>
<tr>
<td>ADL</td>
<td>p &lt; 0.001</td>
<td>p = 0.357</td>
<td>p = 0.3462</td>
<td>p = 0.1217</td>
<td>p = 0.363</td>
</tr>
<tr>
<td>IADL</td>
<td>p = 0.507</td>
<td>p = 0.946</td>
<td>p = 0.6949</td>
<td>p = 0.0994</td>
<td>p = 0.238</td>
</tr>
<tr>
<td>MMSE</td>
<td>p = 0.081</td>
<td>p = 0.449</td>
<td>p = 0.0826</td>
<td>p = 0.3671</td>
<td>p = 0.843</td>
</tr>
<tr>
<td>GDS-15</td>
<td>p = 0.478</td>
<td>p = 0.213</td>
<td>p = 0.9381</td>
<td>p = 0.5714</td>
<td>p = 0.301</td>
</tr>
<tr>
<td>Mob-T</td>
<td>p = 0.085</td>
<td>p = 0.503</td>
<td>p = 0.3616</td>
<td>p = 0.1825</td>
<td>p = 0.069</td>
</tr>
<tr>
<td>CCI</td>
<td>p = 0.829</td>
<td>p = 0.371</td>
<td>p = 0.8309</td>
<td>p = 0.9574</td>
<td>p = 0.066</td>
</tr>
<tr>
<td>Fall history</td>
<td>p = 0.825</td>
<td>p = 0.695</td>
<td>p = 0.8665</td>
<td>p = 0.5555</td>
<td>p = 0.439</td>
</tr>
<tr>
<td>Total GA(^a) score</td>
<td>p = 0.008</td>
<td>p = 0.374</td>
<td>p = 0.8595</td>
<td>p = 0.4747</td>
<td>p = 0.207</td>
</tr>
</tbody>
</table>

PFS was analysed on the reference population. Initial scheme with or without bevacizumab, initial chemotherapy backbone, treatment duration and severe toxicity were analysed on the safety population.

Legend: GA: geriatric assessment; PFS: Progression Free Survival; ECOG-PS: Eastern Cooperative Oncology Group—Performance Status; G8: G8 screening tool; fTTRST: Flemish version of the Triage Risk Screening Tool; MNA: Mini Nutritional Assessment; ADL: activities of daily living; IADL: instrumental activities of daily living; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; Mob-T: Mobility-Tiredness; CCI: Charlson Comorbidities Index.

Bold values indicate significant p values.

\(^a\) Total GA score was based on the presence of the following criteria: living alone, ADL score > 6, IADL score < 5 in men, IADL score < 8 in women, MMSE score < 24, GDS ≥ 5, MNA total score < 24 and presence of at least one comorbidity on the CCI.
Fig. 2. Kaplan Meier Curves. A: Association between baseline ECOG-PS and treatment duration in the safety population; B: Association between baseline ECOG-PS and Progression Free Survival in the reference population; C: Association between baseline Mini Nutritional Assessment and Progression Free Survival in the reference population. Legend: ECOG-PS: Eastern Cooperative Oncology Group - Performance Status; MNA: Mini Nutritional Assessment.
Outline

• Introduction
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Clinical Trials and the Elderly?

I just heard there's a drug in trials that might stop my cancer!!

Of course not...why would I do that?

Great! Are you going to volunteer to participate for the trial?

I wouldn't either. Sure hope they get some results soon...

Axman
Chemotherapy choices and doses in frail and elderly patients with advanced colorectal cancer

Matt Seymour, Tim Maughan, Harpreet Wasan, Alison Brewster, Steve Shepherd, Sinead O’Mahoney, Beth May, Lindsay Thompson, Angela Meade and Ruth Langley, on behalf of The UK NCRI Colorectal Clinical Studies Group and FOCUS2 Investigators
Trial Design: 2x2 Factorial

FU x OxFU
Cap x OxCap

Seymour et al The Lancet 2011;377:1749-1759
Progression free survival

Factorial PFS

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no oxaliplatin vs oxaliplatin</td>
<td>0.84 (0.69, 1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>[FU + Cap] vs [OxFU + OxCap]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FU vs capecitabine</td>
<td>0.99 (0.82, 1.20)</td>
<td>0.93</td>
</tr>
<tr>
<td>[FU = OxFU] vs [Cap + OxCap]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Seymour et al The Lancet 2011;377:1749-1759
### Overall Survival

![Overall Survival Graph]

<table>
<thead>
<tr>
<th>Factorial Overall Survival</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no oxaliplatin vs oxaliplatin</td>
<td>0.99 (0.81, 1.18)</td>
<td>p=0.91</td>
</tr>
<tr>
<td>[FU + Cap] vs [OxFU + OxCap]</td>
<td>0.96 (0.79, 1.17)</td>
<td>p=0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk:</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>94</td>
</tr>
<tr>
<td>115</td>
<td>102</td>
</tr>
<tr>
<td>115</td>
<td>94</td>
</tr>
<tr>
<td>114</td>
<td>100</td>
</tr>
</tbody>
</table>

Seymour et al. The Lancet 2011;377:1749-1759
OTU is a novel clinical outcome measure incorporating objective and subjective measures of anticancer efficacy, tolerability, and acceptability, assessed at the end of protocol therapy and condensed into a simple 3 point score.

OTU may be regarded as asking the clinician: “With the benefit of hindsight, are you glad you gave this treatment?” and asking the patient: “With the benefit of hindsight, are you glad you received it? OTU is scored as good, intermediate or poor, corresponding to “yes”, “uncertain” or “no” replies to these questions.

To score the OTU, the patient is assessed at the end of protocol therapy (see Section 10.0) using the following criteria:

1) **Clinical benefit?** Categorized as:
   a. **Both** radiologically progression-free (RECIST response or stable disease) and no clinical deterioration as assessed by treating consultant
   b. **Either** radiologically progression-free (RECIST progressive disease) or clinical deterioration as assessed by treating consultant

2) **Tolerable and acceptable?** Categorized as:
   a. All of the following:
      No SAE or SUSAR attributed to treatment
      No episodes of grade ≥3 non-hematological toxicity
      Patient response to “How much has your treatment interfered with your normal daily activities” is not “Very much”
      Patient response to “How worthwhile do you think your treatment has been?” is not “Not at all”
   b. Any of the following:
      An SAE or SUSAR (suspected unexpected serious adverse reaction) attributed to treatment
      An episode of grade ≥3 non-hematological toxicity
      Patient response to “How much has your treatment interfered with your normal daily activities” is “Very much”
      Patient response to “How worthwhile do you think your treatment has been?” is “Not at all”

**Scoring (tick one):**

Good OTU: Patient is alive and scores 1a/2a
Intermediate OTU: Patient is alive and scores 1a/2b or 1b/2a
Poor OTU: Patient is alive and scores 1b/2b, or patient is dead
mCRC
≥ 75 years
N=282

LV5FU2
R1

Simplified LV5FU2
R2

No irinotecan

Irinotecan

Stratification criteria:
- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs ≥ 80 yrs)
- Alkaline phosphatase (≤ 2ULN vs > 2ULN)
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>FU</th>
<th>IRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=142</td>
<td>N=140</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>80.4 (74.7-90.4)</td>
<td>80.3 (75.1-91.7)</td>
</tr>
<tr>
<td>&lt; 80 years / ≥ 80 years</td>
<td>44.4 / 55.6</td>
<td>47.9 / 52.1</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male / Female</td>
<td>52.8 / 47.2</td>
<td>54.3 / 45.7</td>
</tr>
<tr>
<td><strong>Karnofsky index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 / 80-90 / 70-60</td>
<td>14.1 / 54.9 / 30.0</td>
<td>13.6 / 55.7 / 30.7</td>
</tr>
<tr>
<td><strong>Charlson index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 / 1-2 / 3+</td>
<td>56.3 / 39.5 / 4.2</td>
<td>57.9 / 36.4 / 5.7</td>
</tr>
<tr>
<td><strong>Alkaline phosphatases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2N / &gt; 2N</td>
<td>78.9 / 21.1</td>
<td>79.3 / 20.7</td>
</tr>
<tr>
<td><strong>Number of metastatic sites</strong></td>
<td>n=141</td>
<td>n=138</td>
</tr>
<tr>
<td>1 / 2 / &gt;2</td>
<td>44.0 / 38.3 / 17.7</td>
<td>42.0 / 31.2 / 26.8</td>
</tr>
<tr>
<td><strong>ACE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2N / &gt; 2N</td>
<td>46.3 / 53.7</td>
<td>47.1 / 52.9</td>
</tr>
</tbody>
</table>

Seymour et al. The Lancet 2011;377:1749-1759

Mitry E, ET AL Ann Oncol 2012; 23(suppl 9): Abstract 529PD.
FFCD 2001-02: Progression-Free Survival

Median PFS (months [95%CI])

FU: 5.2 [3.9;6.1]
IRI: 7.3 [6.5;8.6]

HR=0.84 (95%CI: 0.66;1.07)
   p=0.15

FFCD 2001-02: Overall Survival

Median OS (months [95%CI])

**FU:** 14.2 [9.5;19.0]
**IRI:** 13.3 [11.2;17.9]

HR=0.96 (95%CI: 0.75;1.24)
p=0.77
**Table 3. Multivariate Analysis for Grade 3 to 4 Toxicity**

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.53</td>
<td>0.50 to 4.71</td>
<td>.454</td>
</tr>
<tr>
<td>Primary tumor not resected</td>
<td>1.20</td>
<td>0.34 to 4.21</td>
<td>.779</td>
</tr>
<tr>
<td>No previous adjuvant chemotherapy</td>
<td>3.85</td>
<td>0.67 to 22.03</td>
<td>.130</td>
</tr>
<tr>
<td>Irinotecan arm</td>
<td>5.03</td>
<td>1.61 to 15.77</td>
<td>.006</td>
</tr>
<tr>
<td>Impaired cognitive function (MMSE (\leq) 27/30)</td>
<td>3.84</td>
<td>1.24 to 11.84</td>
<td>.019</td>
</tr>
<tr>
<td>Impaired autonomy (IADL)</td>
<td>4.67</td>
<td>1.42 to 15.32</td>
<td>.011</td>
</tr>
<tr>
<td>Better mood</td>
<td>0.41</td>
<td>0.12 to 1.36</td>
<td>.145</td>
</tr>
</tbody>
</table>

Abbreviations: IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; OR, odds ratio.

AVEX Trial: A prospective trial in elderly patients

Previously untreated mCRC, age ≥70 years
N=280

Randomize 1:1

Stratification factors:
- ECOG PS (0–1 vs 2)
- Geographic region

Capecitabine 1000 mg/m² b.i.d.
days 1–14, q21d
+ Bevacizumab 7.5 mg/kg
day 1, q21d

• Key inclusion criteria
  - ECOG PS 0–2
  - Prior adjuvant chemotherapy allowed if completed >6 month before inclusion
  - Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

• Key exclusion criteria
  - Prior chemotherapy for mCRC or prior adjuvant anti-VEGF treatment
  - Clinically significant cardiovascular disease
  - Current or recent use of aspirin (>325 mg/day) or other NSAID
  - Use of full-dose anticoagulants or thrombolytic agents
## Select baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cape + BEV (n=140)</th>
<th>Cape (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, %</strong></td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years, %</td>
<td>39.3</td>
<td>32.9</td>
</tr>
<tr>
<td>≥75 years, %</td>
<td>60.7</td>
<td>67.1</td>
</tr>
<tr>
<td><strong>ECOG performance status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>50.0</td>
<td>42.9</td>
</tr>
<tr>
<td>1</td>
<td>41.4</td>
<td>47.9</td>
</tr>
<tr>
<td>2</td>
<td>7.1</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Prior adjuvant therapy, %</strong></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Site of metastatic disease, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>62.9</td>
<td>67.9</td>
</tr>
<tr>
<td>Lung</td>
<td>35.7</td>
<td>40.7</td>
</tr>
<tr>
<td>Other</td>
<td>35.0</td>
<td>22.9</td>
</tr>
<tr>
<td>Liver only</td>
<td>37.1</td>
<td>38.6</td>
</tr>
<tr>
<td><strong>Surgical resection, %</strong></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Location of primary disease, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon only</td>
<td>57.9</td>
<td>54.3</td>
</tr>
<tr>
<td>Rectum</td>
<td>31.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10.7</td>
<td>19.3</td>
</tr>
</tbody>
</table>

ITT population. Cape = capecitabine; ECOG PS = Eastern Cooperative Group performance status.

Progression-free survival

HR = 0.53 (95% CI: 0.41–0.69)

\(P < 0.001\)

ITT population. 113 PFS events in the Cape + BEV arm; 127 PFS events in the Cape arm. CI = confidence interval; PFS = progression-free survival

Overall survival

ITT population. 75 OS events in each treatment arm.

## Analysis of Bevacizumab in Older Patients with mCRC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age (yrs)</th>
<th>Median PFS, mos (HR, P value)</th>
<th>Median OS, mos (HR, P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVEX</td>
<td>≥70</td>
<td>9.1 vs. 5.1 (0.53, P&lt;0.001)</td>
<td>20.7 vs. 16.8 (0.79, P=0.182)</td>
</tr>
<tr>
<td>Cape+BV vs Cape (N=280)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGITG MAX</td>
<td>≥75</td>
<td>8.8 vs 5.6 (0.52, P=0.01)</td>
<td>15.7 vs 13.4 (0.80, P=0.41)</td>
</tr>
<tr>
<td>Cape+BV vs Cape (N=99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>≥65</td>
<td>9.2 vs 6.2 (0.52, P&lt;0.001)</td>
<td>19.3 vs 14.3 (0.70, P=0.006)</td>
</tr>
<tr>
<td>(AVF2107&amp;2192) CT+BV vs CT (N=439)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled analysis</td>
<td>≥70</td>
<td>9.2 vs. 6.4 (0.54, P&lt;0.05)</td>
<td>17.4 vs 14.1 (0.79, P&lt;0.05)</td>
</tr>
<tr>
<td>(NO16966/AVF2107&amp;2192/E3200) CT+BV vs CT (N=712)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRITE</td>
<td>≥75</td>
<td>10.0</td>
<td>20.3</td>
</tr>
<tr>
<td>CT+BV (N=363)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIES</td>
<td>≥70</td>
<td>9.9</td>
<td>19.6</td>
</tr>
<tr>
<td>CT+BV (N=424)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KEY:** Cape – capecitabine; BV – bevacizumab; PFS – progression-free survival; mos – months; HR – hazard ratio; OS – overall survival; CT - chemotherapy

Adapted from Papamichael et al. *Ann Oncol*. 2014
Observed benefit and safety of afiblercept in elderly patients with metastatic colorectal cancer: An age-based analysis from the randomized placebo-controlled phase III VELOUR trial

Paul Ruff a,⁎, Eric Van Cutsem b, Radek Lakomy c, Jana Prausova d, Guy A. van Hazel e, Vladimir M. Moiseyenko f, Karen Soussan-Lazard g, Emmanuelle Dochy h, Emmanuelle Magherini i, Teresa Macarulla j, Demetris Papamichael k

ARTICLE INFO

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Afiblercept
mCRC
Second-line
VEGFR-Trap

ABSTRACT

Objective: Afiblercept (ziv-afiblercept) significantly improves progression-free survival (PFS) and overall survival (OS) when added to 5-fluorouracil, leucovorin and irinotecan (FOLFIRI), compared with FOLFIRI alone, in patients with metastatic colorectal cancer previously treated with oxaliplatin-based therapy. This subset analysis of the VELOR trial investigates afiblercept plus FOLFIRI versus placebo plus FOLFIRI according to age.

Methods: Efficacy and safety were analyzed by treatment arm and age (≥65 years).

Results: Overall, 443 patients were ≥65 years old (205 in afiblercept arm; 238 in placebo arm) and 718 were <65 years old (407 in afiblercept arm; 371 in placebo arm). Median OS was 12.6 versus 11.3 months (hazard ratio [HR]: 0.88; 95.4% CI 0.68–1.107) in patients ≥65 years old and 14.5 versus 12.5 months (HR: 0.80; 95.4% CI 0.67–0.985) in those patients ≤65 years old, for patients receiving FOLFIRI plus afiblercept or placebo, respectively. There was no interaction between treatment and age. Treatment-related adverse events (AEs) were comparable for patients ≥65 years old and <65 years old. The incidence of grade 3/4 AEs was higher for patients ≥65 years old than for those <65 years old in both the afiblercept (19.3% versus 8.5%) and placebo (67.4% versus 59.4%) arms. Interaction tests for grade 3/4 antiangiogenic agent-related AEs suggested no heterogeneity between the older and younger patient populations (p > 0.1).

Conclusion: A limited but consistent benefit on both OS and PFS was associated with the addition of afiblercept to FOLFIRI compared with placebo in patients ≥65 and ≤65 years old, with a marked but manageable increase in the toxicity profile in older patients.

Trial Registration: clinicaltrials.gov NCT00961470

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide after lung cancer and breast cancer and the second most common cause of cancer death after lung cancer [1,2]. CRC principally affects individuals aged 65 years and older, with the incidence doubling every 7 years in patients aged over 50 years [1–3]. Almost half of newly diagnosed cases occur in patients aged over 75 years [3,4]. As a result, the medical and social burdens of CRC can be expected to increase over the coming decades as the number of individuals living beyond 70 years of age steadily increases.

There is a scarcity of evidence to support guidelines for the treatment of older patients (≥65 years) with CRC due to the fact that older patients with CRC are generally underrepresented in clinical trials [5]. Also, the so-called ‘fit’ older patients who are recruited into
**STUDY DESIGN**

EudraCT no. 2014-000394-39

160 patients:
- Non-resectable mCRC
- ≥ 70 years
- Not candidate for full-dose combination therapy
- PS 0-2

**Geriatric screening tools**
- G-8
- VES-13
- Timed-Up-and-Go
- Handgrip strength
- Charlson Comorbidity Index

---

**Randomisation**

**Primary endpoint**: Improvement of PFS from 6 to 9 months ($\alpha = 0.05$, $\beta = 0.20$)$^{2,3}$

**Secondary endpoints**: TTFS, OS, RR, toxicity, QoL, correlation between tumormarkers and outcome, predictive value of pre-treatment characteristics

This investigator-initiated study was founded by Taiho Pharmaceutical Co Ltd.

1 Winther et al, BMC Cancer, 2017
2 Seymour et al, Lancet Oncol, 2011
3 Cunningham et al, Lancet Oncol, 2013
EFFICACY

Progression-free survival

HR: 0.71, 95% CI: 0.51-0.99

5.1 vs. 9.1 months

AVEX data

<table>
<thead>
<tr>
<th></th>
<th>S-1</th>
<th>mSOx</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>81</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>27 (34%)</td>
<td>30 (43%)</td>
<td>0.246</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.3 (4.11-6.80)</td>
<td>6.6 (5.32-8.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>11.5 (8.34-15.9)</td>
<td>15.3 (12.3-21.2)</td>
<td>0.216</td>
</tr>
</tbody>
</table>
**EFFICACY**

**Progression-free survival**

- **AVEX data**
- **16.8 vs 20.7 months**

**Overall Survival**
- **HR: 0.79, 95% CI: 0.54-1.15**

**Number allocated**
- A (FU): 115
- B (oxFU): 115
- C (Cap): 115
- D (oxCap): 114

**Survival and response**
- Number started treatment: 111, 107, 111, 111
- RECIST response at week 12-14
  - Response rate: CR + PR (%): 12 (11%), 41 (38%), 16 (14%), 36 (32%)
  - Disease control: CR + PR + SD (%): 51 (45%), 75 (71%), 75 (70%), 73 (65%)
- Median PFS (months; IQR): 3.5 (2.8-6.2), 5.8 (3.2-7.5), 5.2 (2.3-6.7), 5.8 (3.3-7.4)
- HR (95% CI): MedianOS (months; IQR)
  - 10.1 (5.1-17.3)
  - 10.7 (5.7-17.2)
  - 11.0 (5.4-18.6)
  - 12.4 (5.8-18.6)


<table>
<thead>
<tr>
<th>Patients</th>
<th>S-1</th>
<th>mSOx</th>
<th>p-value</th>
</tr>
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<td>15.3 (12.3-21.2)</td>
<td>0.216</td>
</tr>
</tbody>
</table>
NCIC CTG CO.17: Subgroup analysis according to age

Restricting cetuximab use in the elderly or in the setting of significant comorbidities does not appear justified

Cetuximab monotherapy and cetuximab plus capecitabine as first-line treatment in older patients with RAS- and BRAF wild-type metastatic colorectal cancer. Results of the multicenter phase II trial SAKK 41/10

Dirk L. Kienle, Daniel Dietrich, Karin Ribi, Andreas Wicki, Luca Quagliata, Ralph C. Winterhalder, Dieter Koeberle, Daniel Horber, Sara Bastian, Marc Kueng, Piercarlo Saletti, Daniel Helbling, Daniela Baertschi, Alessandro Lugli, Juerg Bernhard, Christiane Andrieu, Roger von Moos

* Kantonsspital Chur, Chur, und Universitätsschulmedizin Ulm, Ulm, Germany
* Swiss Group for Clinical Cancer Research, Coordinating Center, Bern, Switzerland
* International Breast Cancer Study Group, Bern, Switzerland
* Universitätsklinikum Basel, Basel, Switzerland
* Kantonsspital Luzern, Luzern, Switzerland
* Karolinska Institutet, Stockholm, Sweden
* Kantonsspital St. Gallen, Switzerland
* Kantonsspital Chur, Chur, Switzerland
* Canton de Vaud, Lausanne, Switzerland
* Institut Oncologico della Svizzera Italiana, Bellinzona, Switzerland
* Oncocenter AG, Zürich, Zürich, Switzerland
* Inselspital, Bern University Hospital, Bern, Switzerland

A B S T R A C T

Introduction: While the anti-VEGF antibody bevacizumab was studied repeatedly as part of low-intensity regimens in less fit elderly patients with metastatic colorectal cancer (mCRC), anti-EGFR antibodies as upfront treatment modality have been scarcely investigated.

Material and Methods: In SAKK 41/10, the benefit of cetuximab, either alone or in combination with capecitabine, was evaluated in vulnerable elderly patients with RAS/BRAF-wild-type mCRC.

Results and Discussion: The trial was stopped prematurely due to slow accrual after the inclusion of 24 patients (11 in the monotherapy arm, 13 in the combination arm). Median patient age was 80 years (range 71–89), median CIRS-G score 7 (range 2–13), and median IADL score 7 (range 3–8). At week 12, 6 of 11 patients (55%) were progression-free in the cetuximab monotherapy arm and 9 of 13 patients (69%) in the combination arm. Response rate was 6% in the monotherapy arm and 38% combination arm. The 6 patients with right-sided primary tumors were not responsive to cetuximab. NGS revealed additional mutations affecting the RAS/RAF/MAP kinase pathway in 5 patients; 4 of these patients showed early disease progression. Cetuximab was generally well tolerated and a trend toward an improvement of symptom-related QoL was observed. In the combination arm, a higher incidence of toxicities and treatment stoppings was observed.

In conclusion, trial recruitment – requiring both geriatric as well as molecular eligibility criteria – proved more difficult than expected. Bearing in mind the very small sample size, upfront cetuximab treatment appeared tolerable and showed promising activity in left-sided tumors in both treatment arms.

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Study to Estimate the Toxicity, Dose-Intensity, and Benefit of anti-EGFR-Based Treatment in Patients with Advanced Colon Cancer according to age

- **Joint ARCAD/SIOG project**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms Included</th>
<th>No of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal</td>
<td>FOLFIRI +/- Cetuximab</td>
<td>1198</td>
</tr>
<tr>
<td>OPUS</td>
<td>FOLFOX +/- Cetuximab</td>
<td>337</td>
</tr>
<tr>
<td>COIN</td>
<td>FOLFOX/XELOX +/- Cetuximab</td>
<td>1630</td>
</tr>
<tr>
<td>COIN B</td>
<td>FOLFOX4 +/- Cetuximab given intermittently or continuously</td>
<td>226</td>
</tr>
<tr>
<td>FIRE 3</td>
<td>FOLFIRI + Cetuximab</td>
<td>297</td>
</tr>
<tr>
<td>CALGB 80405</td>
<td>FOLFOX/FOLFIRI +/ Cetuximab</td>
<td>578</td>
</tr>
<tr>
<td>PRIME</td>
<td>FOLFOX4 +/- panitumumab</td>
<td>1183</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>5449</strong></td>
</tr>
</tbody>
</table>
Primary aim:

- Estimate the progression free survival of anti-EGFR +combination chemotherapy by age (>= 70 yrs vs. <70 yrs) in patients with advanced colon cancer.
- Examine the pattern or severity of adverse events by age (>= 70 yrs vs. <70 yrs).

Secondary aims:

- Estimate the overall survival of anti-EGFR +combination chemotherapy by age (>= 70 yrs vs. <70 yrs) in patients with advanced colon cancer.
- Estimate the response rate of anti-EGFR +combination chemotherapy by age (>= 70 yrs vs. <70 yrs) in patients with advanced colon cancer.
- Examine the pattern of dose-intensity by age (>= 70 yrs vs. <70 yrs).
Outline

• Introduction
• Geriatric Assessment
• Trials
• Conclusions
Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials

| Draft agreed by Geriatric Expert Group and external experts | March 2015 |
| Draft agreed by Working parties | May 2015 |
| Draft agreed by Guidelines Consistency Group | November 2015 |
| Adopted by CHMP for release for consultation | 16 December 2015 |
| Start of public consultation | 21 December 2015 |
| End of consultation (deadline for comments) | 31 May 2016 |
| Working parties consultation | 26 June 2017 |
| Agreed by Guidelines Consistency Group | November 2017 |
| Adoption by CHMP | 24 January 2018 |

**Keywords**

Frailty, physical frailty, older people, elderly, ICH E7, geriatric, baseline characterisation, ageing
Overall conclusions - recommendations

- Embracing the concept of individualized treatment is an absolute requirement for further improvements in the management of these patients. MDTs are the key to individualized treatment in older patients.

- The treatment challenges presented by older patients with CRC make it important to use some form of GA to inform our clinical decision making.

- The potential for morbidities and the choices if serious complications do occur or treatments fail, should be discussed in advance.

- Investigators should be encouraged to design not only trials using low-toxicity treatments that maintain most of the efficacy of full-dose treatments but patient-centered assessments to expand the evidence base in the treatment of older patients with CRC.

Thank you