Optimizing Chemotherapy for Frail and Elderly Patients with Advanced Gastroesophageal Cancer: The GO2 phase III trial

PS Hall, D Swinson, JS Waters, J Wadsley, S Falk, R Roy, T Tillett, J Nicoll, S Cummings, SA Grumett, K Kamousioras, A Garcia, C Allmark, S Ruddock, E Katona, H Marshall, G Velikova, RD Petty, HI Grabsch, MT Seymour. on behalf of the GO2 Investigators
Background

• The median age of patients diagnosed with advanced (inoperable or metastatic) gastric or oesophageal (GO) cancer is >75 years.¹

• Many patients are frail.

• …but international standard chemo schedules were developed in trials of mostly non-frail patients with median age <65 years.²

• Standard of care for advanced GO cancer in the UK has been EOCap.

Background

• In 2011 we audited 50 UK oncologists: 49 were using reduced chemo schedules in frail/elderly GO patients; high variation and non-evidence based.

• A randomised phase II trial (321GO) compared 3, 2 or 1-drug chemotherapy in frail/elderly GO cancer patients in a “pick-the-winner” (n=55) and found 2 drugs best.³

Aims

In frail or elderly patients with advanced GO cancer:

• Establish the dose of 2-drug chemotherapy achieving the best balance of cancer control, toxicity, patient acceptability and quality of life.

• Identify pre-treatment characteristics which predict for better or worse outcomes from different dose levels.
Trial design

Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial

Eligibility
Not fit for full-dose 3-drug chemotherapy, but suitable for reduced intensity chemotherapy.

Follow-up
Total 1 year; 9 weekly imaging and PROMs

Baseline comprehensive geriatric assessment
Including symptoms, fitness, comorbidity, QoL

Decision
(patient / clinician consensus)

Certain that chemotherapy should be used
(BSC not desirable)

“certain randomisation”
1:1:1

Uncertain whether chemotherapy should be used
(possibility of BSC appropriate)

“uncertain randomisation”
1:1

OxCap Level A*
(100%)

OxCap Level B
(80%)

OxCap Level C
(60%)

OxCap Level C

OxCap Level C

Best supportive care

*Oxaliplatin 130mg/m² day 1 of a 21 day cycle Capecitabine 625mg/m² bd continuously - given until progression

GO2 Trial Summary v2.0_20150129

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## Frailty assessment

### Frailty model

**Comprehensive Geriatric Assessment**

- **9 domains pre-specified**

### Definition

<table>
<thead>
<tr>
<th>Frailty Level</th>
<th>Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not frail</td>
<td>- impairment in 0 domains</td>
</tr>
<tr>
<td>Mildly frail</td>
<td>- impairment in 1-2 domains</td>
</tr>
<tr>
<td>Severely frail</td>
<td>- impairment in ≥3 domains</td>
</tr>
</tbody>
</table>

### Domains and Assessment

<table>
<thead>
<tr>
<th>Domains</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight loss</strong></td>
<td>Weight loss (&gt; 3kg in 3m)</td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td>Timed up and go test (&gt;10 seconds)</td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td>2 or more falls in 6m (EORTC G8)</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td>Dementia/depression diagnosis</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>One or more impairment in IADL</td>
</tr>
<tr>
<td><strong>Social</strong></td>
<td>Place of residence (Requires 24 hour care)</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td>EQ5D question (feelings today)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>EORTC QLQ Fatigue Score</td>
</tr>
<tr>
<td><strong>Polypharmacy</strong></td>
<td>Prescribed regular medications (&gt;4)</td>
</tr>
</tbody>
</table>

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**Frailty model**

Comprehensive Geriatric Assessment

9 domains pre-specified

**Definition**

- Not frail: impairment in 0 domains
- Mildly frail: impairment in 1-2 domains
- Severely frail: impairment in ≥3 domains

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Statistical design

• **Step 1**: assess non-inferiority of lower doses compared with Level A
  • Primary endpoint: Progression Free Survival
    HR 1.34, 80% power; 1-sided 5% significance level (≈34 days median PFS*)
  • Secondary endpoint: overall survival

• **Step 2**: assess patient experience with lower doses
  • Key endpoint: Overall Treatment Utility (OTU)
  • Other endpoints: toxicity, longitudinal QL

• **Step 3**: explore whether optimum dose differs with baseline factors
  • Key endpoint: Overall Treatment Utility (OTU)
  • Baseline factors: age, frailty, performance status

*Non-inferiority boundary agreed by a patient focus group and clinician survey

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“Overall Treatment Utility” (OTU) scored after 9 weeks:

- **good OTU**
  - all of:
    - clinician score “benefit”*
    - patient satisfied
    - no major toxicity
    - no drop in QL⁻¶

- **intermediate OTU**
  - either:
    - clinician score “no benefit”
    - (but patient satisfied and no major toxicity or QL drop)
  - or
    - either patient dissatisfied or major toxicity or QL drop
    - (but clinician scores benefit)

- **poor OTU**
  - both:
    - clinician score “no benefit”
    - and any of
      - patient dissatisfied
      - major toxicity
      - QL deterioration
    - or
      - patient has died

NB: decision rules to ensure OTU can be scored in 100% patients

*clinician score of “benefit”: no clinical/radiological evidence of cancer progression and no general health deterioration
⁻¶drop in QL defined as ≥16% fall (≥2 on the 12-point EORTC global QL scale). Cocks, K et al., Eur J Cancer (2012) 48, 1713–21


For more info see www.blogs.ed.ac.uk/canceroutcomes

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Recruitment
(certain randomisation)

• 512 patients
• 2014 – 2017
• 61 UK hospitals
## Patients

<table>
<thead>
<tr>
<th></th>
<th>Level A (n=170)</th>
<th>Level B (n=171)</th>
<th>Level C (n=173)</th>
<th>Total (n=512)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>76</td>
<td>76</td>
<td>77</td>
<td>76 (51 - 96)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>77%</td>
<td>75%</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Site of primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>32%</td>
<td>42%</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>GO junction</td>
<td>29%</td>
<td>19%</td>
<td>22%</td>
<td>23%</td>
</tr>
<tr>
<td>Gastric</td>
<td>38%</td>
<td>37%</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Squamous histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>11%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Trastuzumab treated</strong></td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td>68%</td>
<td>69%</td>
<td>70%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Performance Status ≥2</strong></td>
<td>31%</td>
<td>32%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Severely frail (≥3 domains)</strong></td>
<td>61%</td>
<td>56%</td>
<td>58%</td>
<td>58%</td>
</tr>
</tbody>
</table>

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Baseline frailty

- Polypharmacy
- Daily activities
- Mobility
- Weight loss
- Fatigue
- Neuropsychiatric
- Falls
- Mood
- Social care

Dr. Peter S. Hall, University of Edinburgh
Primary endpoint
Progression Free Survival

Adjusted hazard ratios

Level B vs A 1.09 [95% CI 0.89 - 1.32]
Level C vs A 1.10 [95% CI 0.90 - 1.33]

The non-inferiority boundary of 1.34 is excluded, so non-inferiority is confirmed
Results: step 1 - non-inferiority

Overall survival

**Median survival**

- Level A: 7.5 months
- Level B: 6.7 months
- Level C: 7.6 months

![Graph showing survival rates](image-url)
Results step 2: the patient experience

Overall Treatment Utility

Overall treatment utility favours **Level C**, which had the highest percentage of Good and lowest percentage of Poor OTU scores.

<table>
<thead>
<tr>
<th>Level</th>
<th>Good</th>
<th>Intermed.</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>36%</td>
<td>26%</td>
<td>38%</td>
</tr>
<tr>
<td>Level B</td>
<td>35%</td>
<td>34%</td>
<td>31%</td>
</tr>
<tr>
<td>Level C</td>
<td>43%</td>
<td>27%</td>
<td>29%</td>
</tr>
</tbody>
</table>

**Adjusted odds ratios (trend for better OTU)**

- Level B vs A: 0.87 [95% CI 0.59 - 1.29]
- Level C vs A: 1.24 [95% CI 0.84 - 1.84]
Results step 2: the patient experience

Quality of life

Mean QL improved from baseline to 9 weeks with Level B and Level C

Complete case analysis, adjusted for baseline QoL
Results step 2: the patient experience

Toxicity

% with toxicity

Grade 4  Grade 3  Grade 2  Grade 1  Grade 0

Fatigue  Neuropathy  Nausea  Anorexia  Diarrhoea  Vomiting  PPE  Vein Pain  Stomatitis
Treatment duration

- Level A
- Level B
- Level C

Mean number of cycles

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Step 3: Effect of baseline factors - age

Tests for heterogeneity not significant (A/B/age: p=0.47; A/C/age: p=0.81)
Step 3: effect of baseline factors - Perf. status

Perf Status 0-1

- Level A: n=117
- Level B: n=116
- Level C: n=121

Perf Status ≥2

- Level A: n=53
- Level B: n=55
- Level C: n=52

OTU at 9 wks:
- good
- intermed
- poor

n=514. Tests for heterogeneity not significant (A/B/PS: p=0.84; A/C/PS: p=0.15)

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Step 3: effect of baseline factors - frailty

n=514. Tests for heterogeneity not significant (A/B/frailty: p=0.10; A/C/frailty: p=0.06)
### Step 3: Effect of baseline factors - PFS and OS

#### A versus B

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFS HR</th>
<th>p(het)</th>
<th>OS HR</th>
<th>p(het)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1.13</td>
<td>0.67</td>
<td>0.88</td>
<td>0.18</td>
</tr>
<tr>
<td>≥75</td>
<td>0.98</td>
<td></td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1.23</td>
<td>0.08</td>
<td>1.21</td>
<td>0.22</td>
</tr>
<tr>
<td>≥2</td>
<td>0.79</td>
<td></td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td><strong>Frailty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.68</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight</td>
<td>1.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.09</td>
<td>0.23</td>
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#### A versus C

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<tr>
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<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1.27</td>
<td>0.24</td>
<td>1.21</td>
<td>0.45</td>
</tr>
<tr>
<td>≥75</td>
<td>0.94</td>
<td></td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1.10</td>
<td>0.98</td>
<td>0.93</td>
<td>0.04</td>
</tr>
<tr>
<td>≥2</td>
<td>1.12</td>
<td></td>
<td>1.51</td>
<td></td>
</tr>
<tr>
<td><strong>Frailty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.82</td>
<td>0.66</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>Slight</td>
<td>0.93</td>
<td></td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1.23</td>
<td></td>
<td>1.14</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.10</td>
<td>1.14</td>
</tr>
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</table>

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No significant interaction between dose level and age, PS or frailty.
Summary

• This is the largest RCT to date specifically investigating frail/elderly advanced GO cancer patients.

• The lowest dose tested provided
  • non-inferior cancer control (PFS and OS)
  • the best patient experience (OTU, toxicity and QoL)

• No subgroup clearly benefited from higher dose treatment
  • Further work is investigating personalised dose selection based on CGA
Conclusions

• Low-dose treatment may be offered to patients too frail or elderly for a full-dose regimen, in the confidence that it may give a better patient experience without compromising cancer control or survival.

• Overall Treatment Utility is a useful clinical trial outcome measure that reflects the goals of palliative therapy.
Acknowledgements

Research teams at 61 UK sites

Trial Management Group
Matthew Seymour (chair), Peter Hall, Daniel Swinson, Russell Petty, Simon Lord, Mike Bennett, Galina Velikova, Heike Grabsch, Christine Allmark, Jo Askey, Anne Crossley, Catherine Handforth, Justin Waters

Data Monitoring and Ethics Committee
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University of Leeds Clinical Trials Unit
Sharon Ruddock, Eszther Katona, Helen Marshall, Jo Webster, Marc Jones, Alina Striha, Fiona Collinson, Julia Brown, Helen Howard, Louise Brook

Trial Steering Committee
Gareth Griffiths (chair), Sally Clive, Vanessa Potter, Jean Gall

Patients and their families

Funder: Cancer Research UK
My family and I would like to say thank you for such a lovely letter, it is so good to know what happens after taking part in a trial and you are not forgotten.

I lost my dear husband of nearly 60 years in May 2015, when he was asked if he would take part in the trial he already knew he was terminally ill but he said “it will be too late for me but if it would help others he would be very pleased” and we hope this too.

Thank you once again for thinking of us and Good luck with the out come.

“...thank you for thinking of us.”