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PHASE II TRIAL OF THE MULTI-DRUG RESISTANCE PROTEIN MODULATING AGENT SULINDAC IN COMBINATION WITH EPIRUBICIN IN PATIENTS WITH ADVANCED MELANOMA

Clinical Trial Results:

The study accrual was closed by the Chief Investigator at the interim accrual stage due to lack of adequate number of responders. At the time of premature termination of the trial, all patients had completed study participation and were off study treatment.

The attached final technical report version 1.0 dated 26 October 2018 is being submitted.

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cancer trials ireland

Together, we're finding answers to cancer.

Epi-Sulindac

A Phase II trial of the multi-drug resistance protein modulating agent sulindac in combination with epirubicin in patients with advanced melanoma

Protocol Number: CTRIAL-IE (ICORG) 06-03
Protocol Version: V2.1 dated 21-Jan-2010

FINAL TECHNICAL REPORT

Version 1.0 Final
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APPROVALS

Approved By:

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ABBREVIATIONS

Abbreviation	Full Form
ALB	ALBumin
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
AST	ASpartate aminoTransferase
CR	Complete Response
CT	Computed Tomography
CTC	Common Terminology Criteria
ECG	ElectroCardioGram
ECHO	ECHOcardiogram
EOT	End Of Treatment
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
HEENT	Head, Eyes, Ears, Nose, And Throat
ICORG	All Ireland Co-Operative Oncology Research Group
IND	Investigational New Drug
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MUGA	MUlti Gated Acquisition
OTR	Optimally Tolerated Regimen
PD	Progressive Disease
PE	Physical Examination
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
StD	Standard Deviation
SDMO	Statistics And Data Management Office
ULN	Upper Limit of Normal
WBC	White Blood Cells

1. INTRODUCTION

The following is the statistical analysis report of the Phase II clinical trial of the multi-drug resistance protein modulating agent sulindac combination with epirubicin in patients with advanced melanoma.

2. SUMMARY

Thirty two patients were registered on the first stage of the trial between 24-May-2007 and 12-May-2009. One patient presented with abnormal ECG at baseline, normal ECG was an inclusion criterion of the trial, and another patient experienced progressive disease after 5 days in the trial, both of them were subsequently withdrawn. A further patient withdrew his consent after 2 cycles of treatment. All three subjects were not considered evaluable for the primary endpoint, leaving 29 evaluable patients.

A total of 586 adverse events (AE)s were reported in the trial, 34 (5.8%) were CTC grade 3 or greater toxicity.

After the first stage of the trial, nine of the 29 evaluable patients *(31%, 95% CI: 14% to 48%)* experienced either partial response for more than four weeks (three patients) or disease stabilization (six patients). However, at the time of the analysis of the first stage data, the main clinical interest was in actual response rather than disease stabilization. Three partial responders would only have been sufficient to rule out a response rate of less than 10% with 80% power, which would have been considered an inadequate response rate (see Section 3 for original sample size calculation). The trial was therefore terminated after the first stage.

3. TRIAL DESIGN

This was a fixed-dose, single arm, open-label, non-randomised Phase II clinical trial. The trial examined a fixed dose combination of sulindac and epirubicin in line with standard Phase II cancer trial protocols. The trial design was based on a Simon's two stage design. To give a 90% probability of ruling out a response rate of less than 5%, 29 patients (evaluable for the primary endpoint) were required to be enrolled in the first cohort, assuming that the true response rate is 20%. If at least 2 patients from the first cohort of 29 fulfilled the criteria for a response (complete response, partial response or stable disease), then a further 9 evaluable patients were to be enrolled, bringing the total number of patients to 38 evaluable patients.

3.1 Primary Objective

To estimate the non-comparative efficacy of this treatment combination in patients with malignant melanoma. Response was assessed using the RECIST Criteria.
Criteria (*Appendix G: protocol version 2.0, date 19/08/2009*)

3.2 Secondary Objective

To characterise the toxicity of this combination in this patient population, using NCI CTCAE v.3.0. (*Appendix D: protocol version 2.0, dated 19/08/2009*)

4. METHODS

All the analysis is performed on an intention to treat basis. All patients who receive at least one dose of treatment were included in the intention to treat population. Analysis was performed using Stata for WINDOWS.

Mean, standard deviation (StD), number of observations (n) and range (minimum - maximum) is used to summarize variables age, vital signs, complete blood count. Frequency and percentage is used to summarize categorical variables. Other variables are summarized using the appropriate descriptive statistics.

Adverse events and prior/concomitant medications are listed and summarized. Adverse events are listed according to the NCI CTCAE grading, relationship to the drug and other important details.

Time to disease progression is measured from the date of first treatment until the date of disease progression or death, whichever is reported first. Patients who do not progress or die were censored at the day of their last tumour assessment. Time-to-event outcomes was analysed by Kaplan-Meier survival method and median survival time (inter-quartile range (IQR)) and 95% CI is reported.

4.1 Primary Outcome Measure

Estimates of tumour response rates (partial and complete responses sustained for ≥4 weeks as per RECIST guidelines, Appendix G) and their 95% CI are calculated using Wilson method with no continuity correction. The number and percentage of patients falling into each response category will be descriptively tabulated.

4.2 Secondary Outcome Measure

Toxicity data is summarized and tabulated appropriately.

4.3 Interim Analysis

An interim analysis was planned after the first cohort of 29 patients completed treatment (first stage) to assess the objective response. If there were 2 or more responders in the first cohort of 29 patients, the trial was to be continued and a further 9 patients were to be accrued. If less than 2 patients fulfilled response criteria (complete response, partial response or stable disease) at the interim stage, the trial was to be stopped.

4.4 Final Analysis

After the first stage of the trial, nine patients had achieved either a partial response (three patients) or stable disease (six patients). However, at the time of the analysis of the first stage data, the main clinical interest was in actual response rather than disease stabilization. Three partial responders would only have been sufficient to rule out a

response rate of less than 10% with 80% power, which would have been considered an inadequate response rate. The trial was therefore terminated after the first stage. The final analysis was performed based on the data for the first stage of the trial.

5. RESULTS

A total of 32 patients in the age range 26 to 75 were registered to the first stage of the trial. One of the registered patients (patient no: 63011) was found to have an abnormal ECG, normal ECG was an inclusion criterion, the patient was withdrawn within 5 minutes of registration. Patient 63022 presented with progressive disease within five days of registration was also withdrawn. No further data of these two patients was collected following registration. Patient no: 63025 withdrew his consent after 2 cycles of treatment. Thus, three patients were not evaluable for the primary endpoint, and these 3 patients were replaced in the trial to provide the required 29 evaluable patients for the first stage. Two of these three patients did not receive any trial treatment and were excluded from the intention to treat population which thus consists of 30 patients.

5.1 Baseline Characteristics

Table 1. Baseline Characteristics

Age at registration (years)	
Mean (StD)	51.95 (13.7)
Range (min to max)	26 to 75
Number (%) of Females registered	16 (53%)
Number (%) of patients with relevant medical history at baseline	30 (100%)
Number (%) of patients on medication at baseline	27 (90%)
Number (%) of patients who had previous chemotherapy	18 (60%)
Number of Cycles of Previous Chemotherapy	
Median	3
Range	1 to 10
Number (%) of patients who had previous radiotherapy	11 (36.7%)

Table 2. Past and Current Illness

Past or current Illness	Frequency	Percentage
Current	137	65.9
Past	71	34.1

Table 3. CTC Grade for the Illness Present At the Baseline

CTC Grade	Frequency
1	76
2	23
3	3
4	1
Not Applicable	18
Not Known	16

Table 4. Baseline Physical Examination

Body system	Frequency	Percentage
Skin		
Abnormal	9	30
Normal	20	66. 7
Not Done	1	3.3
HEENT/NECK		
Abnormal	4	13.3
Normal	25	83.3
Not Done	1	3.3
Lymph nodes		
Abnormal	8	26.7
Normal	20	66.7
Not Done	2	6.7
Pulmonary		
Abnormal	3	10
Normal	27	90
Cardiac		
Abnormal	1	3.3
Normal	29	96.7
Musculoskeletal		
Abnormal	6	20
Normal	21	70
Not Done	3	10
Breast		
Abnormal	2	6.7
Normal	23	76.7
Not Done	5	16.7
Abdominal		
Abnormal	5	16.7
Normal	25	83.3
Other		
Abnormal	6	20.7
Normal	10	34.5
Not Done	13	44.8
WOCBP		
No	23	76.7
Not Applicable	3	10
Yes	4	13.3
HCG Completed		
No	2	6.7
Not Applicable	24	80
Yes	4	13.3
HCG Result		
negative	4	100

5.2 Trial Treatment

Table 5. Trial Treatment

Number (%) of patients who had change in the concomitant medication	29 (96.7)
Number of Cycles Of Epi-Sulindac Melanoma Trial treatment	
Median	3
Range	1 to 6

Table 6. Reason for Treatment Delay

Site	Label	Cycle Number	Reason for Treatment delay
s10	63006	5	5 day delay in Cycle 5 due to patient taking holiday
s26	63014	2	Cycle delay due to platelet < 100 x 10^9/L
s26	63014	3	Second episode of delay in treatment due to low platelet count
s12	63018	2	Treatment delayed for 1 week due to SAE Neutropenia plus fever
s11	63029	2	Patient very symptomatic from chemotherapy
s11	63029	3	Delay in cycle 3 as patient very symptomatic from cycle 2

Table 7. Dose of Sulindac (mg) By Cycle

Number of Patients Sulindac Dose = 600mg	
Cycle 1	30
Cycle 2	27
Cycle 3	25
Cycle 4	13
Cycle 5	8
Cycle 6	8

Table 8. Dose of Epirubicin (mg/m^2) By Cycle

VISIT	Dose of Epirubicin mg/m^2			Total number of patients
	56	60	75	
Cycle 1	0	0	30	30
Cycle 2	1	0	26	27
Cycle 3	1	2	22	25
Cycle 4	0	2	11	13
Cycle 5	0	1	7	8
Cycle 6	0	1	7	8

Table 9. Dose Modification –Epirubicin mg/m^2

Number	Dose Modified		Total
	Yes	No	
Cycle 1	0	30	30
Cycle 2	1	26	27
Cycle 3	3	22	25
Cycle 4	1	12	13
Cycle 5	0	8	8
Cycle 6	0	8	8

5.3 Physical Examination by Visit

Table 10. Body System: Skin

VISIT	Skin			
	Abnormal	Normal	Not Done	Total
Baseline	9	20	1	30
Cycle 1	10	19	1	30
Cycle 2	8	17	2	27
Cycle 3	7	16	2	25
Cycle 4	4	9	0	13
Cycle 5	3	5	0	8
Cycle 6	4	4	0	8
End of treatment	8	12	4	24

Table 11. Body System: HEENT/Neck

VISIT	HEENT/Neck			
	Abnormal	Normal	Not Done	Total
Baseline	4	25	1	30
Cycle 1	6	23	1	30
Cycle 2	3	21	3	27
Cycle 3	1	22	2	25
Cycle 4	0	13	0	13
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	3	17	4	24

Table 12. Body System: Lymph Nodes

VISIT	Lymph nodes			
	Abnormal	Normal	Not Done	Total
Baseline	8	20	2	30
Cycle 1	10	19	1	30
Cycle 2	7	19	1	27
Cycle 3	4	18	3	25
Cycle 4	2	11	0	13
Cycle 5	1	7	0	8
Cycle 6	2	6	0	8
End of treatment	4	16	4	24

Table 13. Body System: Pulmonary

VISIT	Pulmonary			
	Abnormal	Normal	Not Done	Total
Baseline	3	27	0	30
Cycle 1	2	28	0	30
Cycle 2	2	25	0	27
Cycle 3	3	22	0	25
Cycle 4	1	12	0	13
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	2	21	1	23

Table 14. Body System: Cardiac

VISIT	Cardiac		
	Abnormal	Normal	Total
Baseline	1	29	30
Cycle 1	0	30	30
Cycle 2	1	26	27
Cycle 3	0	25	25
Cycle 4	1	12	13
Cycle 5	0	8	8
Cycle 6	0	8	8
End of treatment	22	2	0

Table 15. Body System: Musculoskeletal

VISIT	Musculoskeletal			
	Abnormal	Normal	Not Done	Total
Baseline	6	21	3	30
Cycle 1	5	23	2	30
Cycle 2	5	18	4	27
Cycle 3	4	19	2	25
Cycle 4	1	12	0	13
Cycle 5	2	6	0	8
Cycle 6	1	7	0	8
End of treatment	3	17	4	24

Table 16. Body System: Breast

VISIT	Breast			
	Abnormal	Normal	Not Done	Total
Baseline	2	23	5	30
Cycle 1	2	23	5	30
Cycle 2	1	20	6	27
Cycle 3	1	19	5	25
Cycle 4	0	11	2	13
Cycle 5	0	7	1	8
Cycle 6	0	6	2	8
End of treatment	2	14	8	24

Table 17. Body System: Abdomen

VISIT	Abdomen			
	Abnormal	Normal	Not Done	Total
Baseline	5	25	0	30
Cycle 1	4	26	0	30
Cycle 2	2	25	0	27
Cycle 3	4	21	0	25
Cycle 4	1	12	0	13
Cycle 5	1	7	0	8
Cycle 6	0	8	0	8
End of treatment	3	19	2	24

Table 18. Body System: Other

VISIT	Other			
	Abnormal	Normal	Not Done	Total
Baseline	6	10	13	29
Cycle 1	6	11	12	29
Cycle 2	5	9	12	26
Cycle 3	4	10	10	24
Cycle 4	3	3	6	12
Cycle 5	3	2	2	7
Cycle 6	1	2	3	6
End of treatment	7	7	10	24

5.4 Vital Signs

Table 19. Summary Statistics of Vital Signs Results By Visit

Variable	Obs	Mean	StD	Min	Max
Weight (kg)					
Baseline	30	76.8	22.2	46	178
Cycle 1	29	77.3	22.0	46	175.4
Cycle 2	27	72.4	10.8	45.5	97
Cycle 3	25	73.0	11.2	45.1	97
Cycle 4	13	70.3	12.2	45.5	97.6
Cycle 5	8	75.1	9.1	65.8	94.8
Cycle 6	8	75.2	8.4	66.3	92.8
End of treatment	18	79.5	24.4	53	168
Height (cm)					
Baseline	30	166.7	9.5	151	186
Cycle 1	30	166.7	9.5	151	186
Cycle 2	27	165.7	9.2	151	185
Cycle 3	25	166.0	8.9	151.8	185
Cycle 4	13	167.6	10.4	156	185
Cycle 5	8	166.6	10.1	156	184
Cycle 6	8	166.6	10.1	156	184
End of treatment	22	167.0	9.1	151.8	186
Body Surface Area (m^2)					
Baseline	28	1.81	0.17	1.44	2.22
Cycle 1	30	1.84	0.22	1.44	2.58
Cycle 2	27	1.80	0.17	1.44	2.2
Cycle 3	25	1.81	0.16	1.44	2.19
Cycle 4	13	1.78	0.19	1.44	2.21
Cycle 5	8	1.82	0.16	1.65	2.18
Cycle 6	8	1.83	0.15	1.68	2.16
End of treatment	13	1.91	0.25	1.55	2.58
Karnofsky Performance Status					
Baseline	30	90.0	7.9	80	100
Cycle 1	30	89.7	7.7	80	100
Cycle 2	26	90.4	8.2	80	100
Cycle 3	25	92.4	7.2	80	100
Cycle 4	12	90.8	7.9	80	100
Cycle 5	8	88.8	6.4	80	100
Cycle 6	8	86.3	7.4	80	100
End of treatment	21	79.5	17.2	40	100
Heart Rate (beats per minute)					
Baseline	30	80.1	11.2	58	102
Cycle 1	30	80.9	11.8	60	103

Cycle 2	26	82.4	12.2	59	108
Cycle 3	24	85.5	13.4	60	112
Cycle 4	12	82.3	12.6	65	100
Cycle 5	8	78.5	13.3	63	95
Cycle 6	8	80.4	13.6	65	100
End of treatment	21	84.8	12.6	68	120
Systolic Blood Pressure (mmHg)					
Baseline	30	129.9	20.5	102	196
Cycle 1	30	129.6	18.6	101	196
Cycle 2	26	123.5	13.2	100	147
Cycle 3	24	120.1	15.8	92	156
Cycle 4	12	120.0	17.4	101	155
Cycle 5	8	121.3	16.6	94	150
Cycle 6	8	122.3	16.1	104	155
End of treatment	20	128.4	20.4	86	160
Diastolic Blood Pressure (mmHg)					
Baseline	30	76.6	9.7	60	98
Cycle 1	30	76.5	9.0	57	98
Cycle 2	26	76.3	8.9	55	100
Cycle 3	24	76.5	11.7	52	98
Cycle 4	12	76.6	11.6	58	97
Cycle 5	8	74.4	12.4	53	98
Cycle 6	8	77.1	19.0	49	111
End of treatment	20	78.7	10.9	56	96

5.5 Hematology

Table 20. Summary Statistics Of Hematology Results By Visit

Variable	Obs	Mean	SD	Min	Max
Haemoglobin (g/dl)					
Baseline	30	13.1	1.8	9.6	15.8
Cycle 1	30	13.1	1.8	9.6	16.8
Cycle 2	27	12.8	1.6	8.6	15.9
Cycle 3	25	12.6	1.5	10	15.4
Cycle 4	13	12.0	1.3	9.7	13.7
Cycle 5	8	11.6	1.4	9	13.7
Cycle 6	8	11.4	1.1	10.4	13.6
End of treatment	24	12.4	1.7	8.8	15.3
White Blood Cell Count ($x10^9$/L)					
Baseline	30	7.3	2.6	2.6	14.1
Cycle 1	30	7.4	2.5	2.9	15.6
Cycle 2	27	7.4	3.3	3.5	18.5

Cycle 3	25	6.8	2.6	2.9	11.9
Cycle 4	13	6.1	2.0	3.4	9.71
Cycle 5	8	6.7	2.2	4.3	10.4
Cycle 6	8	7.1	3.0	2.7	11.8
End of treatment	24	8.5	3.9	4.4	20.8
Platelets (x10⁹/L)					
Baseline	30	300.6	108.2	106	494
Cycle 1	30	293.9	100.5	135	508
Cycle 2	27	362.2	125.1	103	693
Cycle 3	25	344.1	110.9	104	632
Cycle 4	13	327.6	93.3	153	540
Cycle 5	8	357.1	80.1	240	458
Cycle 6	8	376.1	99.9	232	520
End of treatment	24	336.2	126.8	129	585
Absolute Neutrophil Count (x10⁹/L)					
Baseline	30	5.0	2.4	1.44	12.5
Cycle 1	30	5.2	2.4	1.82	13.9
Cycle 2	26	4.8	2.8	1.9	14.6
Cycle 3	25	4.4	2.3	1.5	9.6
Cycle 4	13	3.8	1.9	1.8	8
Cycle 5	8	4.2	1.9	2.5	7.9
Cycle 6	8	4.8	2.8	1.5	9.4
End of treatment	22	5.8	4.0	1.9	18.3

Table 21. Summary Statistics for Haematology Abnormalities By Visit

Variable	Low	Normal	High	Total
Haemoglobin (g/dl)				
Baseline	8	22	0	30
Cycle 1	8	22	0	30
Cycle 2	8	19	0	27
Cycle 3	8	17	0	25
Cycle 4	6	7	0	13
Cycle 5	5	3	0	8
Cycle 6	5	3	0	8
End of treatment	10	14	0	24
White Blood Cell Count (x10⁹/L)				
Baseline	3	25	2	30
Cycle 1	2	26	2	30
Cycle 2	0	25	2	27
Cycle 3	4	20	1	25
Cycle 4	3	10	0	13
Cycle 5	0	8	0	8
Cycle 6	1	6	1	8
End of treatment	0	19	5	24

Platelets (x10⁹/L)				
Baseline	1	23	6	30
Cycle 1	1	24	5	30
Cycle 2	1	18	8	27
Cycle 3	1	20	4	25
Cycle 4	0	12	1	13
Cycle 5	0	6	2	8
Cycle 6	0	5	3	8
End of treatment	2	15	7	24
Absolute Neutrophil Count (x10⁹/L)				
Baseline	3	24	3	30
Cycle 1	1	26	3	30
Cycle 2	1	20	5	26
Cycle 3	5	17	3	25
Cycle 4	2	10	1	13
Cycle 5	0	7	1	8
Cycle 6	1	6	1	8
End of treatment	1	17	4	22

5.6 Clinical Chemistry

Table 22. Summary Statistics of Clinical Chemistry by Visit

Variable	Obs	Mean	StD	Min	Max
Alanine Aminotransferese (U/L)					
Baseline	27	27.2	19.4	6	107
Cycle 1	26	25.8	19.9	7	107
Cycle 2	23	24.1	10.0	5	41
Cycle 3	21	22.0	9.8	8	44
Cycle 4	12	19.2	8.1	7	38
Cycle 5	8	21.9	6.6	13	32
Cycle 6	8	25.4	18.2	12	67
End of treatment	19	23.9	16.5	8	72
Aspartate Aminotransferase (U/L)					
Baseline	29	22.6	7.6	8	51
Cycle 1	23	23.2	8.7	11	51
Cycle 2	24	22.1	5.9	12	35
Cycle 3	21	21.2	5.0	10	32
Cycle 4	10	19.7	6.8	8	28
Cycle 5	7	22.7	5.8	14	32
Cycle 6	8	26.1	19.6	15	74
End of treatment	20	21.2	7.2	5	34
Serum Albumin (g/L)					
Baseline	29	38.0	4.9	28	50
Cycle 1	29	37.9	4.9	25	50
Cycle 2	26	36.7	4.9	27	46
Cycle 3	25	37.3	4.7	26	44
Cycle 4	13	36.1	3.5	31	43
Cycle 5	8	37.6	2.6	34	42
Cycle 6	8	36.4	3.0	33	42
End of treatment	24	36.8	4.5	29	44
Alkaline Phosphatase (U/L)					
Baseline	30	93.2	47.1	52	237
Cycle 1	30	91.2	40.3	50	199
Cycle 2	27	87.0	31.2	49	168
Cycle 3	25	78.8	30.1	42	164
Cycle 4	13	75.3	20.7	43	109
Cycle 5	8	78.8	25.9	50	132
Cycle 6	8	75.8	18.5	58	109
End of treatment	24	81.9	33.0	44	187
Total Bilirubin (umol/L)					
Baseline	30	7.8	4.3	4	22

Cycle 1	30	7.8	4.5	4	24
Cycle 2	27	6.2	2.7	2	14
Cycle 3	24	7.1	2.8	3	14
Cycle 4	12	6.5	3.0	4	12
Cycle 5	8	5.9	1.4	4	8
Cycle 6	8	5.6	1.3	4	7
End of treatment	23	8.3	3.1	3	16
Blood Urea Nitrogen (BUN) (mmol/L)					
Baseline	30	5.1	1.4	1.9	9.5
Cycle 1	30	5.0	1.3	1.9	8
Cycle 2	27	4.9	1.8	2.8	12
Cycle 3	25	4.7	1.3	1.9	6.7
Cycle 4	13	4.2	1.8	1.3	7.3
Cycle 5	8	4.9	1.1	3.1	6.3
Cycle 6	8	5.0	0.8	4.2	6.2
End of treatment	24	4.8	1.9	1.9	10
Calcium (mmol/L)					
Baseline	27	2.4	0.1	2.11	2.52
Cycle 1	27	2.4	0.1	2.12	2.52
Cycle 2	26	2.3	0.1	1.95	2.52
Cycle 3	25	2.3	0.1	2.13	2.62
Cycle 4	13	2.3	0.1	2.17	2.61
Cycle 5	8	2.4	0.1	2.29	2.6
Cycle 6	8	2.3	0.1	2.22	2.42
End of treatment	23	2.4	0.1	2.15	2.59
Creatinine (umol/L)					
Baseline	30	76.8	22.8	44	171
Cycle 1	30	76.5	20.4	44	157
Cycle 2	27	73.6	19.3	36	137
Cycle 3	25	72.7	19.3	46	139
Cycle 4	13	61.7	26.4	0.55	119
Cycle 5	8	78.4	21.7	54	118
Cycle 6	8	72.9	26.8	44	131
End of treatment	24	71.2	17.0	32	107
Gamma Glutamyl Transpeptidase (U/L)					
Baseline	28	54.4	52.1	11	236
Cycle 1	28	50.5	43.5	10	206
Cycle 2	25	49.1	36.9	11	167
Cycle 3	24	44.0	43.5	13	235
Cycle 4	11	53.8	45.9	15	181
Cycle 5	7	61.9	31.2	27	107
Cycle 6	7	69.6	52.8	31	178
End of	23	49.3	41.6	9	179

treatment					
Magnesium (mmol/L)					
Baseline	22	0.9	0.1	0.57	1.02
Cycle 1	18	0.9	0.1	0.59	1.02
Cycle 2	18	0.9	0.1	0.63	1.01
Cycle 3	16	0.9	0.1	0.76	1
Cycle 4	8	0.9	0.0	0.8	0.93
Cycle 5	6	0.9	0.0	0.82	0.89
Cycle 6	6	0.9	0.1	0.77	0.93
End of treatment	15	0.9	0.1	0.76	1.05
Potassium (mmol/L)					
Baseline	29	4.1	0.4	3.4	5.1
Cycle 1	28	4.0	0.4	3.3	5.1
Cycle 2	27	4.0	0.5	2.9	4.9
Cycle 3	24	3.9	0.4	2.7	4.5
Cycle 4	12	4.0	0.3	3.6	4.7
Cycle 5	8	4.3	0.5	3.8	5.1
Cycle 6	8	4.1	0.2	3.8	4.5
End of treatment	24	3.9	0.5	3	5
Sodium (mmol/L)					
Baseline	30	139.8	2.6	133	143
Cycle 1	30	139.9	2.7	133	145
Cycle 2	27	140.0	2.5	135	143
Cycle 3	25	139.8	3.2	131	146
Cycle 4	13	140.0	2.4	136	145
Cycle 5	8	140.4	1.8	138	144
Cycle 6	8	141.1	3.1	137	146
End of treatment	24	138.2	4.2	124	145

Table 23. Summary Statistics for Clinical Chemistry Abnormalities By Visit

Variable	Low	Normal	High	Total
Alanine Aminotransferese (U/L)				
Baseline	2	21	4	27
Cycle 1	2	21	3	26
Cycle 2	2	21	0	23
Cycle 3	2	19	0	21
Cycle 4	2	10	0	12
Cycle 5	1	7	0	8
Cycle 6	0	7	1	8
End of treatment	2	15	2	19
Aspartate Aminotransferase (U/L)				
Baseline	2	26	1	29
Cycle 1	2	20	1	23
Cycle 2	2	22	0	24

Cycle 3	0	21	0	21
Cycle 4	1	9	0	10
Cycle 5	1	6	0	7
Cycle 6	1	6	1	8
End of treatment	1	19	0	20
Serum Albumin (g/L)				
Baseline	6	23	0	29
Cycle 1	5	24	0	29
Cycle 2	9	17	0	26
Cycle 3	7	18	0	25
Cycle 4	4	9	0	13
Cycle 5	1	7	0	8
Cycle 6	2	6	0	8
End of treatment	9	15	0	24
Alkaline Phosphatase (U/L)				
Baseline	0	25	5	30
Cycle 1	0	25	5	30
Cycle 2	0	24	3	27
Cycle 3	0	24	1	25
Cycle 4	0	13	0	13
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	0	22	2	24
Total Bilirubin (umol/L)				
Baseline	0	29	1	30
Cycle 1	0	29	1	30
Cycle 2	0	27	0	27
Cycle 3	0	24	0	24
Cycle 4	0	12	0	12
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	0	23	0	23
Blood Urea Nitrogen (BUN) (mmol/L)				
Baseline	2	27	1	30
Cycle 1	1	28	1	30
Cycle 2	0	26	1	27
Cycle 3	1	24	0	25
Cycle 4	2	10	1	13
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	1	20	3	24
Calcium (mmol/L)				
Baseline	0	27	0	27
Cycle 1	2	25	0	27
Cycle 2	2	24	0	26
Cycle 3	3	22	0	25
Cycle 4	1	12	0	13
Cycle 5	0	8	0	8
Cycle 6	0	8	0	8
End of treatment	3	20	0	23

Creatinine (umol/L)				
Baseline	0	28	2	30
Cycle 1	0	28	2	30
Cycle 2	2	23	2	27
Cycle 3	1	22	2	25
Cycle 4	2	10	1	13
Cycle 5	0	8	0	8
Cycle 6	0	7	1	8
End of treatment	2	21	1	24
Gamma Glutamyl Transpeptidase (U/L)				
Baseline	0	17	11	28
Cycle 1	0	19	9	28
Cycle 2	1	16	8	25
Cycle 3	1	18	5	24
Cycle 4	0	8	3	11
Cycle 5	0	3	4	7
Cycle 6	0	4	3	7
End of treatment	1	14	8	23
Magnesium (mmol/L)				
Baseline	2	20	0	22
Cycle 1	3	15	0	18
Cycle 2	4	14	0	18
Cycle 3	0	16	0	16
Cycle 4	0	8	0	8
Cycle 5	1	5	0	6
Cycle 6	1	5	0	6
End of treatment	0	14	1	15
Potassium (mmol/L)				
Baseline	1	27	1	29
Cycle 1	4	23	1	28
Cycle 2	5	22	0	27
Cycle 3	6	18	0	24
Cycle 4	1	11	0	12
Cycle 5	1	7	0	8
Cycle 6	1	7	0	8
End of treatment	4	20	0	24
Sodium (mmol/L)				
Baseline	2	28	0	30
Cycle 1	1	29	0	30
Cycle 2	0	27	0	27
Cycle 3	2	22	1	25
Cycle 4	0	13	0	13
Cycle 5	0	8	0	8
Cycle 6	0	7	1	8
End of treatment	2	22	0	24

5.7 Primary Outcome Measure- Response Rate

Table 24. Response Rate and 95% CI

	Number	Response Rate	95% Confidence Interval Lower	Upper
Response (PR/SD)	9	0.31	0.14	0.48

Three patients experienced partial response for at least 4 weeks with a median (range) duration of 73 (29-88) days. Disease was stabilised for seven patients. Five patients experienced disease stabilisation during the third cycle of trial treatment. One patient presented with stabilized disease at cycle 3 and a partial response after 196 days.

Table 25. Gender, Age, Cycles Of Treatment Received, Response, Serious Adverse Event(SAE)s

Label	Gender	Age	Cycles of treatment received	Total Dose Sulindac	Total Dose Epirubicin	Response	SAE
63006	M	30	6	3600	450	SD	Urosepsis with normal ANC
63007	F	61	6	3600	450	SD	Fracture Right Shoulder
63009	M	26	4	2400	300	PR	Right Sided Chest Pain
63009							Right Pleuretic Chest Pain
63009							Haemorrhage Liver
63012	F	31	6	3600	450	SD	No SAE
63013	M	57	6	3600	450	SD, PR	No SAE
63015	M	45	6	3600	450	SD	No SAE
63028	M	73	3	1800	225	SD	Diarrhoea/Melena
63029	F	63	6	3600	390	SD	Sepsis
63029							Thrombosis
63032	F	70	6	3600	450	PR	No SAE

5.8 Secondary Outcome Measure- Toxicity

All 30 patients experienced adverse events. A total of 586 adverse events were reported in the trial. Most frequently occurring adverse events were fatigue, nausea and constipation. Among the 40 reported fatigue events, 37 (92.5%) were considered to have a (definite/possible/probable) relationship to the trial drug.

Table 26. AE's By Visit

Visit	Frequency	Percent

Cycle 1	210	35.8
Cycle 2	119	20.3
Cycle 3	97	16.6
Cycle 4	58	9.9
Cycle 5	32	5.5
Cycle 6	19	3.2
End of treatment	47	8.0
Follow-up	4	0.7
Total	**586**	**100.0**

Table 27. AE's by Grade

CTC GRADE	FREQUENCY	PERCENT
Grade 1	443	75.6
Grade 2	100	17.1
Grade 3	28	4.8
Grade 4	6	1.0
Not Known	9	1.5
Total	**586**	**100.0**

Out of 586 AEs reported, 443 (75.6%) were categorised as CTC Grade 1 event and 100 (17.06%) were categorised as CTC Grade 2 event at onset. CTC grade of 9 (1.54%) adverse events was "Not Known".

Table 28. AE's by Relationship

Relationship	Frequency	Percent
Definite	70	12.0
Possible	216	36.9
Probable	75	12.8
Unlikely	78	13.3
Unrelated	123	21.0
Unknown	24	4.1
Total	**586**	**100.0**

Among the 586 reported AEs, 361 (61.60%) events were considered to have a (definite/possible/probable) relationship to the drug and 201 (34.30%) were reported as unlikely or not related to the trial drug. Relationship of 24 (4.1%) adverse events to the trial drug was reported as 'unknown'.

Table 29. AE's CTC Grade X Relationship

CTC Grade	Definite	Possible	Probable	Unlikely	Unrelated	Unknown	Total
Grade 1	45	175	60	64	83	16	443
Grade 2	17	34	14	8	26	1	100
Grade 3	6	5	1	5	9	2	28
Grade 4	2	2	0	1	1	0	6
Not Known	0	0	0	0	4	5	9
Total	**70**	**216**	**75**	**78**	**123**	**24**	**586**

Twenty eight grade 3 events were reported in the trial. Twelve (42.86%) of the Grade 3 events were considered to be related to the drug. A total of 6 events were Grade 4 and four of the reported events were considered to be related to the drug.

Table 30. Outcome of AE

Outcome	Frequency	Percent
Resolved	396	67.6
Not Resolved	189	32.3
Not Known	1	0.2
Total	**586**	**100**

The majority of AEs were resolved 396 (67.58%%) during the trial period. Among the unresolved AEs, 106 (56.08%) were considered to be related to the trial drug. Ten Grade 3 events and a Grade 4 event were unresolved.

Table 31. Frequently Occurring AEs

Adverse Event	N	Episodes	Related† to drug	Not Related‡ to the drug	Relation : Unknown	Total number of Events
Fatigue	22	1 to 5	37 (92.5%)	3 (7.5%)	0	40
Nausea	19	1 to 5	35 (94.6%)	2 (5.4%)	0	37
Constipation	18	1 to 5	27 (75%)	9 (25%)	0	36
Alopecia	21	1 to 2	23 (100%)	0	0	23
Low Haemoglobin	14	1 to 5	15 (68.2%)	7 (31.82%)	0	22
Diarrhoea	11	1 to 5	18 (81.8%)	2 (9.1%)	2 (9.1%)	22
Vomiting	10	1 to 4	13 (72.2%)	5 (27.8%)	0	18
Neutropenia	9	1 to 2	13 (100%)	0	0	13
Taste Changes	8	1 to 2	11 (100%)	0	0	11
Stomatitis	7	1 to 3	11 (100%)	0	0	11
Elevated GGT	7	1 to 3	3 (30%)	5 (50%)	2 (20%)	10
Hypernatraemia	3	1 to 6	2 (22.2%)	6 (66.7%)	1 (11.1%)	9
Elevated Transaminase	4	1 to 2	0	5 (71.4%)	2 (28.6%)	7

† Relation to the drug quoted as Definite/Probable/Possible in the Adverse Event form

‡ Relation to the drug quoted as Unlikely/Unrelated in the Adverse Event form

Table 31 detail the frequently occurred adverse events in the trial. Among the 30 patients who received at least one dose of treatment, 22 experienced fatigue. The number of episodes of fatigue ranged from 1 to 5. Low haemoglobin and Neutropenia were the frequently reported haematological disorders which were predominantly considered to be related to the drug.

Table 32. List of Grade 3 AEs

Adverse Event	Frequency	Percent
Diarrhoea/Melena	2	7.1
Elevated GGT	2	7.1
Haemorrhage Liver	1	3.6
Hypokalaemia	3	10.7
Hypernatraemia	1	3.6
Leucopoenia	1	3.6
Low Neutrophil	1	3.6

Low Platelets	1	3.6
Low WBC	2	7.1
Neurology other spinal cord compression	1	3.6
Neutropenia	3	10.7
Neutropenic Sepsis	1	3.6
Pain neck radiating to shoulder and hand	1	3.6
Respiratory Tract Infection	1	3.6
Right Pleuretic Chest Pain	1	3.6
Right Sided Chest Pain	1	3.6
Sepsis	1	3.6
Severe Neck Pain	1	3.6
Speech Dysphasia	1	3.6
Thrombosis	1	3.6
Urosepsis with normal ANC	1	3.6
Total	**28**	**100.0**

Table 33. List of Grade 4 AEs

Adverse Event	Frequency
Decreased level of Consciousness	1
Dyspnoea at rest	1
Neutropenia	3
Thrombocytopenia	1
Total	**6**

Thirty four adverse events were categorised with a CTC Grade 3 or greater. Twelve patients experienced one or more Grade 3 adverse event and 5 patients experienced Grade 4 events. Neutropenia was the most frequently occurring adverse events with a CTC Grade 3 or greater. Six patients were presented with Grade 3 or greater Neutropenia. All the cases of Neutropenia was considered to have a (definite/possible) relation to the trial drug

Table 34. SAE

Serious Adverse Event	Frequency	Percent
No	569	97.1
Yes	17	2.9
Total	**586**	**100**

Thirteen (43.33%) patients experienced serious adverse events. Three of the patients reported with a serious adverse event experienced Neutropenia.

Table 35. List of SAEs

Label	Cycles of treatment	Toxicity	CTC Grade	Relationship

	received			
63003	3	Nausea - Brain Mets Confirmed by CT Scan	Grade 2	Possible
63006	6	Urosepsis with normal ANC	Grade 3	Possible
63007	6	Fracture Right Shoulder	Grade 2	Unrelated
63009	4	Right Sided Chest Pain	Grade 3	Unrelated
63009	4	Right Pleuretic Chest Pain	Grade 3	Unrelated
63009	4	Haemorrhage Liver	Grade 3	Unrelated
63010	3	Neutropenic Sepsis	Grade 3	Definite
63018	6	Neutropenia	Grade 4	Definite
63019	1	Herpes Zoster Opthalmicus	Grade 2	Possible
63021	4	Motor Neuropathy	Grade 2	Unrelated
63024	2	Haemorrhagic Brain Mets	Not Known	Unrelated
63024	2	Neutropenia	Grade 4	Definite
63025	2	Respiratory Tract Infection	Grade 3	Unlikely
63026	1	Neurology other spinal cord compression	Grade 3	Unrelated
63028	3	Diarrhoea/Melena	Grade 3	Possible
63029	6	Sepsis	Grade 3	Possible
63029	6	Thrombosis	Grade 3	Possible

5.9 Tumour Evaluation

Table 36. Baseline Tumour Evaluation

Sum of Target Lesions	
Mean (SD)	10.44 (9.2)
Median	7.7
Range	2.7 to 41
Number of Target Lesions	
Median	2
Range	1 to 9
Number of non-target lesions	
Median	2
Range	1 to 16

Table 37. Method Of Evaluation

Method of Evaluation	Frequency
Clinical Examination	1
CAT Scan	1
PET / CT Scan	1
Spiral CT Scan	26

*Patient number 63014 did not have measurable lesion. Inclusion criteria did mention that the patient should have measurable or evaluble lesion.

Table 38. New Lesions

New Lesions	Frequency	Percent
Yes	15	51.7
No	14	48.3

Total	29	100

5.10 Survival Analysis

Figure 1. Kaplan-Meier Curve - Time to Progressive Disease

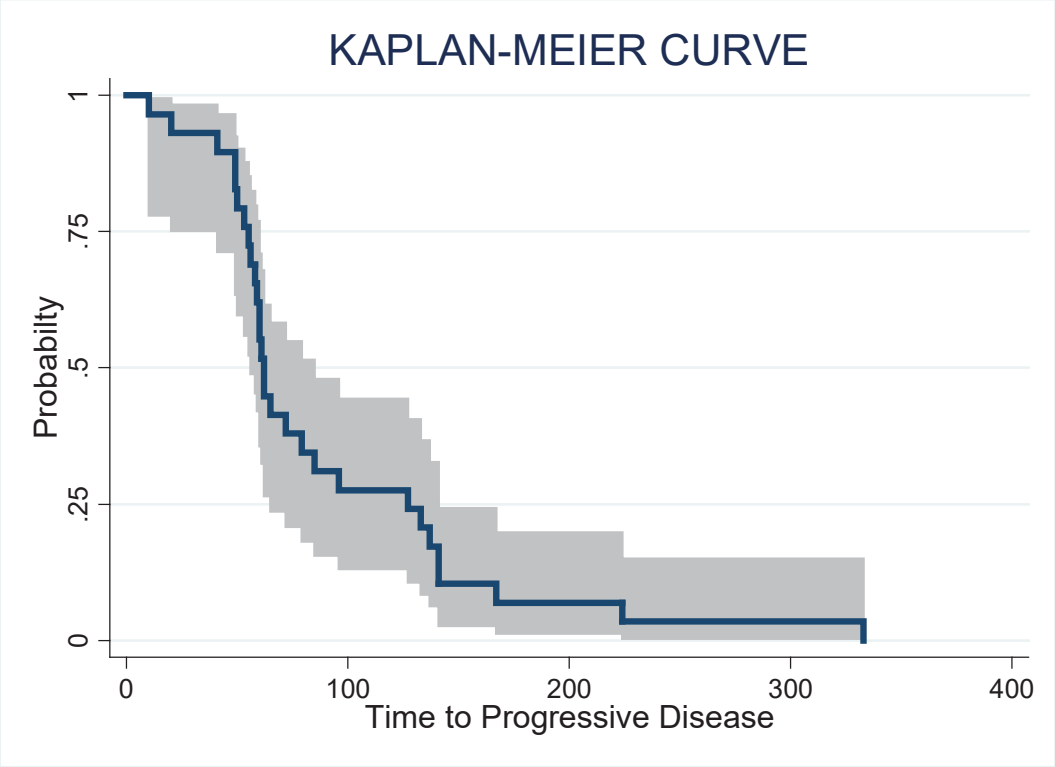

Table 39. Median (Inter-Quartile Range) Time to Progressive Disease and 95% CI

			95 % Confidence Interval	
	Observations	Median (IQR)	Lower	Upper
Total	29	62 (55 to 127)	56	85

Figure 2. Time to Withdrawal from the Trial

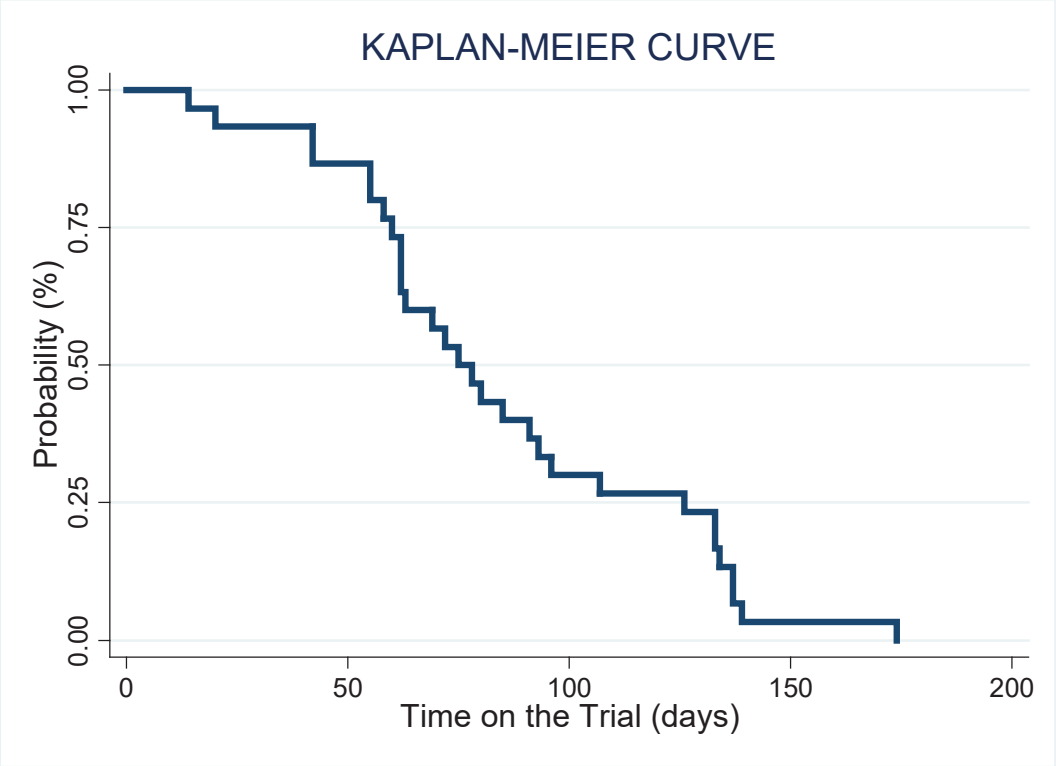

Table 40. Median (IQR) Time To Withdrawal From The Trial And 95% CI

	Observations	Median (IQR)	95 % Confidence Interval Lower	Upper
Total	29	75 (60 to 126)	62	96

6. SUMMARY OF RESULTS

1. The primary objective of the trial was to estimate the efficacy of the treatment combination by evaluating the tumour response rates. After the first stage of the trial, nine of the 29 evaluable patients *(31%, 95% CI: 14% to 48%)* experienced either partial response for more than four weeks (three patients) or disease stabilization (six patients). However, at the time of the analysis of the first stage data, the main clinical interest was in actual response rather than disease stabilization. Three partial responders would only have been sufficient to rule out a response rate of less than 10% with 80% power, which would have been considered an inadequate response rate. The trial was therefore terminated after the first stage.

2. The secondary objective was to characterize the toxicity of the combination. A total of 586 AEs were reported in the trial, and 34 (5.8%) were of CTC grade 3 or greater toxicity. Fatigue and nausea was the most frequently occurring AE. Twenty

two events of low hemoglobin levels were reported by 14 (46.7%) patients, 15 events were related to the drug. Thirteen events of Neutropenia were reported by 9 (30%) patients, all of them were related to the trial drug.