Analysis of a Phase2 clinical trial in pancreatic cancer

NHMRC Clinical Trials Centre - The University of Sydney

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Context

The GoFurtGo study was a non-randomised open label single arm phase II study of treatment for pancreatic cancer. The treatment was one cycle of induction gemcitabine and oxaliplatin, followed by radiotherapy with concurrent continuous infusion 5FU, followed by 3 cycles of consolidation gemcitabine-oxaliplatin. The primary outcome was feasibility measured as the proportion of patients receiving ≥80% of the planned dose for each component of treatment on time. Secondary outcomes were patient safety, treatment activity and efficacy and quality of life.

Contribution

The initial analysis of this trial was conducted in 2008 under my direct supervision. Now with complete survival data, this subsequent analysis of baseline prognostic factors, quality of life and survival was conducted by me in the process of preparing the trial for presentation at a major conference and for publication.

Statistical issues

- Analysis of time-to-event efficacy endpoints of the study
- Univariate and multivariate modelling of baseline prognostic factors for outcomes
- Assessment of the association between CA19.9 biomarker with study outcomes
- Analysis of health related quality of life (QOL) measures
Declaration

I declare this project is evidence of my own work, with direction and assistance provided by my project supervisor. This work has not been previously submitted for academic credit.

Chris Brown

Project develops BCA subject

Advanced Clinical Trials, Survival Analysis, LMR

Supervisor Statement

I declare that Chris Brown has performed the statistical analysis alone on this project under my supervision and was actively involved in the evolution of the project. This work has not been previously submitted for publication or academic credit. To my knowledge, Chris’s involvement and effort on this project is highly satisfactory for the requirements of the BCA Workplace Project.

Prof. Val Gebski.
AGITG Group and Trial Statistician

Related Publication

The work discussed in this report has since been published:

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1. Project description

1.1 Cancer and treatment

Pancreatic cancer is the most deadly cancer in Australia. Approximately only 75% of people diagnosed survive longer than 12 months and the 5-year survival proportion is about 5% [1]. After diagnosis the preferred treatment option is surgery (resection to remove tumour cells), followed by radiotherapy (to burn and kill tumour cells) and chemotherapy (to poison tumour cells including those circulating through the body). Surgery results in improved patient survival but is not possible in all patients due to the location of the disease or the health of the patient. In these cases, treatment options are restricted to chemotherapy and radiotherapy and various timing combinations.

Until the recent advent of targeted chemotherapy agents, the number of chemotherapy options for pancreatic cancer has been limited to a small number of drugs. With the majority of the available treatment combinations of these drugs and radiotherapy having been tested, research has became focused on questions regarding sequencing and scheduling to improve outcomes.

Clinical trials are scientific experiments conducted in humans. In cancer trials, participants are treated in new and promising ways which may improve outcomes such as survival (efficacy) or side effects (safety). New drugs or combinations are initially tested in small numbers of patients until a maximum tolerated dose is determined (phase I). Once identified, another cohort of patients are tested to determine the range of potential treatment outcomes at this dose (phase II). If the results of this are considered promising the treatment may then be compared in a
randomised comparison with the current standard treatment to obtain evidence of any improvement in outcomes (phase III).

### 1.2 GoFurtGo Trial

In some cases, pancreatic cancer spreads from the pancreas by the time it is diagnosed or during the initial treatments and this is known as metastatic disease. The outcomes for these patients are usually very poor and they are treated usually with palliative intent, rather than with a focus on cure for those in whom the disease is still restricted to the pancreas.

The GoFurtGo trial of 48 non-resectable (non-metastatic) patients assessed the feasibility of administering the chemotherapy combination of Gemcitabine and Oxaliplatin before and after radiotherapy given concurrently with 5-FU chemotherapy (Figure 1 – GoFurtGo Trial Schema). This type of treatment schedule is often referred to as a ‘treatment sandwich’.

**Figure 1 – GoFurtGo Trial Schema**

![GoFurtGo Trial Schema](image)

Patients were to receive 1 four-week (induction) cycle of the combination chemotherapy before six weeks of radiotherapy and 5-FU then 3 further four-week cycles of (consolidation) treatment afterwards. This trial built upon a previous
study conducted by the same investigators of Gemcitabine as a single agent with a similar sandwich therapy design [2].

This treatment regimen was expected to be physically demanding. If patients were unable to tolerate the chemotherapy or radiotherapy due to side effects doses may have to be delayed or skipped, thus reducing the efficacy of the combination. The primary endpoint of the study was therefore the proportion of patients able to complete the 80% of the planned regimen within the planned schedule. Other study endpoints were survival, tumour response and quality of life.

The initial analysis found that only 14/48 = 29%, 95% Confidence Interval (CI) (18%, 43%), of patients were able to complete the entire treatment package. A further 10 patients (i.e. a total of 50%) were able to complete the 6 month regimen but required treatment delays or a dose reduction of more than 20% in at least one cycle.

1.3 Project Objectives

The analysis in this project addresses the secondary outcomes of the study now that longer term survival data has been collected. The objectives of this project are:

1. Update the analysis of time to event (efficacy) study endpoints:
   - Time to disease progression
   - Overall survival

2. Determine the effect of various baseline prognostic factors on outcomes

3. Assess the association of CA19.9 biomarker with other study outcomes

4. Summarise the analysis of health related quality of life (QOL) measures
2 Data Management

The trial was run by the NHMRC Clinical trials centre (CTC) at the University of Sydney on behalf of the Australasian Gastrointestinal Trials Group (AGITG). Ten sites from Australia participated in the trial and recruited patients between June 2005 and December 2007.

The trial data was collected on pre-specified case report forms (CRFs) by the staff at the trial sites and was entered and checked by CTC staff at a central location. Comprehensive data quality checks were performed by the CTC trial staff and any anomalies queried and clarified with the study sites. The main trial statistician was involved in this data cleaning process which I supervised.

The trial data was then processed into statistical data sets in preparation for analysis. A number of key data sets were created in this process including one summary of survival times and patient status (section 3.1), another summary of tumour response (section 3.3) and two containing tumour marker and quality of life data in clean and simple formats for use with methods which incorporate changes over time.

The data analysis was conducted in SAS V9.1 and SPSS V17. Some graphs were created using Sigmaplot V11.
3 Statistical Methods

The complete details for the analysis of the GoFurtGo (GFG) trial are contained in the trial Statistical Analysis Plan (SAP). The following section summarises parts of that document and describes additional methods relating to exploratory analysis conducted on the trial data which were not pre-specified in the trial protocol. It is of value to distinguish between analyses pre-specified and those exploratory as results from questions posed a priori have higher scientific merit than those posed after viewing the trial data [3].

3.1 Time to event data

When analysing time to event data we are studying the time between some starting point (in this case trial registration) and a subsequent event of interest. Examples of these are time to first serious adverse event, time to disease progressing (getting worse) by some fixed amount or time to death. Our primary interest in these analyses is not how many subjects experience a particular event, but how long it takes subjects to have these events. With multiple groups, we can assess whether there is a difference in risk (per unit time) of having an event between groups.

Subjects who have not experienced the event are said to be censored. An important assumption of censoring is that it is non-informative i.e. that the probability of a patient being censored does not depend on their baseline risk. For censored individuals, we only know that their possible event times (noting that they may never have one) are greater than their current observed time in the study. To the best of our knowledge these patients are at risk of having the event until the time they are censored.
The Kaplan Meier survival estimate [4] incorporates the censored observations until such time as they are no longer at risk and is therefore an unbiased estimate of survival probability at a particular time point (Equation 1 - Kaplan Meier estimate).

**Equation 1 - Kaplan Meier estimate**

\[
\hat{S}(t) = \prod_{i: t_i \leq t} \left( 1 - \frac{d_i}{n_i} \right) = \prod_{i: t_i \leq t} \left( \frac{n_i - d_i}{n_i} \right)
\]

where \(d_i\) is the number of patients who have the event from the \(n_i\) patients at risk at time \(t_i\), and \(S(t) = P(t > t)\) is the proportion of patients who have not had the event.

The main descriptive summary measure of this data is the median survival (\(t\) such that \(S(t)=0.5\)) as this is the estimate of the time at which half the patients will have had the event. It is presented with an appropriate estimate of the 95% CI using the method of Brookmeyer and Crowley [5].

The explicit definitions of outcomes for our analysis are as follows:

**Progression free survival (months):** Number of days between date of randomisation date of first documented progression / 30.4. Patients are censored at the date last known not to have progressed. Patients who start subsequent chemotherapy or have surgery are censored at that time as these significantly reduce the likelihood of the patient progressing.

**Overall survival (months):** Number of days between date of randomisation and date of death of any cause / 30.4. Patients are censored at the date of last follow-up.

In this study only a single group is observed and the median summary discussed above will be presented in addition to survival estimates at 3, 6 and 9 months.
3.2 **Univariate and multivariate models**

There exist methods which enable us to compare survival data between groups. These methods can be used to compare pre-specified known or potentially prognostic groups based on baseline status. These groups are referred to as subgroups.

It is possible to compare the survival function of subgroups without assuming any underlying distributional form. The log rank statistic [6] is a test which compares the number of events in each group over each period of time for which there are survival estimates. This test does not involve estimation of the overall difference between the curves and hence we do not get an estimate of the magnitude of the difference if one is found to exist.

The unadjusted hazard ratio (HR) from a Cox-proportional hazards model [7] is widely accepted as the best comparison of the risk of having an event provided we can assume that the hazards in separate groups are proportional to one another. The standard error of the log-HR can be easily computed and used to test whether the HR differs significantly from no difference (0 on the log scale). In the majority of situations this test performs similarly the log rank statistic provided the assumption of proportional hazards is reasonable.

Univariate and multivariate models will be used to assess impact of baseline prognostic factors. The pre-specified variables of interest include: ECOG disease status (0/1/2), age, white blood cell count, tumour size, CA19.9 tumour biomarker, tumour stage (T-Stage: 0/1/2/3/4) and lymph-node stage (N-Stage: 0/1/2).
ECOG status is grouped into categories 0 and 1/2. T-Stage is grouped into two groups 0/1 and ≥2. Categorical grouping of continuous variables (age and CA19.9) will be made by considering clinically intuitive cut-points which will enable easy interpretation (and here for the purpose of illustrating statistical analysis). These variables will also be investigated as continuous variables in the models to check for consistency.

Ignoring here issues of multiple comparisons, variables will be considered significant univariate predictors if they have a p-value smaller than 0.05.

**Proportional hazards assumption**

The proportional hazards assumption underlies the Cox-regression model. As with any assumption it can be tested by computing the partial residuals from the model and determining if there is any trend in these over time [8] these are referred to as Schoenfeld residuals [9].

**Multivariate models / Variable selection techniques**

There are a number of approaches towards multivariate modelling [10]. One, known as forward selection, starts with no variables and adds factors if they contribute some degree of significant improvement in the model performance. In contrast are backwards selection approaches where all variables of interest are initially included and removed one-by-one if they are not significant contributors to the model. Both these methods can be used with a variety of threshold values for adding/removing variables and a number of combination approaches exist. Other methods exist for the selection of variables to best form a model. The choice of method depends on the purpose of the model and the job it will have once constructed.
The approach used here is a variation on backwards selection in which the variables which are reasonably associated at the univariate level (p-value<0.1) will be used to fit a multivariate model. This approach is used so as to restrict the number of variables considered as the primary objective in our analysis is to form a simple explanatory model which may have potential value in the oncology clinic.

### 3.3 Association of tumour marker with outcome

Changes in CA19.9 (a blood biomarker) over time will be investigated as a potential predictive marker of patient time to event outcomes using a number of approaches, each considering a different aspect of the problem. The main motivation for monitoring and assessing tumour markers is that they may be able to predict changes in the patient before they are otherwise detectable. Measuring the marker is easier and cheaper to perform on a more frequent basis than physical scanning. The observation of significant changes in the marker could be used as a trigger for the ordering of further more complex/expensive assessments.

Association of CA19.9 'response' (reduction) will be assessed against tumour radiological ‘response’ (shrinkage or disappearance). Response Evaluation Criteria in Solid Tumours (RECIST) is the current gold standard method of assessing response [11]. The first assessment of association will be by way of a 2x2 contingency table comparing RECIST with reductions in CA19.9 levels of 50%. A chi-square test statistic and odds ratio will be computed to indicate potential association but will not enable quantification of predictive value.

The landmark method [12] is the best unbiased approach for estimation of the effect from a fixed time point (in this case 6 weeks). It considers patient outcomes from the landmark time, excluding any patient for whom the intermediate measurement
is not available or whose outcome occurred before that point. The 6-week time was chosen here since all patients should then have had three measurements. It was also unlikely they would have progressed or dropped out of the study before this time making it a potentially valuable assessment in the clinic.

Another way of assessing the impact of changes in the tumour marker is to consider the changes at various time-points and incorporate their dynamic nature into the estimation of the parameter. This is known as time-dependent Cox regression [8].

### 3.4 Patient reported Quality of Life

Quality of life (QOL) is subjective and therefore a difficult thing to quantify [13]. Much research has been conducted into finding valid and appropriate measure to collect this important aspect of cancer treatment [14]. This trial collected quality of life using the widely used EORTC’s Quality of Life Questionnaire Core-30 (QLQ-C30) and Pancreatic-26 (PAN-26) questionnaires [15]. These questionnaires, consisting of 30 and 26 questions respectively, compile into a total of 7 scales measuring general functioning and 15 symptom scales which represent key areas in which patients are affected during treatment (Table 1 – EORTC Quality of life - Scales).
### Table 1 – EORTC Quality of life - Scales

<table>
<thead>
<tr>
<th>QLQ-C30 – Functioning</th>
<th>QLQ-C30 – Symptoms</th>
<th>QLQ-PAN26 - Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status</td>
<td>Fatigue</td>
<td>Pancreatic pain</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>Nausea and vomiting</td>
<td>Digestive</td>
</tr>
<tr>
<td>Role functioning</td>
<td>Pain</td>
<td>Altered bowel habit</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>Dyspnoea</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>Insomnia</td>
<td>Body image</td>
</tr>
<tr>
<td>Social functioning</td>
<td>Appetite Loss</td>
<td>Sexuality</td>
</tr>
</tbody>
</table>

**QLQ-PAN26 - Functioning**

<table>
<thead>
<tr>
<th>Satisfaction with health care</th>
<th>Constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Financial difficulties</td>
<td></td>
</tr>
</tbody>
</table>

Symptom questions are answered on a item of 1 to 5 where 1 represents no impact and 5 represents major impact. Functioning questions are answered on 1 to 5 items (1 to 7 for global health status) where higher numbers represent better quality of life / functioning. The compilation of scales is by direct averaging of the relevant questions and rescaling to a score which ranges between 0 and 100. Where more than half of the questions comprising a scale have not been answered, the overall score is set as missing.

The focus of this analysis is to graphically summarise the effects of treatment on QOL over time and to determine if there are any factors which are key components of QOL or if global wellbeing comprises something over and above what we can otherwise measure in patients (e.g. tumour size, lab values and toxicities). Average QOL over treatment duration will be computed and compared with baseline scores to identify components which are affected by treatment.
4 Results

4.1 Time to event data

At the time of the final analysis, all patients had been on study for at least 24 months. Patients had recent follow up at the time of the analysis and therefore, patients were censored with times shorter than the minimum “time on study” only for reasons other than follow-up. There were two patients who were discovered ineligible and not treated in the study but are included this intention to treat analysis.

All the patients had either experienced disease progression (44) or been adjudicated as censored due to receipt of non-protocol treatment, surgery or because their disease was no longer being scanned (i.e. study progression data was final). Only 4 of the 48 patients were still alive at the time of this analysis.

Figure 2 – Progression free survival
The black line in Figure 2 is the Kaplan-Meier estimate for the GFG study. The median PFS was 10.9 months 95%CI (8.4, 11.5) and 6 month estimate was 80% 95%CI (66, 91). The grey line in the graph is the Kaplan-Meier estimate for a similar study previously conducted by the investigators with only Gemcitabine chemotherapy. This is not a randomised comparison and therefore no direct comparison of the curves was made. There appears to be a trend towards longer progression free survival using this new treatment (black line).

The median overall survival (Figure 3 – Overall Survival) for the GFG study was 15.7 months 95%CI (13.0, 18.3). The 12 month survival estimate is 69% 95%CI (56, 82). Again, there appears to be a possibly longer overall survival for the new treatment which includes Oxaliplatin.

Figure 3 – Overall Survival

```
<table>
<thead>
<tr>
<th>Months from randomisation</th>
<th>GoFurtGo</th>
<th>Previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
```

Number at Risk
GoFurtGo 48 43 32 18 10 7
4.2 Univariate and multivariate models

To identify which baseline factors influenced patient outcomes, univariate Cox-regression models were computed for the pre-specified variables of interest (Table 2 – Univariate results – progression free survival). Age was grouped into two categories with the cut point of 60 years and also considered continuously as years/10. There were only two patients with ECOG performance status of 2 (severe). Despite them being quite clinically different to a status of 1 (severe but not restricted) they are grouped together due to the small sample. CA19.9 tumour marker exhibits positive skew but under a log transformation is normally distributed. Groups of <100, 100-1000, ≥1000 are clinically appropriate.

Table 2 – Univariate results – progression free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>(Group, Reference Group)*</th>
<th>Hazard Ratio, (95% CI), p-value</th>
<th>Test of proportional hazards assumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG status (1/2 v 0)</td>
<td>1.7 (0.9, 3.2), p=0.09</td>
<td>p=0.85</td>
<td></td>
</tr>
<tr>
<td>White cell count</td>
<td>1.0 (0.9, 1.2), p=0.55</td>
<td>p=0.46</td>
<td></td>
</tr>
<tr>
<td>Age group (≥60 v &lt;60)</td>
<td>0.7 (0.4, 1.2), p=0.18</td>
<td>p=0.76</td>
<td></td>
</tr>
<tr>
<td>*Age (continuous, 10years)</td>
<td>0.8 (0.5, 1.1), p=0.15</td>
<td>p=0.20</td>
<td></td>
</tr>
<tr>
<td>Tumour stage (T3/T4 v T2/T1)</td>
<td>1.0 (0.6, 2.0), p=0.87</td>
<td>p=0.66</td>
<td></td>
</tr>
<tr>
<td>Nodal stage (N1 v N0)</td>
<td>0.8 (0.4, 1.5), p=0.45</td>
<td>p=0.63</td>
<td></td>
</tr>
<tr>
<td>CA19.9 group (100-1000 v &lt;100)</td>
<td>0.9 (0.5, 1.8), p=0.79</td>
<td>p=0.23</td>
<td></td>
</tr>
<tr>
<td>CA19.9 group (≥1000 v &lt;100)</td>
<td>1.7 (0.7, 4.0), p=0.21</td>
<td>p=0.75</td>
<td></td>
</tr>
<tr>
<td>*CA19.9 (continuous, log₁₀)</td>
<td>1.3 (0.9, 1.7), p=0.13</td>
<td>p=0.74</td>
<td></td>
</tr>
</tbody>
</table>

* For categorical variables, the table summarises the effect of the stated group versus that of the reference group as specified in brackets following the variable.
There are a number of possible associations between baseline variables and PFS. None of the variables exhibit relationships strong enough to be significant in this repetitively small sample. ECOG has the strongest association of all the variables.

**Figure 4 – Progression free survival by ECOG performance status**

To illustrate the analysis of subgroups, the graph above (Figure 4) shows the progression free survival Kaplan Meier estimates for the two ECOG performance status groups 0 (solid line) and 1/2 (dotted line). The trend toward shorter PFS in the worse ECOG status group is obvious but the 95% confidence interval for the HR (0.91, 2.52) indicates that the level of evidence is weak.

**Figure 5 – Test of proportional hazards for ECOG performance status**
This graph illustrates the scaled partial residuals plotted against time for all observations in the dataset. The y-axis is the residual, displayed is a line showing the trend in the residuals over time.

The graph of the residuals from this model (Figure 5) shows that despite the influence of the early events, there does not appear to be any major trend over time. This is confirmed in the non-significant correlation of $r=0.1$ ($p=0.48$).

**Multivariate modelling**

In Figure 6 the correlation of the variables of interest is graphically examined. No relationships appear to exist which could cause colinearity problems so a complete backwards selection model is used to check that no variable interactions become significant.

**Figure 6 – Scatterplots of baseline variables**

*Age and ECOG status are recoded into two groups (CA19.9 into three).*
Despite the fact that no variables remain significant multivariate predictors and are hence removed one-by-one from the model, Table 3 contains the initial multivariate model (with all variables) for illustrative purposes.

### Table 3 – Multivariate results – progression free survival

<table>
<thead>
<tr>
<th>Factor (Group, Reference)</th>
<th>HR, (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG status (1/2 v 0)</td>
<td>1.70 (0.80, 3.63), p=0.17</td>
</tr>
<tr>
<td>White cell count (continuous)</td>
<td>0.99 (0.85, 1.16), p=0.99</td>
</tr>
<tr>
<td>Age group (≥60 v &lt;60)</td>
<td>0.68 (0.33, 1.41), p=0.30</td>
</tr>
<tr>
<td>Tumour stage (T3/T4 v T2/T1)</td>
<td>0.97 (0.43, 2.18), p=0.94</td>
</tr>
<tr>
<td>Nodal stage (N1 v N0)</td>
<td>0.74 (0.37, 1.45), p=0.38</td>
</tr>
<tr>
<td>CA19.9 group (100-1000 v &lt;100)</td>
<td>0.85 (0.34, 2.08), p=0.72</td>
</tr>
<tr>
<td>CA19.9 group (≥1000 v &lt;100)</td>
<td>1.69 (0.65, 4.41), p=0.28</td>
</tr>
</tbody>
</table>

If the backwards selection methodology is followed, no variables remain significant predictors in the model of progression free survival.

### Overall Survival

We also assess the impact of the baseline variables on overall survival (Table 4).

### Table 4 – Univariate results – overall survival

<table>
<thead>
<tr>
<th>Factor (Group, Reference)</th>
<th>HR, (95% CI), p-value</th>
<th>PH test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG status (1/2 v 0)</td>
<td>1.41 (0.78, 2.58), p=0.26</td>
<td>p=0.91</td>
</tr>
<tr>
<td>White cell count (continuous)</td>
<td>0.93 (0.83, 1.04), p=0.19</td>
<td>p=0.51</td>
</tr>
<tr>
<td>Age group (≥60 v &lt;60)</td>
<td>0.66 (0.36, 1.22), p=0.19</td>
<td>p=0.62</td>
</tr>
<tr>
<td>*Age (continuous, 10years)</td>
<td>0.88 (0.61, 1.22), p=0.45</td>
<td>p=0.84</td>
</tr>
<tr>
<td>Tumour stage (T3/T4 v T2/T1)</td>
<td>1.12 (0.63, 2.16), p=0.61</td>
<td>p=0.11</td>
</tr>
<tr>
<td>Nodal stage (N1 v N0)</td>
<td>0.90 (0.48, 1.71), p=0.75</td>
<td>p=0.69</td>
</tr>
<tr>
<td>CA19.9 group (100-1000 v &lt;100)</td>
<td>1.01 (0.49, 2.03), p=0.99</td>
<td>p=0.82</td>
</tr>
<tr>
<td>CA19.9 group (≥1000 v &lt;100)</td>
<td>2.33 (0.98, 5.51), p=0.053</td>
<td>p=0.60</td>
</tr>
<tr>
<td>*CA19.9 (continuous, log_{10})</td>
<td>1.44 (1.02, 2.04), p=0.037</td>
<td>p=0.88</td>
</tr>
</tbody>
</table>
There is a potential association with high baseline values of CA19.9 tumour marker and worse overall survival. The categorical model is easier to interpret than that based on the log continuous scale (despite the potential influence of the chosen cut-points). The p-value for the likelihood ratio of the two groups considered simultaneously is 0.11 and there is therefore a high probability that these results could be seen due to chance alone.

### 4.3 Association of tumour marker with outcome

#### Response outcome

There were 16 patients (35%) whose tumour size shrunk by at least 30% as measured by RECIST. The Wilson 95% CI for this response rate is 23% to 49%.

<table>
<thead>
<tr>
<th>Table 5 – Tumour response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 46</strong></td>
</tr>
<tr>
<td>Confirmed complete response (CR)</td>
</tr>
<tr>
<td>Confirmed partial response (PR)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
</tr>
<tr>
<td>Clinical benefit (CR + PR + SD)</td>
</tr>
</tbody>
</table>

#### Comparison of CA19.9 reduction and RECIST response status

The clinical interest is whether CA19.9 reductions are associated with better RECIST outcomes and how accurate such a relationship is. CA19.9 is a blood biomarker which expected to reduce in response to treatment. A simple graphical way of assessing if there is potential association is to plot the smallest % of baseline value reached for patients classified by response status. The following analysis was not pre-specified in the protocol for the trial.
Figure 7 shows some potential relationship but is biased towards lower values in the responders due to the fact that they are on treatment longer and therefore have more chance of observing a lower reading. Conversely, the patients in the PD group had progressed (and were withdrawn study treatment) before their second tumour assessment and therefore are less likely (even by chance) to have observed a low CA19.9 value. Despite this we can compare the number of patients who had reductions of 50% of their baseline CA19.9 value.

Table 6 – Association with RECIST and CA19.9 reduction

<table>
<thead>
<tr>
<th>RECIST Response</th>
<th>Yes</th>
<th></th>
<th>No</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>%</td>
<td>Count</td>
<td>%</td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Reduced (&gt;=50%)</td>
<td>13</td>
<td>50%</td>
<td>13</td>
<td>50%</td>
<td>26</td>
<td>100.0%</td>
</tr>
<tr>
<td>Not Reduced (&gt;= 50%)</td>
<td>3</td>
<td>15%</td>
<td>17</td>
<td>85%</td>
<td>20</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>35%</td>
<td>30</td>
<td>65%</td>
<td>46</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Despite the small sample size there is indication of a weak relationship of increased odds of response if CA19.9 is reduced (OR=5.2, 95%CI (1.3, 24), p-value=0.019). This suggests that CA19.9 reduction was generally associated with RECIST response. Half the patients who had a 50% reduction also had a confirmed
response by RECIST. This compares with 15% of those that did not. The bias discussed above is still inherent in this analysis, treatment time confounds results.

Landmark analysis

The landmark analysis method enables us to unbiasedly assess the changes of CA19.9 over the first 6 weeks. For each patient, the available measurements before that time point are identified and linear regression used to estimate whether the values are increasing or decreasing over time.

Of the 48 patients, 27 are classified as having increasing CA19.9 at the 6 week (1.5 month) time point. 13 patients have reducing CA19.9 and 8 patients did not have a second measurement after baseline and hence cannot be classified.

The line plots (Figure 8) illustrate how the initial changes over the 6 week period potentially predict the duration of study assessments (which could be considered a proxy for progression / survival).

Figure 8 – Plots of CA19.9 values during the study grouped by 6 week trend
No patients progress or die within the 6 week landmark time and therefore all patients can be included in the analysis. The increasing patients were used as the reference category for the regression model as it is the largest (and therefore the most reliable). Using is also enables a simple interpretation which is important.

Table 7 – Time to progression using CA19.9 status at 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Progression (48 patients)</th>
<th>Survival (48 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI for HR</td>
</tr>
<tr>
<td>CA 19.9 after 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown vs. Increasing</td>
<td>0.34</td>
<td>0.14</td>
</tr>
<tr>
<td>Reducing vs. Increasing</td>
<td>0.36</td>
<td>0.18</td>
</tr>
</tbody>
</table>
There appears to be a strong relationship between the reducing and unknown status and progression free survival. It is unlikely that this relationship is observed entirely due to chance (p=0.005) however the reduction in risk of progression could be as small as a 27%. There also appears to be reduction in risk of death but the data is also consistent with the estimate of no difference.

**Figure 9 – PFS after 6 week landmark**

The graph of progression free survival illustrates the adverse impact on PFS of an initially increasing CA19.9 value over the first 6 weeks (1.5 months).

**Figure 10 – OS after 6 week landmark**
The trend seen in overall survival is smaller than that observed of PFS.

**Time dependent Cox regression**

We can further assess the effect of ca19.9 progression on the risk of RECIST progression using a Cox time dependent regression model. As will all these exploratory analysis, results are affected by the relatively small sample size.

**Table 8 – Time dependent Cox regression model**

<table>
<thead>
<tr>
<th>RECIST Progression</th>
<th>95% CI for HR</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>CA 19.9 Progression (doubling)</td>
<td>1.15</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Time dependent Cox regression model estimates that there is a 15% increase in risk of RECIST PD if a CA19.9 doubling is observed (P=0.69). A large number of these exploratory models could be fitted to also incorporate CA19.9 reductions or RECIST response however it is likely that they would not provide additional information which would otherwise be intuitive.

**4.4 Patient reported Quality of Life**

The final secondary outcome for the trial was patient reported QOL. The first task in the analysis of this data is to graphically summarise the changes over the trial.

The functioning scales appear to slightly increase (improve) over the trial apart from at the end of treatment (EOT) time point (just after the three months of demanding chemotherapy) (Figure 11 – QOL scales over time.
A number of the symptom scales appear to increase (worsen) during the course of the trial which was expected. The majority of the scales appear to return to pre-study values after treatment and some (e.g. pain, appetite loss) appear to improve.

**Figure 11 – QOL scales over time**

![Chart showing QOL scales over time](chart.png)
We can see from Figure 12 that on average, patients QOL over treatment is significantly worse for diarrhea, altered bowel habit and physical functioning which is to be expected from this chemotherapy. There also possibly exists reduced body image, worse fatigue and less satisfaction with health care. Despite the symptoms, there appears to be reduced nausea, vomiting and pancreatic pain and global health status appears to be reasonably stable.
Figure 12 – Average QOL change from baseline

Differences in QOL up to Progression (95% CI)

Global health status / QoL
Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning
Fatigue
Nausea and vomiting
Pain
Dyspnoea
Insomnia
Appetite loss
Constipation
Diarrhoea
Financial difficulties
Pancreatic pain
Digestive
Altered bowel habit
Hepatic
Body image
Satisfaction with health care

Change from baseline
5 Interpretation and discussion

Overall this study has provided valuable information into the additional benefit of the more demanding combination therapy over the single agent Gemcitabine treatment. The progression free survival is promising and the 12m overall survival appears to be consistent with the current Australian statistics which is promising when taking into account the inoperable (and non-metastatic) restriction on trial population. There are a number of baseline factors which appear to be associated with the time-to-event outcomes however the small size of the study has limited the value of this analysis.

The patient reported quality of life correlates well with the toxicity results from the initial analysis (not presented). There are a number of scales which reflect the burden of treatment and they appear to revert back to baseline levels (or improve) after chemotherapy is completed.

The analysis of the CA19.9 tumour marker raises interesting questions regarding how best to analyse data which contains inherent bias toward better measurements for patients who are measurable.

The landmark analysis is limited by the small trial sample size and particularly by the small number of patients who were observed to have reduced CA19.9 levels from baseline. Despite being an exploratory analysis it has generated an interesting hypothesis and a larger study may be able to validate this important outcome.
References


## Appendix – Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>GFG / GoFurtGo</td>
<td>Gemcitabine + Oxaliplatin, 5-FU + Radiation therapy, Gemcitabine + Oxaliplatin</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>PH</td>
<td>Proportional Hazards</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response evaluation criteria in solid tumours</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>QLQ</td>
<td>Quality of Life Questionnaire</td>
</tr>
</tbody>
</table>