PACIFICO

Purine-Alkylator Combination In Follicular Lymphoma Immuno-Chemotherapy for Older patients: A phase III comparison of first-line R-CVP versus R-FC

EudraCT Number: 2008-004759-31

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Final Statistical Analysis Report

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2 Recruitment and Disposition

Table 2-1 Recruitment by Site

					R-FC Combined		
Site Name	**Date of Green Light**	**Date of First Randomisation**	**Date of Last Randomisation**	**R-CVP**	**R-FC Full**	**R-FC Lite**	**Total Randomised**
Kent and Canterbury Hospital	03MAR2010	19MAR2010	13AUG2015	14	5	7	26
Royal Liverpool University Hospital	09SEP2009	07OCT2009	11APR2016	9	3	6	18
Torbay District General Hospital	19MAR2010	18MAY2010	12SEP2014	9	2	6	17
Blackpool Victoria	27JUL2011	29SEP2011	16OCT2015	6	1	6	13
Birmingham Heartlands	18OCT2010	24JAN2011	28JUL2014	6	4	3	13
Sandwell Hospital	21JUN2011	12JUL2012	29JUL2015	6	0	7	13
Royal Devon & Exeter Hospital	16JUN2010	04SEP2012	29SEP2015	6	0	5	11
Queens Hospital, Romford	03AUG2010	18NOV2010	05FEB2015	5	4	2	11
University College Hospital	31MAR2010	15APR2010	20DEC2013	5	2	3	10
Basingstoke and North Hampshire Hospital	14MAY2010	12OCT2010	05FEB2016	4	1	4	9
Conquest Hospital	09MAR2012	19MAR2012	08OCT2014	4	0	5	9
Ysbyty Gwynedd	10NOV2010	17NOV2010	21MAR2016	2	1	5	8
Kent Oncology Centre	09APR2010	17SEP2010	09JAN2014	4	1	2	7
Southampton General Hospital	24FEB2010	05JUL2010	12FEB2014	4	2	1	7
Derriford Hospital	07JUL2010	06MAY2011	17APR2015	3	0	4	7
Raigmore Hospital	20JUL2010	08SEP2010	14MAY2015	4	1	2	7
Beatson Oncology Centre	22OCT2010	07APR2011	22APR2016	3	1	3	7

					R-FC Combined		
Site Name	**Date of Green Light**	**Date of First Randomisation**	**Date of Last Randomisation**	**R-CVP**	**R-FC Full**	**R-FC Lite**	**Total Randomised**
Arrowe Park Hospital	17MAY2010	06DEC2011	10JUL2015	3	0	3	6
Northwick Park Hospital	29JUN2010	13APR2012	02APR2015	2	0	4	6
Worthing Hospital	23JUL2010	07APR2014	26JAN2016	4	0	2	6
Worcester Royal Infirmary	24FEB2011	03NOV2011	16MAR2016	4	1	1	6
The Christie	19JUL2010	12OCT2010	06OCT2015	1	1	3	5
Diana Princess of Wales Hospital	29OCT2010	06JUL2012	28APR2015	3	0	2	5
Southend Hospital	11DEC2012	12FEB2013	03MAR2015	3	0	2	5
St James University Hospital	26MAY2010	14FEB2011	22APR2013	2	2	1	5
University Hospital Aintree	11JAN2010	09APR2010	30NOV2010	3	2	0	5
Salisbury District Hospital	01APR2011	12JUL2012	19JAN2016	3	0	2	5
Frenchay Hospital	27AUG2010	14MAR2011	14AUG2015	3	1	1	5
Aberdeen Royal Infirmary	10MAY2010	03JUN2010	30DEC2014	3	2	0	5
Glan Clwyd Hospital	20DEC2010	24FEB2011	02NOV2015	3	1	1	5
Royal Marsden Hospital SM2 5PT	12MAY2011	02JUN2011	20MAR2012	2	1	1	4
Castle Hill Hospital	19JAN2011	14FEB2011	22OCT2014	2	0	2	4
Bradford Royal Infirmary	21JUL2010	19OCT2010	31JUL2014	2	2	0	4
West Suffolk Hospital	18SEP2013	02DEC2013	13OCT2015	2	0	2	4
Velindre Hospital	15DEC2010	17JAN2011	07JAN2014	3	0	1	4
Princess Royal Hospital, Bromley	11OCT2010	05APR2013	17JUL2014	3	0	1	4
Northampton General Hospital	12NOV2010	10OCT2012	11MAR2015	1	0	2	3
Huddersfield Royal Infirmary	09FEB2011	18FEB2011	13AUG2013	1	1	1	3

					R-FC Combined		
Site Name	**Date of Green Light**	**Date of First Randomisation**	**Date of Last Randomisation**	**R-CVP**	**R-FC Full**	**R-FC Lite**	**Total Randomised**
Countess of Chester Hospital	11JUN2010	16JUL2013	17FEB2015	1	0	2	3
Sunderland Royal Hospital	29JUN2010	29NOV2011	02OCT2014	1	0	2	3
Russels Hall Hospital	18JUN2010	29JAN2015	18FEB2016	1	0	2	3
Luton & Dunstable Hospital	01OCT2010	11APR2011	18MAR2015	1	1	1	3
Royal Hampshire County Hospital	29JAN2014	30JAN2014	27MAR2014	0	0	3	3
St Richards Hospital	24FEB2010	31JAN2011	10MAY2013	1	1	1	3
Weston General Hospital	20JAN2012	18JAN2013	14JAN2015	1	0	2	3
James Cook University Hospital	01JUN2012	31JUL2014	27APR2015	0	0	2	2
Addenbrookes Hospital	22JAN2010	16APR2015	22SEP2015	1	0	1	2
Kettering General Hospital	29OCT2010	26JUL2011	11NOV2011	1	1	0	2
Nottingham City Hospital	28MAY2010	14APR2011	13MAY2011	1	1	0	2
Pinderfields General Hospital	07JAN2011	31JAN2011	03JUL2013	2	0	0	2
Stoke Mandeville Hospital	17JAN2012	09FEB2012	15JAN2015	0	0	2	2
Whiston Hospital	05FEB2010	12JUL2011	09AUG2011	1	1	0	2
Royal Victoria Infirmary	22DEC2010	18MAY2011	10JUN2011	2	0	0	2
Royal Hallamshire Hospital	02MAR2011	30MAY2013	21AUG2013	1	0	1	2
Stafford Hospital	19JUL2010	09AUG2010	30MAY2014	2	0	0	2
Poole Hospital	10APR2012	26APR2012	20AUG2013	2	0	0	2
Royal United Hospital	18MAY2011	04JUL2014	07JUL2014	1	0	1	2
North Devon District Hospital	20OCT2011	01MAR2012	23SEP2013	0	0	2	2
Royal Cornwall Hospital (Treliske)	27JAN2010	11FEB2010	06MAY2011	2	0	0	2

					R-FC Combined		
Site Name	**Date of Green Light**	**Date of First Randomisation**	**Date of Last Randomisation**	**R-CVP**	**R-FC Full**	**R-FC Lite**	**Total Randomised**
Barnet and Chase Farm Hospitals	19JUL2012	26OCT2012	16JAN2013	2	0	0	2
Mount Vernon Hospital	04DEC2009	09APR2010	15JAN2013	1	0	1	2
Royal Sussex County Hospital	16AUG2013	02DEC2014	20JAN2016	1	0	1	2
Queen Elizabeth Hospital, Kings Lynn	14MAR2011	04JUL2012	10FEB2014	1	0	1	2
Hemel Hempstead General	01MAR2011	11OCT2012	07JUL2014	0	0	2	2
Leighton Hospital	21JAN2011	09NOV2012	25SEP2013	2	0	0	2
Guys & St Thomas Hospital	12OCT2010	28OCT2010	27APR2011	0	2	0	2
Leicester Royal Infirmary	14JAN2011	17JAN2012	17JAN2012	0	0	1	1
York District Hospital	26MAY2010	02SEP2010	02SEP2010	0	1	0	1
Manchester Royal Infirmary	25MAY2010	23FEB2011	23FEB2011	0	1	0	1
Royal Bournemouth Hospital	15MAR2011	14AUG2013	14AUG2013	0	0	1	1
Ealing Hospital	05DEC2011	07MAR2014	07MAR2014	1	0	0	1
Hillingdon Hospital	28JAN2010	30SEP2010	30SEP2010	0	1	0	1
Royal Shrewsbury Hospital	24FEB2015	11MAY2015	11MAY2015	1	0	0	1
Kings College Hospital	UNKNOWN	16AUG2010	16AUG2010	0	1	0	1
Royal Derby Hospital	26MAY2011	28OCT2013	28OCT2013	1	0	0	1
Queen's Hospital, Burton	10MAY2010	30NOV2010	30NOV2010	1	0	0	1
St Mary's Hospital, London	26AUG2011	13SEP2011	13SEP2011	1	0	0	1
Royal Gwent Hospital	11OCT2012	24OCT2014	24OCT2014	1	0	0	1
Falkirk & District Royal Infirmary	08NOV2010	11APR2013	11APR2013	1	0	0	1
Nevill Hall Hospital	05NOV2012	17DEC2014	17DEC2014	1	0	0	1

					R-FC Combined		
Site Name	**Date of Green Light**	**Date of First Randomisation**	**Date of Last Randomisation**	**R-CVP**	**R-FC Full**	**R-FC Lite**	**Total Randomised**

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\05 - Recruitment.sas

Figure 2-1 Kaplan Meier Plot: Progression Free Survival

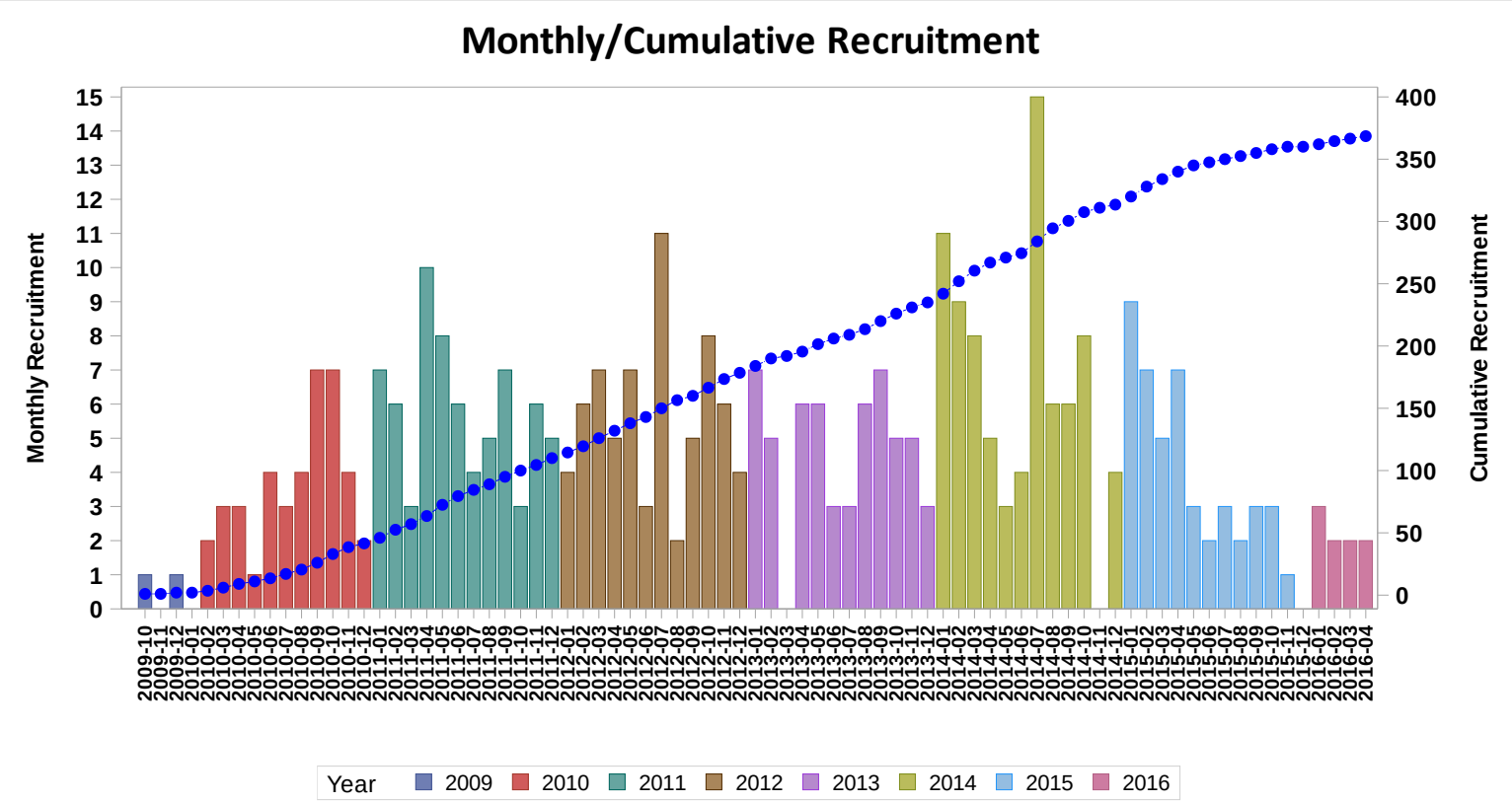

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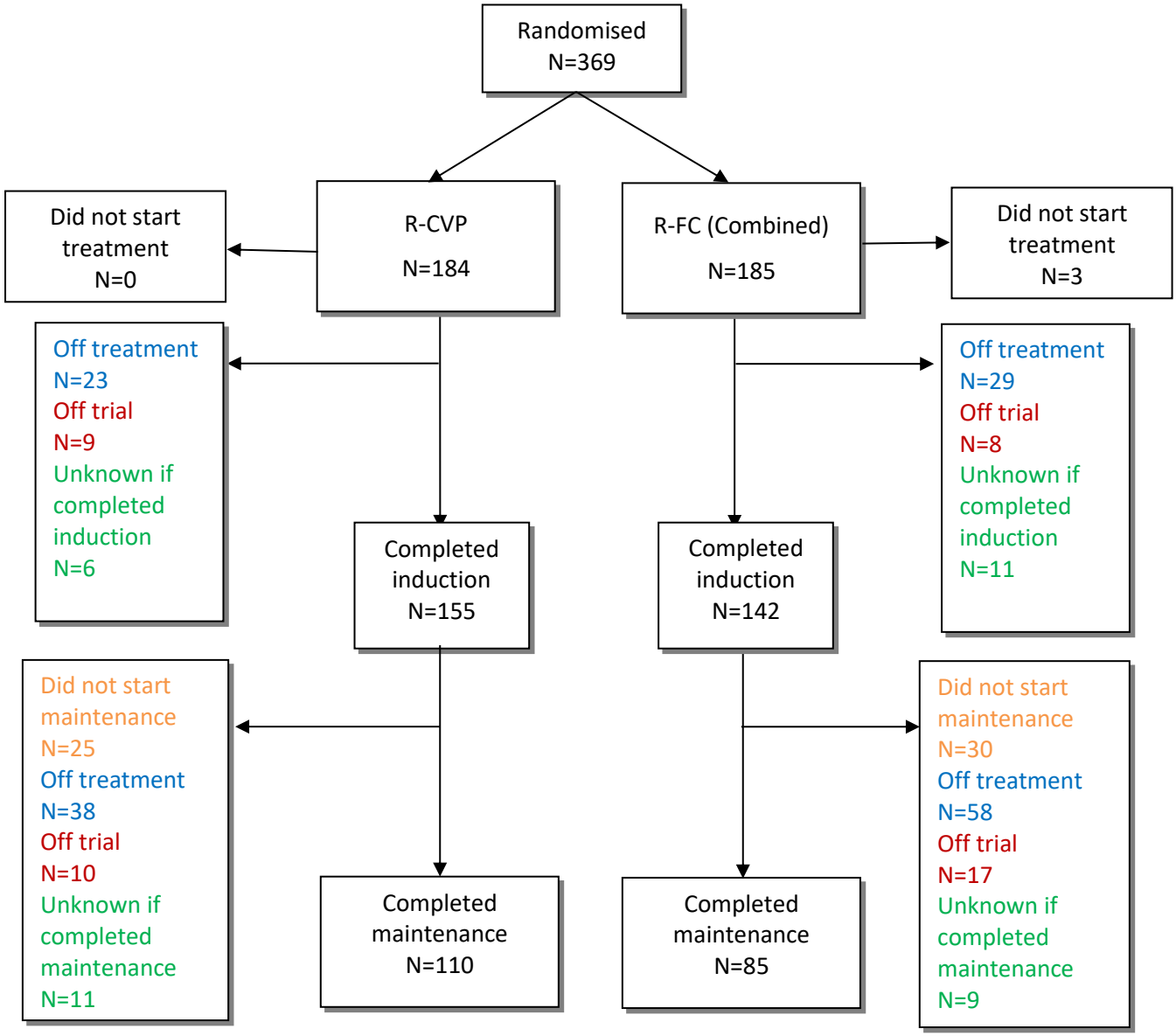
Figure 2-2 Patient Disposition



Note: One patient withdrew consent between randomisation and starting therapy and one patient was found ineligible after randomisation, leaving 367 patients in the ITT population. Screening data was found to be unreliable therefore unable to present in the patient disposition figure.

3 Assessment of Data Quality

Table 3-1 Protocol Treatment & Trial Dropouts

		R-FC Combined (N=185)	
Reason	**R-CVP (N=184)**	**R-FC Full (N=53)**	**R-FC Lite (N=132)**
End of induction treatment reasons, n (%)			
Death	2 (1%)	0 (0%)	0 (0%)
Disease progression	3 (2%)	1 (2%)	2 (2%)
Inadequate response to induction	7 (4%)	1 (2%)	1 (1%)
Toxicity	5 (3%)	7 (13%)	7 (5%)
Other (free text)	6 (3%)	2 (4%)	8 (6%)
Completed induction	155 (84%)	39 (74%)	103 (78%)
Did not start any induction treatment	0 (0%)	1 (2%)	2 (2%)
Unknown if completed induction (missing end of treatment CRF)	6 (3%)	2 (4%)	9 (7%)
***Days from recruitment to early discontinuation of induction treatment:**			
Median	90	72	112.5
IQR	37, 106	65, 82	86, 191
Range	9, 138	28, 118	12, 279
Ended trial reasons, n (%)			
Consent withdrawn	5 (3%)	3 (6%)	8 (6%)
Death	33 (18%)	19 (36%)	20 (15%)
Other (free text)	39 (21%)	12 (23%)	26 (20%)
Unknown end of trial reason (missing end of trial CRF)	107 (58%)	19 (36%)	78 (59%)
****Days from recruitment to end of trial:**			
Median	1514	1321.5	1125
IQR	599, 2285	643, 2618	524, 2257
Range	24, 3661	36, 3646	12, 2942

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\07 - Dropouts.sas

*Calculated using patients with an end of treatment CRF with reasons as death, disease progression, inadequate response to induction, toxicity or other (free text).

**Calculated using patients with an end of trial CRF with reasons as consent withdrawn, death or other (free text).

Table 3-2 Other Free Text Reasons for Induction Treatment Discontinuation

Arm	Other Reasons (Free Text)
R-CVP	Baseline bone marrow showed high grade lymphoma
	Disease Progression
	Patient's choice alongside clinician due to recent SAE and patient's 'struggling' with toxicities - according to clinic annotation
	Severe reaction to rituximab
	Suboptimal Clinical Response
	clinical decision
R-FC Full	Liver had failed to respond to R-FC, unlike other lymph nodes. Liver biopsy showed liver adenocarcinoma of unknown primary probaby present @ time of registration, although it was thought to be follicular lymphoma. Liver biopsy was sent with SAE.
	Polyneuropathy - reported as an SAE
R-FC Lite	Bowel perforation
	Patient transromed to Diffuse Large B Cell Lymphoma
	Platelets after Cycle 4 were <75 10g/l maintenance did not start
	Primary Lung cancer
	SAEs
	Toxicity and CI confirmed
	Transformed disease to DLBCL
	pt underwent CABG x 3

Table 3-3 Other Free Text Reasons for Ending Trial

Arm	Other Reasons (Free Text)
R-CVP	1.Consultants decision patient not fit for maintenance treatment
	Bone Marrow Shows high grade lymphoma
	CLOSE OUT OF STUDY
	CLOSE OUT OF STUDY
	Close out of study
	Close out of study
	Close out of study
	Close out of study
	Closure of study by trial centre
	Disease Progression
	End of study
	End of study
	Investigator decision - patient too unwell
	Lost to follow up
	Lost to follow up
	Lost to follow up
	Lost to follow up
	Lost to follow up
	Mobility issues
	Not responding
	Pt declined to come to any further appointments. Frail and some dementia. Contacted GP practice who have not seen him for 2 years. They contacted his son who has confirmed his condition is poor and had a recent fall. GP will visit at home.
	Second primary malignanacy - needing treatment
	See below
	Sematic dementia
	Study Closure
	Study Closure
	Study Closure
	Subjected diagnosed with Alzheimers and metastatic adenocarcinoma of unknown origin. Currently residing in a care home.
	Trigger reached for LPLV
	Trigger reached for LPLV
	Trigger reached fro LPLV
	clinical decision
	closure of study by trials centre

Arm	Other Reasons (Free Text)
	closure of study by trials centre
	closure of study by trials centre
	disease progression
	end of study
	end of study
	worsening dementia
R-FC Full	Cord Compression at C6
	Disease Progression
	Interstital lung disease
	Lost to follow up
	Lost to follow up
	Pacifico trial has now reached trigger for last patients
	Pacifico trial has now reached trigger fro last patient
	Patient has developed a second malignancy (see below) Clinician decision + patient decision to take off trial
	Study Closure
	close out of study
	end of study
	end of study
R-FC Lite	Bone marrow subsequently reported as transformed disease with infiltrated difuse large B cell lymphona already received 1st cycle of R-FC on trial, therefore taken off trial to commence R-CHOP.
	CLOSE OUT OF STUDY
	CLOSE OUT OF STUDY
	Clinical decision patient not well
	Close out of study
	Close out of study
	Close out of study
	Closure of study by trials centre
	Consultant Decision & decision agreement
	Deteriorating ECOG following aspiration pneumonia and fractured humerous. No evidence of relapse of Lymphoma.
	End of Pacifico trial
	End of Study
	Pacifico trial has now reached trigger pint for last patient
	Patient is now being treated for Colon cancer and does not feel she can continue with trial follow up too.
	Patient moved for treatment so not being seen now
	Patient relocated

Arm	Other Reasons (Free Text)
	Patient too unwell to attend clinic significant deterioration in general health discharged from clinic F/U
	Relapse
	Study Closure
	Study Closure
	Study Closure
	Study closure
	closure of study by trials centre
	end of study
	end of study
	transferred all care

Table 3-4 Summary of Deviations

Type	Category & Description of Deviation	Total No.
Major	3: Major: Administration of wrong treatment or incorrect dose etc	28
	5: Major: Major protocol deviation in patient management and/or assessment	21
	1: Major: Violation of entry criteria	17
	6: Major: Other major protocol deviation	4
	13: Major: Patient Management/Assessment - Blood Results	2
	17: Major: Patient Management/Assessment - Patient examination/Test	2
	12: Major: Other - IMP Issue	1
	16: Major: Patient Management/Assessment - Visit Timepoint	1
	4: Major: administration of an excluded concomitant medication	1
Minor	7: Minor: Protocol Deviations not expected to have an impact on defined endpoints of the trial	3997
Other	33: COVID-19 Patient Safety/Feasibility	8

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\08 - Protocol Deviations.sas

Table 3-5 Details of Major Deviations by Site

Site	Date	Deviation Details
Aberdeen Royal Infirmary	01/20/2011	Patient experienced grade 3/4 infection between induction cycles 6 and 7. Per protocol, subsequent chemotherapy should be given at 50% dose following such an event, however site continued on giving patient 100% dose for induction cycle 7 and 8.
Basingstoke and North Hampshire Hospital	01/19/2011	Bone marrow biopsy not performed at post cycle 4 assessment.
Blackpool Victoria Hospital	09/10/2012	Cycle 7 - Phosphate, GGT and ALT blood tests were not requested at this visit therefore results are not available.
Castle Hill Hospital (Cottingham)	02/16/2015	Patient dose reduced by 25% at cycle 2 due to a delay in treatment due to haematological toxicity. Patient subsequently administered cycle 3 at full dose. Deviation occurred due to medical and pharmacy staff error. Deviation discovered at cycle 4 when decided to delay treatment and subsequent dose reduction required, it was identified that this patient had already been dose reduced but cycle 3 subsequently given at full dose. Site staff indicated patient had not encountered significant additional problems as a result of the deviation outside of their neutrophil and platelet counts failing to recover to treatment levels for cycle 4.
Conquest Hospital	06/18/2013	The site Pharmacist asks if they can give the patient Allopurinol 300mg OD continuously (i.e. 21 days for R-CVP pts and 28 days for R-FC pts) for cycles 1 & 2 as per local practice. The protocol states “Allopurinol 300mg OD on day 1 to 7 of cycles 1 & 2 only” The CI confirmed via email on 18/06/2013 that this is acceptable.
Countess of Chester Hospital	06/18/2015	Patient JR administered R-FC treatment at cycle 5. PACIFICO trial regimen is R-FC at cycle 1-4 with Rituximab only at cycle 5-8. Error noted at administration of Cycle 6. Rituximab only given at cycle 6 onwards.
Derriford Hospital (Plymouth)	10/14/2013	A bone marrow biopsy was not taken at Post Maintenance. Queried with site and they confirmed 'A bone marrow biopsy was not taken post maintenance as it was not involved at baseline'.
Derriford Hospital (Plymouth)	06/11/2018	12 month follow up - MCQ-30, HADS and B-IPQ questionnaires were not completed at this visit.
Derriford Hospital (Plymouth)	09/03/2018	12 month follow up - Visit conducted 3 months 20 days after last instead of 4 months
Diana Princess of Wales Hospital	10/29/2015	Research site informed LCTU that patient had been diagnosed with secondary malignancy of Hodgkins lymphoma. progression assessment would not therefore be possible.
Frenchay Hospital (Bristol)	08/18/2011	Treatment cycles 5, 6, 7 and 8 - Patient experienced haematological toxicity in Cycle 5 but no G-CSF given at this cycle or any of the following treatment cycles. 'Clinician decision not to give G-CSF' is stated as the the reason for exclusion of medication at Cycle 7 and 8.
Guy's & St Thomas' Hospital (London)	11/05/2010	Patient had impaired renal function at baseline (44ml/min), however fludarabine and cyclophosphamide doses not adjusted to 50% and 75% of full dose respectively for cycle 1.
Huddersfield Royal Infirmary	08/12/2013	Baseline - UP & Go not completed
Kent Oncology Centre (Maidstone)	12/05/2012	Cycle 5 and 6 - Patient experienced haematological toxicity at cycle 2 however cyclophosphamide dose was not adjusted at this visit although blood counts were in normal parameters.

Site	Date	Deviation Details
Kent Oncology Centre (Maidstone)	12/24/2012	Cycle 6 - 80mg of prednisolone was given at this visit rather than 85mg as per protocol.
Kent Oncology Centre (Maidstone)	10/23/2017	32 month follow up - Blood tests were not taken within 14 days of visit as per protocol.
Kent and Canterbury Hospital	.	Treatment cycle 2 - Rituximab given IV instead of Subcut as per protocol
Kent and Canterbury Hospital	05/27/2013	Screening CT scan did not involve neck as per inclusion criteria.
Kent and Canterbury Hospital	03/30/2015	2 Vials of Subcut Rituximab dispensed from Mabcute trial stock instead of PACIFICO labelled and administered to PACIFICO patients. Rituximab for Mabcute trial is the same preparation as used on the PACIFICO trial and is supplied directly from Roche. Research site informed LCTU that dispensing error was due to human error in selecting stock for preparation.
King's College Hospital (London)	.	Site did not have any Rituximab for the PACIFICO trial on site so had to treat a patient with their own site stock
Leighton Hospital (Crewe)	09/09/2013	Patient DAL 222 000 0174 completed Treatment Cycle 8 on 01/07/13 on trial therapy.When he started Maintenance Cycle 1 on 09/09/13 his treatment was issued on a non-trial prescription and continued on a non-trial prescription until he completed Maintenance Cycle 12 on 06/07/15.He was originally prescribed Rituximab IV but was transferred to subcutaneous at Cycle 9 on 12/01/2015 in error by the research site.
Luton & Dunstable Hospital	07/08/2011	Patient had involved bone marrow at baseline, however bone marrow biopsy not performed at post cycle 4 assessment. As patient had no measurable lymph nodes post cycle 4, it was thus impossible to confirm if response was CR or PR.
Mount Vernon Hospital (Northwood)	07/07/2010	Per sum square of largest lymph nodes in post-cycle 4 assessment, response should have been assessed as stable disease, and patient should have gone off study treatment. Site initially assessed response this as PR and patient continued on to receive cycle 5 of treatment. Later, site realised their error, and that patient should not have received further study treatment after induction cycle 4.
Mount Vernon Hospital (Northwood)	05/27/2015	Research site contacted LCTU indicating that the patient had rituximab maintenence treatment stopped in September 2014 as it was suspected that she had Shingles. Unfortunately due to this being a suspected diagnosis the patient did not have a CT scan after 2 months in accordance with the protocol at post maintenance. First follow up visit also missed
Princess Royal Hospital (Bromley)	04/05/2013	CT scan and BM biopsy a few days out the 42 day window (Bone marrow – four days out, CT Scan – eight days out). CI allowed patient to enter study.
Queen Elizabeth Hospital (King's Lynn)	03/07/2014	It came to light that when patient attended for RCVP cycle 2 treatment on Friday 7th March 2014 they received chemo drugs before SC Rituximab not after as per protocol. The chemo team were made aware that week about patient having first SC Rituximab treatment and had been given p34/35 of protocol highlighting the details of administration. At that time they were asked if any further information was required. On the day of treatment the chemo nurse asked to see the SC training video again, a member of the site trials team gave a re-run of the video to the nurse. The chemo nurse sort further advice from pharmacy and was then told to treat as per local policy (hence the administration of the chemo drugs first). The patient did have a drop in blood pressuere following treatment, but needed no intervention. Patient was seen on 12th March 2014 and had no issues or problems.

Site	Date	Deviation Details
Queen's Hospital (Romford)	01/19/2011	Patient was given treatment at induction cycles 4, 5 and 8 and maintenance cycles 1 and 3 even though neutrophil count was <1x10*9/L at these cycles.Patient was not given G-CSF at induction cycles 4-6.
Queen's Hospital (Romford)	02/10/2011	Patient had involved bone marrow at baseline. Site did not perform post cycle 4 bone marrow biopsy as they believe it is "not standard practice in the middle of treatment". Per CT scan results patient had a potential CR, but this could not be confirmed because it was unknown if bone marrow was involved.
Queen's Hospital (Romford)	05/16/2011	Patient had baseline eFGR of 60ml/min, and was randomised to R-FC arm. However, flurarabine dose not attenuated by 75% as required by study protocol.
Queen's Hospital (Romford)	05/16/2011	Treatment Cycle 1 - Fludarabine not given as per protocol in error.
Queen's Hospital (Romford)	05/18/2011	Treatment Cycles 6, 7 & 8 - Platelet count was less than 75 on all three occasions. Treatment was not given in line with the protocol.
Queen's Hospital (Romford)	06/06/2011	Treatment Cycle 2 - Treatment not given as per protocol in error.
Queen's Hospital (Romford)	07/18/2011	Treatment Cycle 4 - Dose of Fludarabine provided on CRF was not given as per protocol in error.
Queen's Hospital (Romford)	08/08/2011	Treatment Cycle 5 - Fludarabine not given at cycle 5 in error.
Queen's Hospital (Romford)	08/09/2011	Maintenance cycle 2 - Patient was given maintenance treatment even though platelet count was <75 x 10*9/L. Treatment was not delayed until platelet count increased as stated in protocol.
Queen's Hospital (Romford)	08/30/2011	Treatment Cycles 6, 7 & 8 - 800mg dose of Rituximab given to patient in error. Dose much higher than expected.
Queen's Hospital (Romford)	09/19/2011	At Treatment Cycle 5, treatment was given to the patient even though their neutrophil count was 0.6 x 10^9/L and their platelet count was 32 x 10^9/L. The bone marrow was not involved at Baseline and there is no record of hypersplenism. Site was queried as to why treatment was given and their response was 'Clinician's decision to give chemotherapy'.
Queen's Hospital (Romford)	12/01/2011	Maintenance Cycle 1 - Gamma GT and Serum IgA bloods not doen in error.
Queen's Hospital (Romford)	03/23/2012	Maintenance Cycle 3 - Rituximab dose of 800mg was higher than expected. Queried with site. Site responded that Rituximab had not been prescribed in line with the protocol.
Queen's Hospital (Romford)	12/19/2013	Post maintenance visit - Bone marrow biopsy not done. Queried with site. Site responded that bone marrow was not involved at diagnosis. Misunderstanding of when bone marrow biopsy can be omitted.
Royal Cornwall Hospital (Truro)	04/01/2010	The following concomitant medications were not administered with induction cycle 3 for this patient:Paracetamol - Because of prescribing errorAllopurinol - PI did not think allopurinol was required by the patient
Royal Cornwall Hospital (Truro)	06/22/2011	Patient on maintenance treatment cycle 6 (rituximab supplied by Roche), however commercial stock was dispensed 22 June 2011. In addition to this, stock dispensed was not labelled as a clinical trial supply.Site informed LCTU of these mistakes on 27 June 2011.

Site	Date	Deviation Details
Royal Devon & Exeter Hospital	11/10/2014	Maintenance 4 1.Calcium,Phosphate,LDH and GT not done2.Microglobuli not done3.Physical Exam not doneMaintenance 5 - Physical Exam not doneMaintenacne 61.Serum tests not done2.Protein,Phosphate and GT not done3.QOL not doneMaintenance 8 - Phosphate not donePost Maintenance1.IgG,IgA and IgM not done2.Total Protein not done
Royal Free Hospital (London)	11/05/2013	Maintenance Cycles 4 & 5 - Total protein not tested in error.
Royal Liverpool University Hospital	.	Patient is on the RFC lite arm, did not take any of his Fludarabine and Cyclophosphamide for cycle 3. (date of deviation - awaiting CRFs)
Royal Liverpool University Hospital	04/29/2010	Maintenace cycle 1 rituximab administered 650mg, should have been rounded to 700mg (nearest '00mg) per study protocol.Patient had received rituximab dose of 650mg during induction, no deviation raised as induction treatment began when protocol v2 was current - rounding rituximab to nearest '00mg not included to v3.As patient had received rituximab dose of 650mg during induction, site PI (Chief Investigator Andrew Pettitt) thougt it clinically reasonable to maintain this dose through maintenance (unless patient has a dramatic change in weight).
Royal Marsden Hospital (Sutton)	.	Screening - CT Scan of left axillary node: no measurement on CT scan for this node.
Royal Marsden Hospital (Sutton)	.	Screening CT scan. No measurement on CT scan for Retrocrural and 2 'other' nodes given.
Royal Marsden Hospital (Sutton)	03/21/2012	Treatment cycle 1 - Billirubin upper limit for this site was 17umol/L and patient was 18umol/L therefore vincristine should have been halved - Site error
Royal Sussex County Hospital (Brighton)	02/04/2015	Aseptic department at research site reconstituted SC Rituximab from regular hospital stock. This was subsequently administered to patient at cycle 3 of Induction therapy. Batch number of Rituximab vial: B0009, expiry 11/2015.
Royal Victoria Infirmary (Newcastle)	01/29/2014	Post Maintenance Assessment - No Bone Marrow taken - reason given by site - not involved at Baseline. Blood Samples for Biobank also not taken at this visit site could not confirm reason why they were missed.
Salisbury District Hospital	02/22/2013	The potential patient had a CT scan (done at a different hospital) of her thorax, abdomen and pelvis but not neck, but she has had an MRI of her neck done. Nagesh Kalakonda confirmed this would suffice in entering the trial.
Salisbury District Hospital	01/09/2019	24 month follow up - B2-microglobulin blood test result was not reported at this visit.
Sandwell Hospital (Birmingham)	05/28/2013	Site wants to discontinue induction therapy at cycle 6 and not perform cycles 7 and 8. The site wants the patient to move straight to maintenance therapy as the post cycle 4 tumour assessment showed a CR. Email received from site on 23/05/13:"The CT scan was done 08/04/13 (2 weeks post cycle 4 RCVP) as per protocol. He was in CR at this point and received a further 2 course of RVCP. The PI would not like to proceed with a further 2 cycles (as per protocol) but we would like to know whether the patient can continue on study. He is starting Rituximab maintenance next month." Chief Investigator advised in response dated 28/05/13: "So in fact the patient achieved a CR after 4 cycles and a further 2 cycles were given. The patient can remain in the study but it should be recorded as a protocol deviation."
Sandwell Hospital (Birmingham)	02/20/2014	baseline - Coombs test omitted in errorCycle 2 - treatment date one day late due to errorMaintenance 4 - physical exam not done due to research nurse being absentMaintenance 4 - QOL not given to patient in errorMaintenance 5 - B2 micro globin omitted in error Maintenance 5 - GGT test omitted in errormaintenance 6 - cycle 6 was omitted in error

Site	Date	Deviation Details
Southampton General Hospital	.	Site unable to provide the compulsory biopsy samples to confirm follicular lymphoma for the above patients. Please find attached supporting emails and a file note from site
Southampton General Hospital	08/16/2010	Patient was given study treatment when neutrophil count <1.0x10^9/L. Induction Cycle 3.
Southampton General Hospital	03/02/2011	Cycle 2 full blood count taken 28-Feb-2011 - neutrophil count 0.9x10^9/L.
Southend Hospital (Westcliff-on-Sea)	06/25/2013	For Treatment Cycle 5, patient was mistakenly given RFC instead of just Rituximab - 25th, 26th & 27th 200 MG per day of Cyclophosphamide and 40 Mg per day of Fludarabine.
St. James's University Hospital (Leeds)	12/18/2014	Maintenance cycle 7 - Total protein and GGT blood tests were missed in error.
St. Mary's Hospital (London)	10/18/2011	Cycle 2 - Cyclophosphamide dose was not reduced to two thirds of the full dose after treatment had been delayed for 1 week due to toxicity. PI decided patient would have treatment even though platelet count was 35x10*9/L. Protocol states treatment should be delayed if platelets are <75x10*9/L and should not be given until this resolves.
St. Mary's Hospital (London)	11/07/2011	Cycle 3 - Patient was not given G-CSF although the patient experienced haematological toxicity at an earlier cycle. Cyclophosphamide dose was not reduced to two thirds of the full dose after treatment had been delayed due to toxicity.
St. Mary's Hospital (London)	11/30/2011	Cycle 4 - Cyclophosphamide dose was not reduced to two thirds of the full dose after treatment had been delayed due to toxicity.
St. Mary's Hospital (London)	12/21/2011	Cycle 5 - Cyclophosphamide dose was not reduced to two thirds of the full dose after treatment had previously been delayed due to toxicity.
St. Mary's Hospital (London)	01/11/2012	Patient was not given G-CSF although the patient experienced neutropenia at an earlier cycle.
St. Mary's Hospital (London)	02/01/2012	Cycle 7 - Patient was not given G-CSF although the patient experienced neutropenia at an earlier cycle.
St. Mary's Hospital (London)	02/22/2012	Cycle 8 - Cyclophosphamide dose was not reduced to two thirds of the full dose after treatment had previously been delayed due to toxicity.
St. Richard's Hospital (Chichester)	01/31/2011	Patient randomised to R-FC, and received induction cycles 1-4 before going off study treatment. When drug accountability logs requested, pharmacist contacted LCTU and stated that they had not been completed. Batch numbers for rituximab dispensed are in storage, and are not available for fludarabine and cyclophosphamide.
Torbay District General Hospital (Torquay)	04/16/2013	Neck CT scan was incomplete however this would not affect the FLIPI. This was checked with the CI who confirmed that we should randomise but the site are to complete a full CT scan at the next assessment, physical exam showed no abnormality in the neck.
University Hospital Aintree	07/30/2010	Patient was given 100mg IV hydrocortisone on day 1 of induction cycle 2, instead of 55mg oral prednisolone (R-CVP arm)
Velindre Hospital (Cardiff)	11/17/2014	Maintenance cycle 2 - Neutrophil count was 0.90x10*9/L on 19/11/2014 however rituximab was administered on 19/11/2014 even though protocol states treatment should be delayed until neutrophil count has recovered.

Site	Date	Deviation Details
York District Hospital	.	At the site close out visit, the trial monitor noticed that following review of the supporting medications given for chemotherapy detailed on the chemo chart during Cycles 6 and 7 that the administration of co-trimoxazole could not be verified from the source material. The site has confirmed that there is no evidence that Co-trimoxazole (Septrin) was actually administered to the patient for this point of treatment. The site has stated in all likelihood it would have been administered as is standard practice and that there is no patient safety issue. Therefore a filenote is to be placed in the CRF file documenting it is standard practice to administer Co-trimoxazole as a supportive medication however due to a nurse not documenting so on the chemo care chart this cannot be proven to be administered during Cycle 6 but in all likelihood it would have been administered and that there are no safety issues.
York District Hospital	09/07/2010	The site has confirmed that no monoclonal paraprotein testing had been conducted at baseline.
York District Hospital	12/01/2010	Patient had involved bone marrow at baseline. Bone marrow biopsy not repeated at post cycle 4 assessment as patient refused it. As a result it was impossible to determine whether patient had CR or PR (per CT scan patient had met criteria for CR).
York District Hospital	12/30/2010	It cannot be proven that Co-trimoxazole was administered during R-FC Cycle 6.
Ysbyty Gwynedd (Bangor)	06/15/2014	Post Cycle 4 not completed
Ysbyty Gwynedd (Bangor)	03/30/2016	Patient 349-2-0-0367 was dispensed his day 2 (30/03/16) dose of cyclophosphamide (200mg) at 7am, prescription was not signed by the relevant nursing staff. Evening nursing staff noted that the cyclophosphamide was not signed for by the early nursing staff and then dispensed a dose of cyclophosphamide (200mg) at 7pm. The drug dispensing error was noted on the 31/3/16 medical and pharmacy team informed.Currently no effect on the patient noted. Chemotherapy advice and contact numbers given as per standard practice to patient.Advised by the pharmacist to omit day 3 cyclophosphamide and then continue as per regime on day 4.

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\08 - Protocol Deviations.sas

Note: Deviation details may contain spelling errors due to data entered as free text.

4 Baseline Characteristics

Table 4-1 Baseline Characteristics

			R-FC Combined (N=185)	
		R-CVP (N=184)	**R-FC Full (N=53)**	**R-FC Lite (N=132)**
Demographic Characteristics				
Age (years)	Median (IQR)	75.0 (72.0,81.0)	75.0 (73.0,79.0)	76.5 (72.0,80.0)
	Mean (SD)	76.2 (6.6)	75.5 (5.5)	76.1 (6.1)
	Range	52, 93	58, 88	60, 95
Gender, n (%)	Female	100 (54%)	28 (53%)	73 (55%)
	Male	84 (46%)	25 (47%)	59 (45%)
Physical Findings				
WHO Performance Status, n (%)	0	93 (51%)	34 (64%)	48 (36%)
	1	77 (42%)	18 (34%)	76 (58%)
	2	14 (8%)	1 (2%)	8 (6%)
FLIPI Score, n (%)	High	117 (64%)	36 (68%)	84 (64%)
	Intermediate	48 (26%)	13 (25%)	36 (27%)
	Low	19 (10%)	4 (8%)	12 (9%)
Creatinine	Median (IQR)	80.0 (71.0,95.5)	80.0 (71.0,95.0)	81.0 (68.5,97.5)
	Mean (SD)	84.9 (20.3)	80.6 (14.9)	86.9 (24.7)
	Range	51, 167	47, 108	48, 175
Cumulative Illness Rating Score, n (%)	>6	35 (19%)	9 (17%)	26 (20%)
	≤6	149 (81%)	44 (83%)	106 (80%)
Histology Grade, n (%)	1	53 (29%)	14 (26%)	40 (30%)
	2	83 (45%)	26 (49%)	61 (46%)
	3a	40 (22%)	12 (23%)	26 (20%)
	Missing	8 (4%)	1 (2%)	5 (4%)

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5 Exposure to Treatment and Compliance

Table 5-1 Details of Number of Cycles Delivered

			R-FC Combined (N=185)	
Variable	**Cycle/Statistic**	**R-CVP (N=184)**	**R-FC Full (N=53)**	**R-FC Lite (N=132)**
No. patients (induction cycles)	Cycle 1	184	52	130
	Cycle 2	180	52	129
	Cycle 3	176	50	126
	Cycle 4	175	49	118
	Cycle 5	170	40	110
	Cycle 6	164	39	106
	Cycle 7	156	39	103
	Cycle 8	152	39	100
No. induction cycles	Median (Min, Max)	8.0 (1.0,8.0)	8.0 (2.0,8.0)	8.0 (1.0,8.0)
	Mean (SD)	7.4 (1.6)	6.9 (1.9)	7.1 (1.8)
No. overall (induction & maintenance) cycles	Median (Min, Max)	20.0 (1.0,20.0)	17.5 (2.0,20.0)	18.0 (1.0,20.0)
	Mean (SD)	16.4 (5.7)	14.5 (6.5)	14.9 (6.1)

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Table 5-2 Patients Receiving Concomitant Medication During Treatment

		R-FC Combined (N=185)	
No. patients receiving at least one of the following:	**R-CVP (N=184)**	**R-FC Full (N=53)**	**R-FC Lite (N=132)**
Blood transfusion, n (%)	6 (3%)	7 (13%)	11 (8%)
Immunoglobulin replacement therapy, n (%)	1 (1%)	3 (6%)	7 (5%)
Growth factor support, n (%)	39 (21%)	18 (34%)	45 (34%)
Antibiotics, n (%)	117 (64%)	34 (64%)	103 (78%)

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Table 5-3 Details of Individual Treatment Dose Admistered

Arm	Drug	Route	Statistic	Cumulative Dose Received	% Planned Dose Received
R-CVP	Cyclophosphamide (Induction)	IV	n	184	183
			Mean (SD)	9749.5 (2637.5)	97.2 (7.4)
			Median (IQR)	10400.0 (8800,11520)	99.4 (97.3,101.0)
			Range	900, 14400	64, 112
	Prednisolone (Induction)	PO	n	184	183
			Mean (SD)	2617.5 (718.3)	98.0 (8.5)
			Median (IQR)	2800.0 (2400,3198)	99.2 (97.2,101.9)
			Range	250, 4000	41, 111
	Rituximab (Induction)	IV	n	122	122
			Mean (SD)	4337.2 (2044.9)	99.9 (4.0)
			Median (IQR)	5150.0 (3000,5750)	99.8 (98.0,102.7)
			Range	600, 7200	85, 112
		SC	n	86	85
			Mean (SD)	9166.4 (2509.1)	100.1 (1.6)
			Median (IQR)	10400.0 (9100,10500)	100.0 (99.8,100.1)
			Range	500, 10700	96, 109
	Rituximab (Maintenance)	IV	n	89	89
			Mean (SD)	7326.4 (2437.3)	104.3 (24.7)
			Median (IQR)	8350.0 (7100,8880)	99.6 (97.3,102.9)
			Range	675, 12600	87, 258
		SC	n	73	73
			Mean (SD)	14479.5 (4303.8)	99.8 (1.7)
			Median (IQR)	16800.0 (15400,16800)	100.0 (100.0,100.0)
			Range	2800, 16800	86, 100
	Vincristine (Induction)	IV	n	122	122
			Mean (SD)	11.2 (5.7)	71.0 (15.6)
			Median (IQR)	15.0 (4.5,16.0)	74.1 (66.7,80.0)
			Range	1, 16	9, 99
		SC	n	86	85
			Mean (SD)	12.5 (4.8)	70.6 (19.5)
			Median (IQR)	14.0 (9.0,16.0)	72.7 (60.3,80.0)
			Range	2, 34	23, 175
R-FC Full	Cyclophosphamide (Induction)	IV	n	3	3
			Mean (SD)	4480.0 (2711.0)	96.0 (1.2)

Arm	Drug	Route	Statistic	Cumulative Dose Received	% Planned Dose Received
			Median (IQR)	6000.0 (1350,6090)	96.0 (94.7,97.1)
			Range	1350, 6090	95, 97
		PO	n	52	52
			Mean (SD)	4980.8 (913.6)	196.1 (17.0)
			Median (IQR)	5400.0 (4500,5450)	200.2 (190.9,208.6)
			Range	2400, 6600	143, 223
	Fludarabine (Induction)	IV	n	3	3
			Mean (SD)	630.0 (340.7)	144.0 (22.3)
			Median (IQR)	780.0 (240.0,870.0)	138.7 (124.8,168.4)
			Range	240, 870	125, 168
		PO	n	52	52
			Mean (SD)	749.2 (174.8)	140.9 (20.7)
			Median (IQR)	765.0 (615.0,845.0)	146.3 (127.6,154.9)
			Range	330, 1080	69, 168
	Rituximab (Induction)	IV	n	52	52
			Mean (SD)	4796.2 (1372.2)	100.2 (3.9)
			Median (IQR)	5200.0 (4100,5725)	100.4 (98.0,102.3)
			Range	1300, 6400	90, 110
	Rituximab (Maintenance)	IV	n	40	40
			Mean (SD)	6720.9 (2223.3)	99.6 (3.7)
			Median (IQR)	7200.0 (5250,8400)	99.5 (97.6,102.0)
			Range	1680, 9600	90, 107
R-FC Lite	Cyclophosphamide (Induction)	IV	n	2	2
			Mean (SD)	1600.0 (1131.4)	101.0 (17.5)
			Median (IQR)	1600.0 (800.0,2400)	101.0 (88.7,113.4)
			Range	800, 2400	89, 113
		PO	n	130	130
			Mean (SD)	2621.2 (763.8)	94.1 (11.8)
			Median (IQR)	2600.0 (2400,3200)	96.0 (88.3,101.5)
			Range	800, 4000	50, 114
	Fludarabine (Induction)	IV	n	2	2
			Mean (SD)	320.0 (226.3)	96.9 (16.7)
			Median (IQR)	320.0 (160.0,480.0)	96.9 (85.1,108.7)
			Range	160, 480	85, 109
		PO	n	130	130
			Mean (SD)	530.9 (160.6)	91.4 (12.4)

Arm	Drug	Route	Statistic	Cumulative Dose Received	% Planned Dose Received
			Median (IQR)	560.0 (480.0,640.0)	93.0 (84.7,97.7)
			Range	160, 1160	48, 131
	Rituximab (Induction)	IV	n	73	73
			Mean (SD)	1537.9 (1441.6)	101.0 (10.9)
			Median (IQR)	700.0 (625.0,2000)	99.6 (97.3,102.6)
			Range	500, 5250	91, 186
		SC	n	130	130
			Mean (SD)	6156.9 (3089.0)	99.5 (3.3)
			Median (IQR)	5600.0 (3850,9800)	100.0 (99.6,100.0)
			Range	600, 10600	85, 110
	Rituximab (Maintenance)	IV	n	62	61
			Mean (SD)	6381.5 (2891.4)	102.1 (19.0)
			Median (IQR)	7200.0 (4800,8400)	98.4 (95.8,101.6)
			Range	500, 12300	86, 196
		SC	n	48	48
			Mean (SD)	12950.0 (5573.9)	100.0 (0.0)
			Median (IQR)	16800.0 (8400,16800)	100.0 (100.0,100.0)
			Range	1400, 16800	100, 100

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6 Primary Outcome 1 – Progression Free Survival (PFS)

6.1 Primary Analysis (Progression Free Survival)

Table 6-1 Cox PH Model Results for Progression Free Survival

Treatment Arm	No. patients	No. events (%)	Median PFS in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	80 (43%)	2513 (2066, NA)	94% (89%, 97%)	0.80 (0.58, 1.11)	0.188
R-FC (Combined)	183	64 (35%)	3464 (3123, NA)	91% (86%, 94%)		

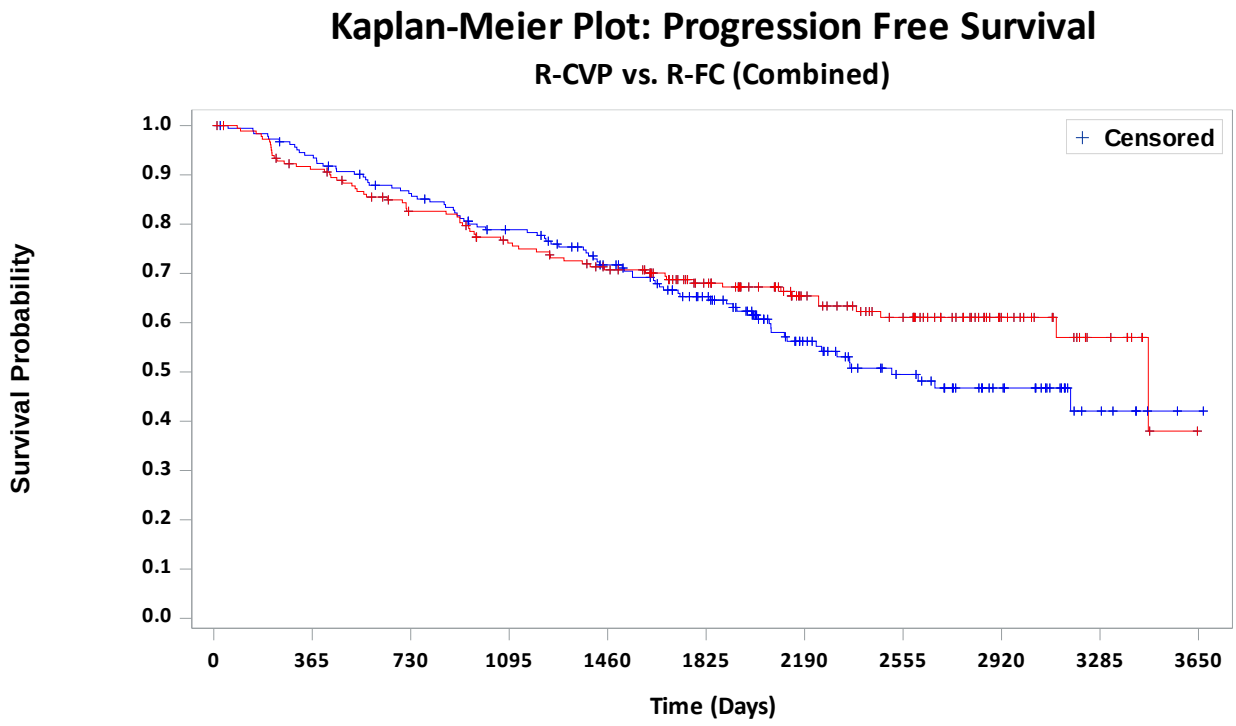
*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Table 6-2 Adjusted Cox PH Model Results for Progression Free Survival

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	80 (43%)	2513 (2066, NA)	94% (89%, 97%)	0.65 (0.40, 1.05)	0.077
R-FC (Combined)	183	64 (35%)	3464 (3123, NA)	91% (86%, 94%)		

*Stratified Cox PH model
**Stratified log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Figure 6-1 Kaplan Meier Plot: Progression Free Survival



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6.2 Further Analysis (Progression Free Survival)

Upon inspection of Schenfeld residuals and correlation against the rank of time, there was significant evidence (p=0.019) of non-proportionality of the Cox model used in Table 6-1. Therefore further analysis was performed using Restricted Mean Survival Time (RMST). The minimum of the largest observed PFS event time within each treatment arm was selected for the restricted time, therefore 3176 days was used. Table 6-3 below shows that on average, patients in the R-FC (Combined) arm survive 120 days longer than those in the R-CVP arm when patients were followed up for 3176 days, however there is not enough evidence to suggest that there is a difference in these times within this timeframe (p>0.05).

Table 6-3 Progression-Free Survival Using Restricted Mean Survival Time

Treatment Arm	No. patients	No. events (%)	RMST for PFS in days (95% CI)	RMST difference in days (95% CI)	Ratio of RMST (95% CI)	RMST p-value
R-CVP	184	80 (43%)	2214 (2052, 2377)	120 (-115, 357)	1.05 (0.95, 1.17)	0.317
R-FC (Combined)	183	64 (35%)	2335 (2163, 2507)			

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6.3 Sensitivity Analysis (Progression Free Survival)

Sensitivity analysis was not performed as per protocol set could not be reasonably defined.

6.4 Subgroup Analysis 1 – Old vs. New Cohort (Progression Free Survival)

Table 6-4 Cox PH Model Results for Progression Free Survival by Old and New Cohort

Cohort	Treatment Arm	No. patients	No. events (%)	Median PFS in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
Old Cohort	R-CVP	53	25 (47%)	3176 (2115, NA)	91% (83%, 98%)	1.03 (0.59, 1.82)	0.911
	R-FC Full	50	23 (46%)	3464 (1678, NA)	90% (81%, 98%)		
New Cohort	R-CVP	131	55 (42%)	2357 (2017, NA)	95% (92%, 99%)	0.70 (0.46, 1.05)	0.084
	R-FC Lite	130	39 (30%)	NA (NA, NA)	91% (87%, 96%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Note: 3 patients were removed from cohort analysis as they were randomised to R-FC Full in the new cohort, rather than R-FC Lite.

Figure 6-2 Kaplan Meier Plot: Progression Free Survival by Old Cohort (R-CVP vs. R-FC Full)

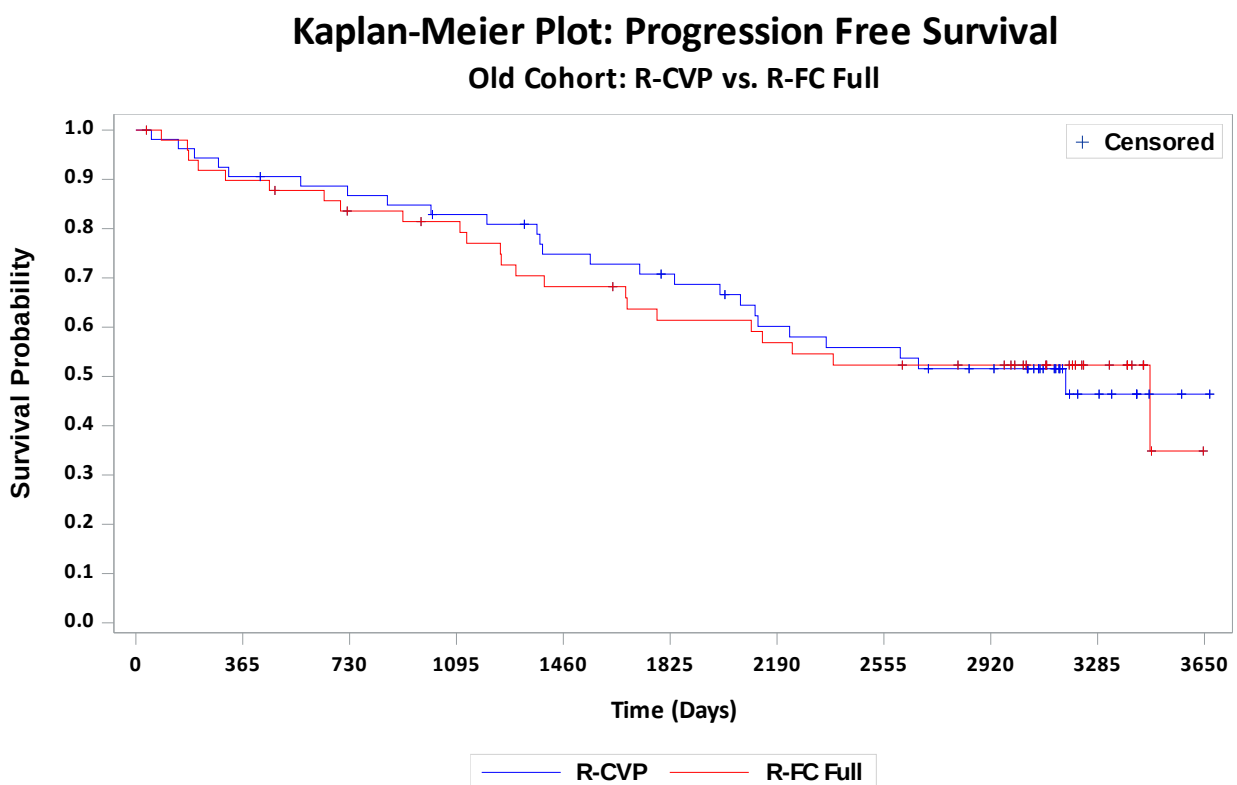

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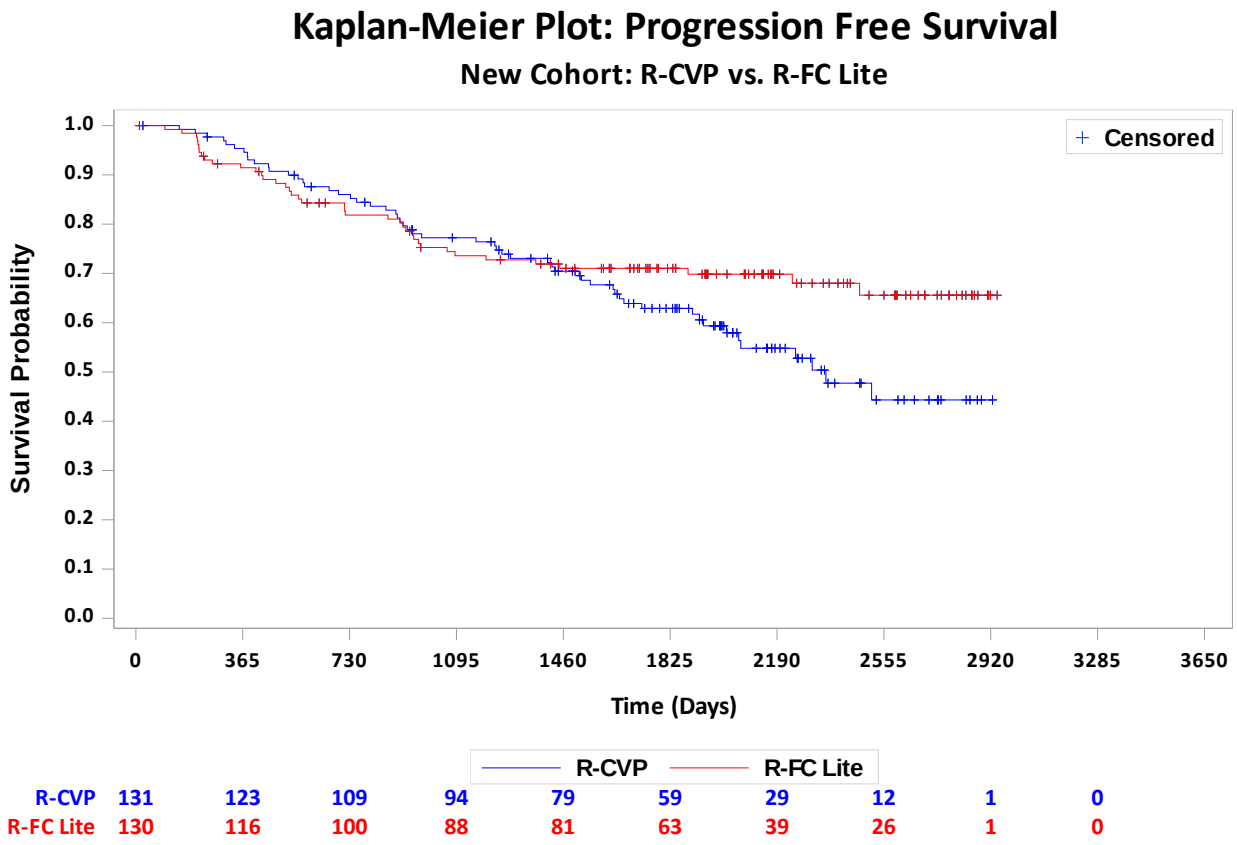
Figure 6-3 Kaplan Meier Plot: Progression Free Survival by Old Cohort (R-CVP vs. R-FC)



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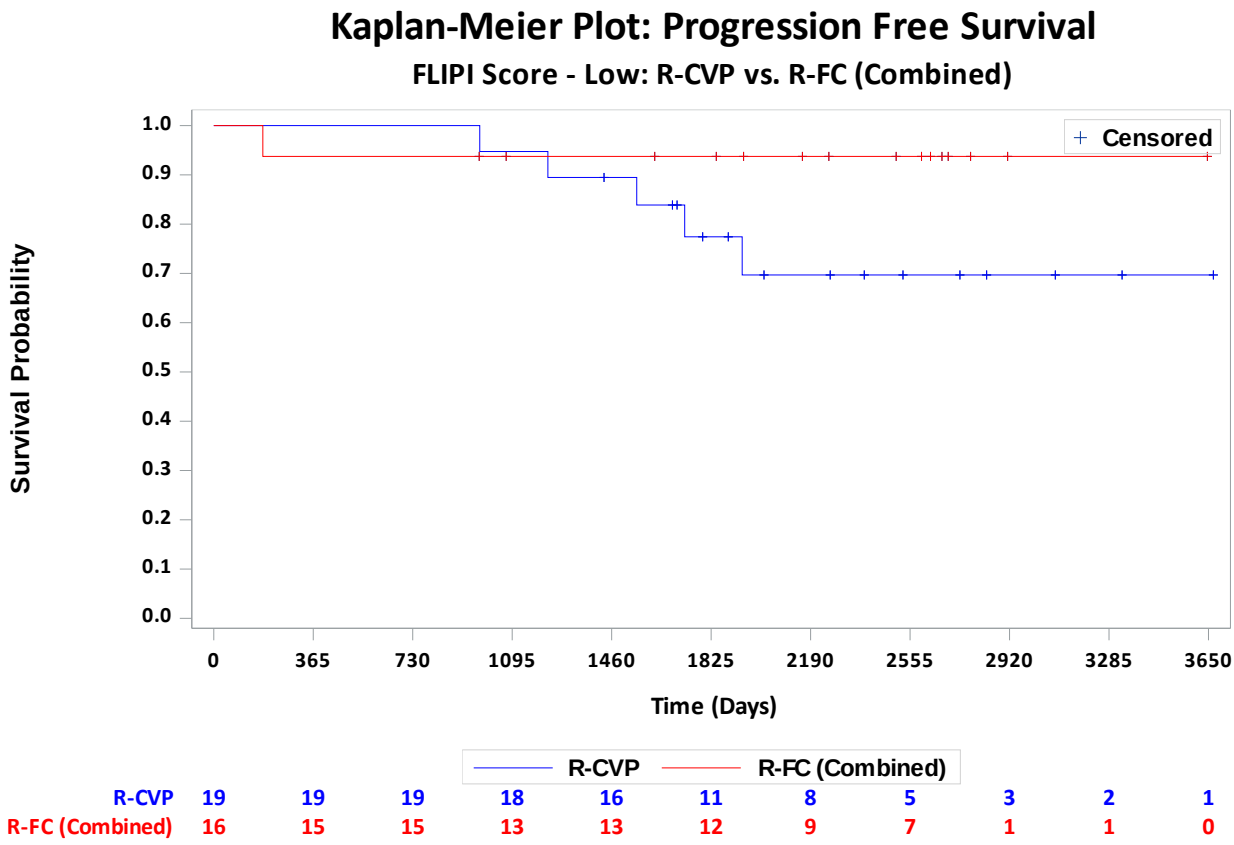
6.5 Subgroup Analysis 2 – FLIPI Score (Progression Free Survival)

Table 6-5 Cox PH Model Results for Progression Free Survival by FLIPI Score

Minimisation Factor	Treatment Arm	No. patients	No. events (%)	Median PFS in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
FLIPI Score - Low	R-CVP	19	5 (26%)	NA (1939, NA)	100% (100%, 100%)	0.23 (0.03, 2.01)	0.150
	R-FC (Combined)	16	1 (6%)	NA (NA, NA)	94% (63%, 99%)		
FLIPI Score - Intermediate	R-CVP	48	18 (38%)	3176 (2065, NA)	96% (84%, 99%)	0.71 (0.35, 1.43)	0.338
	R-FC (Combined)	48	14 (29%)	NA (2472, NA)	100% (100%, 100%)		
FLIPI Score - High	R-CVP	117	57 (49%)	2233 (1901, 2673)	92% (86%, 96%)	0.85 (0.58, 1.25)	0.413
	R-FC (Combined)	119	49 (41%)	3123 (2102, 3464)	87% (80%, 92%)		

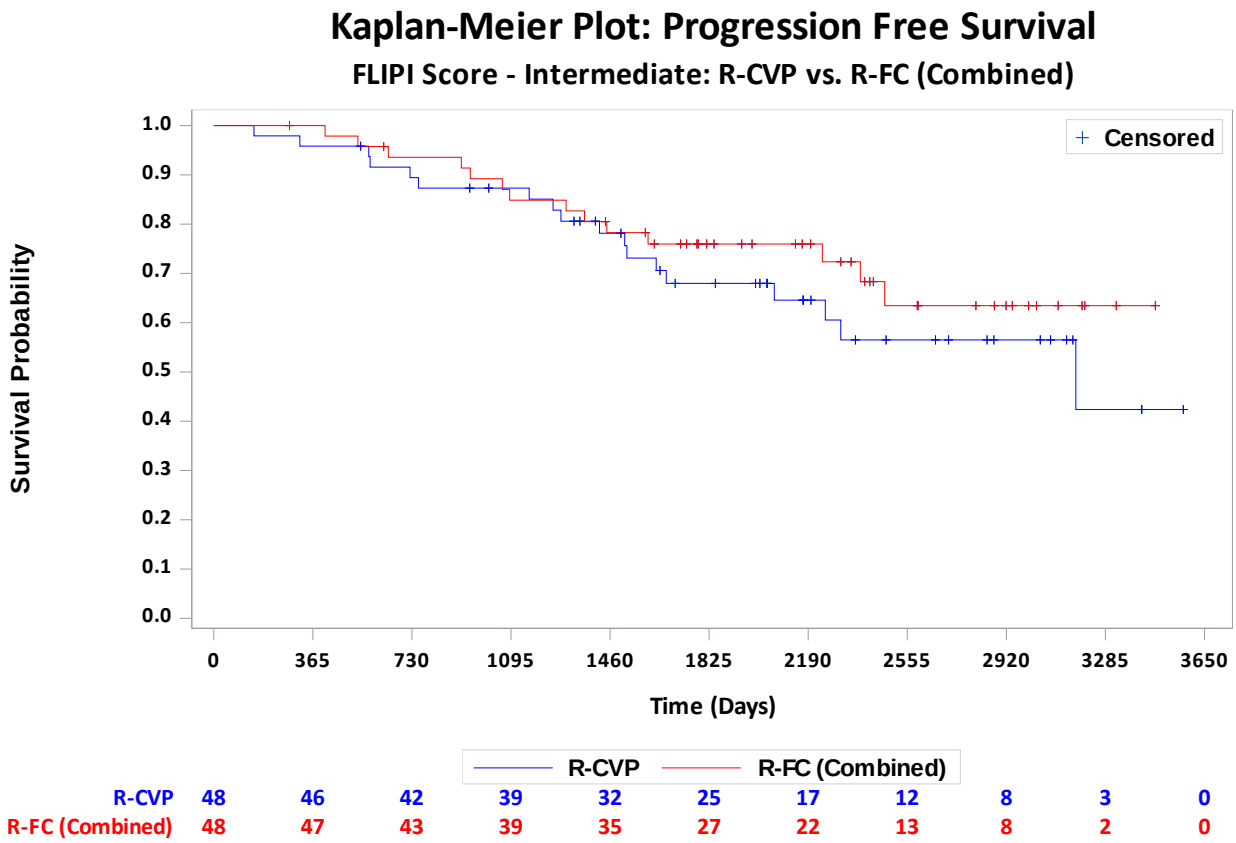
*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Figure 6-4 Kaplan Meier Plot: Progression Free Survival by FLIPI Score (Low)



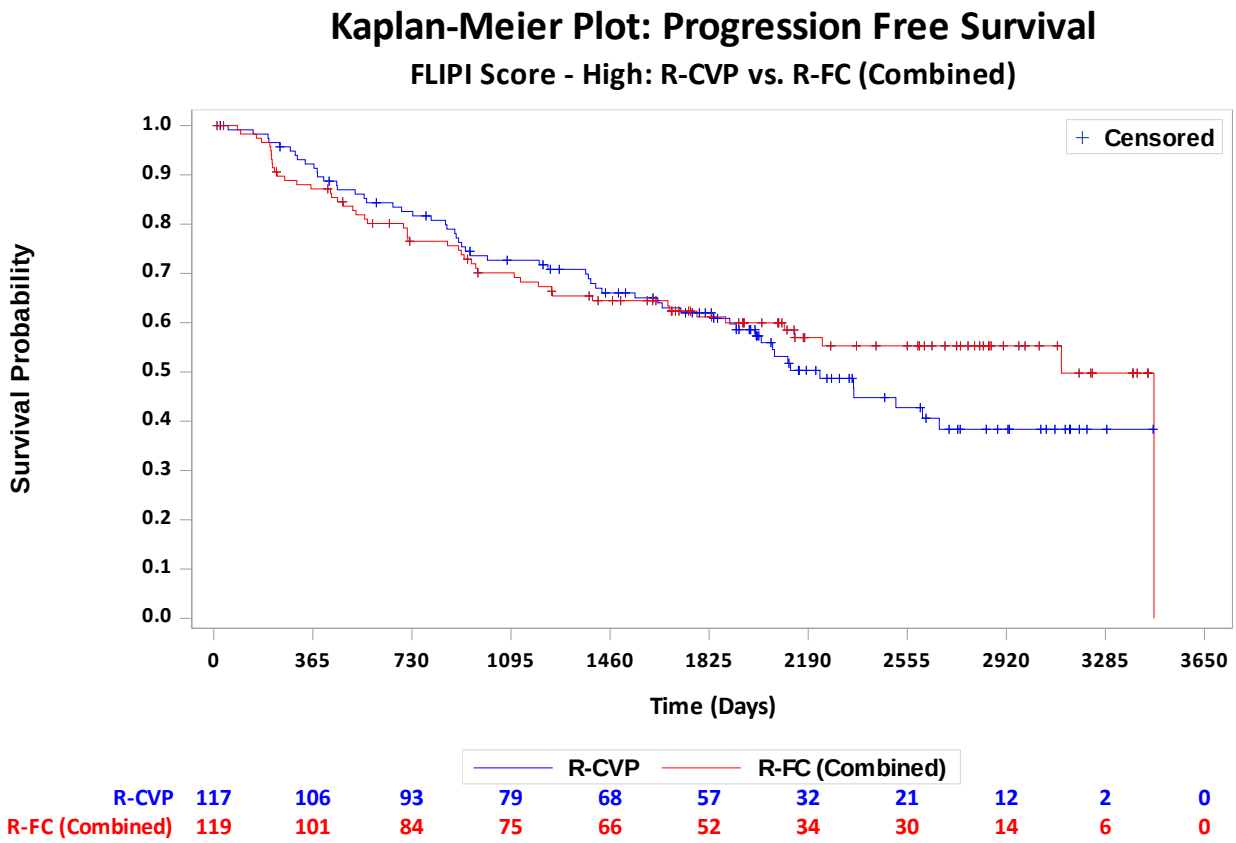
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Figure 6-5 Kaplan Meier Plot: Progression Free Survival by FLIPI Score (Intermediate)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Figure 6-6 Kaplan Meier Plot: Progression Free Survival by FLIPI Score (High)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

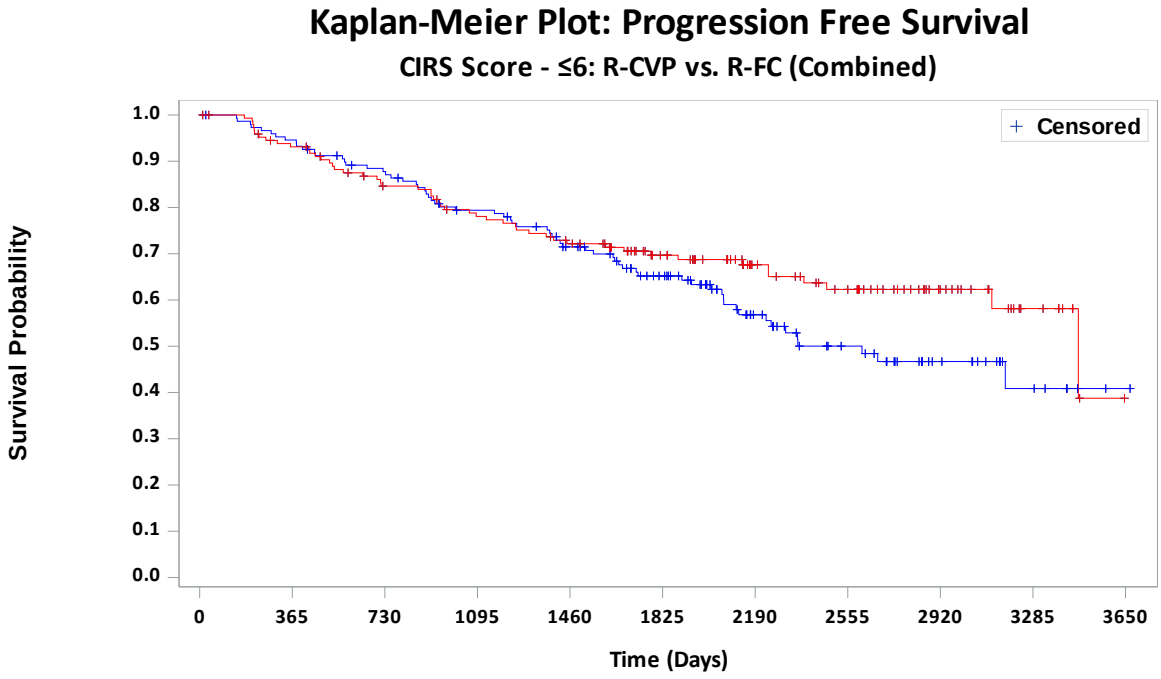
6.6 Subgroup Analysis 3 – CIRS Score (Progression Free Survival)

Table 6-6 Cox PH Model Results for Progression Free Survival by CIRS Score

Minimisation Factor	Treatment Arm	No. patients	No. events (%)	Median PFS in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
CIRS Score - ≤6	R-CVP	149	65 (44%)	2611 (2066, NA)	95% (89%, 97%)	0.76 (0.52, 1.09)	0.135
	R-FC (Combined)	148	50 (34%)	3464 (3123, NA)	93% (88%, 96%)		
CIRS Score - >6	R-CVP	35	15 (43%)	2513 (1552, NA)	91% (75%, 97%)	1.01 (0.49, 2.08)	0.988
	R-FC (Combined)	35	14 (40%)	NA (972, NA)	83% (66%, 92%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

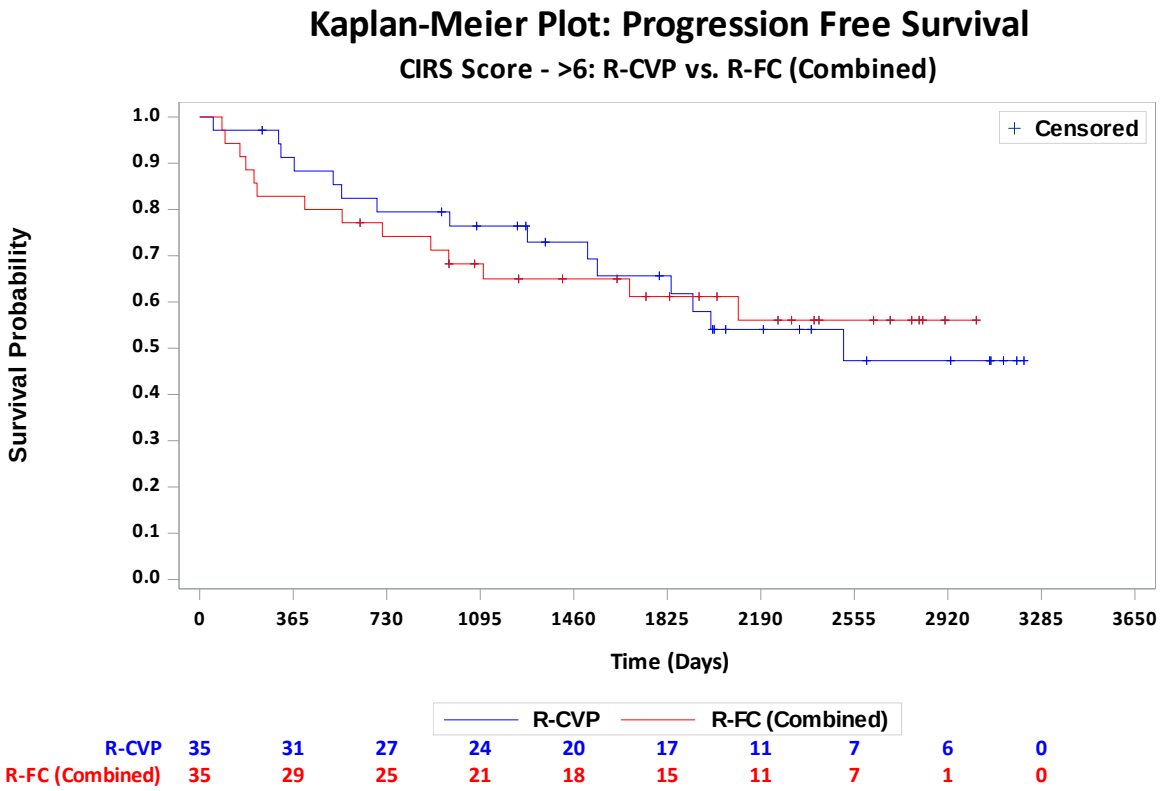
Figure 6-7 Kaplan Meier Plot: Progression Free Survival by CIRS Score (≤6)



R-CVP	149	140	127	112	96	76	46	31	17	7	1
R-FC (Combined)	148	134	117	106	96	76	54	43	22	9	0

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

Figure 6-8 Kaplan Meier Plot: Progression Free Survival by CIRS Score (>6)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\12 - Progression-Free Survival.sas

7 Primary Outcome 2 – Grade 3-4 Infections

7.1 Primary Analysis (Grade 3-4 Infections)

Table 7-1 Proportion of Grade 3-4 Infections

Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
R-CVP	184	48	0.03 (-0.06, 0.12)	1.11 (0.80, 1.55)	0.617
R-FC (Combined)	183	53			

*Chi-Square test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

Table 7-2 Grade 3-4 Infections Model Results

Comparison	Odds Ratio (95% CI)
R-CVP vs. R-FC (Combined)	1.16 (0.73, 1.83)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

7.2 Sensitivity Analysis (Grade 3-4 Infections)

Table 7-3 Model Results of Sensitivity Analyses for Grade 3-4 Infections

Sensitivity Analysis – Allowance For:	Comparison	Odds Ratio (95% CI)
Safety Set (N=366)	R-CVP vs. R-FC (Combined)	1.16 (0.74, 1.84)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

7.3 Subgroup Analysis 1 – Old vs. New Cohort (Grade 3-4 Infections)

Table 7-4 Proportion of Grade 3-4 Infections by Old and New Cohort

Cohort	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
Old Cohort	R-CVP	53	12	0.01 (-0.15, 0.18)	1.06 (0.53, 2.14)	1.000
	R-FC Full	50	12			
New Cohort	R-CVP	131	36	0.04 (-0.07, 0.15)	1.15 (0.79, 1.67)	0.560
	R-FC Lite	130	41			

*Chi-Square test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

Note: 3 patients were removed from cohort analysis as they were randomised to R-FC Full in the new cohort, rather than R-FC Lite.

Table 7-5 Grade 3-4 Infections Model Results by Old and New Cohort

Cohort	Comparison	Odds Ratio (95% CI)
Old Cohort	R-CVP vs. R-FC (Full)	1.08 (0.43, 2.69)
New Cohort	R-CVP vs. R-FC (Lite)	1.22 (0.71, 2.07)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

7.4 Subgroup Analysis 2 – FLIPI Score (Grade 3-4 Infections)

Table 7-6 Proportion of Grade 3-4 Infections by FLIPI Score

FLIPI Score	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
Low	R-CVP	19	6	-0.19 (-0.46, 0.07)	0.40 (0.09, 1.70)	0.350
	R-FC (Combined)	16	2			
Intermediate	R-CVP	48	11	0.04 (-0.13, 0.21)	1.18 (0.59, 2.37)	0.814
	R-FC (Combined)	48	13			
High	R-CVP	117	31	0.05 (-0.06, 0.17)	1.21 (0.81, 1.80)	0.438
	R-FC (Combined)	119	38			

*Chi-Square test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

Table 7-7 Grade 3-4 Infections Model Results by FLIPI Score

FLIPI Score	Treatment Arm	Odds Ratio (95% CI)
Low	R-CVP vs. R-FC (Combined)	0.31 (0.05, 1.82)
Intermediate	R-CVP vs. R-FC (Combined)	1.25 (0.49, 3.16)
High	R-CVP vs. R-FC (Combined)	1.30 (0.74, 2.29)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

7.5 Subgroup Analysis 3 – CIRS Score (Grade 3-4 Infections)

Table 7-8 Proportion of Grade 3-4 Infections by CIRS Score

CIRS Score	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
≤6	R-CVP	149	36	0.05 (-0.05, 0.15)	1.20 (0.82, 1.76)	0.411
	R-FC (Combined)	148	43			
>6	R-CVP	35	12	-0.06 (-0.27, 0.16)	0.83 (0.42, 1.67)	0.797
	R-FC (Combined)	35	10			

*Chi-Square test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

Table 7-9 Grade 3-4 Infections Model Results by CIRS Score

CIRS Score	Treatment Arm	Odds Ratio (95% CI)
≤6	R-CVP vs. R-FC (Combined)	1.29 (0.77, 2.15)
>6	R-CVP vs. R-FC (Combined)	0.77 (0.28, 2.11)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\13 - Grade 3-4 Infections.sas

8 Secondary Outcome 1 – Response Rates

8.1 Response Rates Following Initial Therapy

Evaluable patients for this outcome are based on those who commenced initial therapy and also had a response assessment.

Table 8-1 Responses Following Initial Therapy

Response	R-CVP (N=184)	R-FC Combined (N=183)	Total (N=367)
Evaluable patients:			
Complete response	60 (39%)	60 (42%)	120 (40%)
Partial response	94 (61%)	78 (55%)	172 (58%)
Stable disease	0 (%)	0 (%)	0 (%)
Progressive disease	1 (1%)	5 (3%)	6 (2%)
Total	155	143	298
Non-evaluable patients:			
Did not start any trial treatment	0 (0%)	1 (3%)	1 (1%)
Off treatment during induction	23 (79%)	27 (68%)	50 (72%)
Completed induction but missing response	0 (0%)	1 (3%)	1 (1%)
Unknown if completed induction	6 (21%)	11 (28%)	17 (25%)
Total	29	40	69

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\14 - Response Rates Following Induction Therapy.sas

Table 8-2 Overall Response (CR/PR) Rates Following Initial Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Overall Response	Proportion of Events	p-value*
R-CVP	184	155	154	99%	0.108
R-FC (Combined)	183	143	138	97%	

*Fisher's Exact Test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\14 - Response Rates Following Induction Therapy.sas

Table 8-3 Complete Response Rates Following Initial Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Complete Response	Proportion of Events	p-value*
R-CVP	184	155	60	39%	0.636
R-FC (Combined)	183	143	60	42%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\14 - Response Rates Following Induction Therapy.sas

Table 8-4 Partial Response Rates Following Initial Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Partial Response	Proportion of Events	p-value*
R-CVP	184	155	94	61%	0.293
R-FC (Combined)	183	143	78	55%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\14 - Response Rates Following Induction Therapy.sas

Table 8-5 Model Results for Responses Following Induction Therapy (Overall, Complete & Partial)

Response	Treatment Arm	Odds Ratio (95% CI)
Overall Response	R-CVP vs. R-FC (Combined)	0.18 (0.02, 1.53)
Complete Response	R-CVP vs. R-FC (Combined)	1.14 (0.72, 1.81)
Partial Response	R-CVP vs. R-FC (Combined)	0.78 (0.49, 1.24)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\14 - Response Rates Following Induction Therapy.sas

8.2 Response Rates Following Maintenance Therapy

Evaluable patients for this outcome are based on those who commenced maintenance therapy and also had a response assessment.

Table 8-6 Responses Following Maintenance Therapy

Response	R-CVP (N=184)	R-FC Combined (N=183)	Total (N=367)
Evaluable patients:			
CR	59 (59%)	52 (63%)	111 (61%)
PR	23 (23%)	23 (28%)	46 (25%)
SD	2 (2%)	4 (5%)	6 (3%)
PD	16 (16%)	4 (5%)	20 (11%)
Total	100	83	183
Non-evaluable patients:			
Did not start any trial treatment	0 (0%)	1 (1%)	1 (1%)
Did not start maintenance	25 (30%)	30 (30%)	55 (30%)
Off treatment during maintenance	18 (21%)	36 (36%)	54 (29%)
Completed maintenance but missing response	30 (36%)	24 (24%)	54 (29%)
Unknown if completed maintenance	11 (13%)	9 (9%)	20 (11%)
Total	84	100	184

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Rates Following Maintenance Therapy.sas

Table 8-7 Overall Response (CR/PR) Rates Following Maintenance Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Overall Response	Proportion of Events	p-value*
R-CVP	184	100	82	82%	0.137
R-FC (Combined)	183	83	75	90%	

*Fisher's Exact Test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Rates Following Maintenance Therapy.sas

Table 8-8 Complete Response Rates Following Maintenance Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Complete Response	Proportion of Events	p-value*
R-CVP	184	100	59	59%	0.650
R-FC (Combined)	183	83	52	63%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Rates Following Maintenance Therapy.sas

Table 8-9 Partial Response Rates Following Maintenance Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Partial Response	Proportion of Events	p-value*
R-CVP	184	100	23	23%	0.496
R-FC (Combined)	183	83	23	28%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Rates Following Maintenance Therapy.sas

Table 8-10 Model Results for Responses Following Maintenance Therapy (Overall, Complete & Partial)

Response	Treatment Arm	Odds Ratio (95% CI)
Overall Response	R-CVP vs. R-FC (Combined)	2.06 (0.85, 5.01)
Complete Response	R-CVP vs. R-FC (Combined)	1.17 (0.64, 2.12)
Partial Response	R-CVP vs. R-FC (Combined)	1.28 (0.66, 2.51)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Rates Following Maintenance Therapy.sas

9 Secondary Outcome 2 – Response Duration

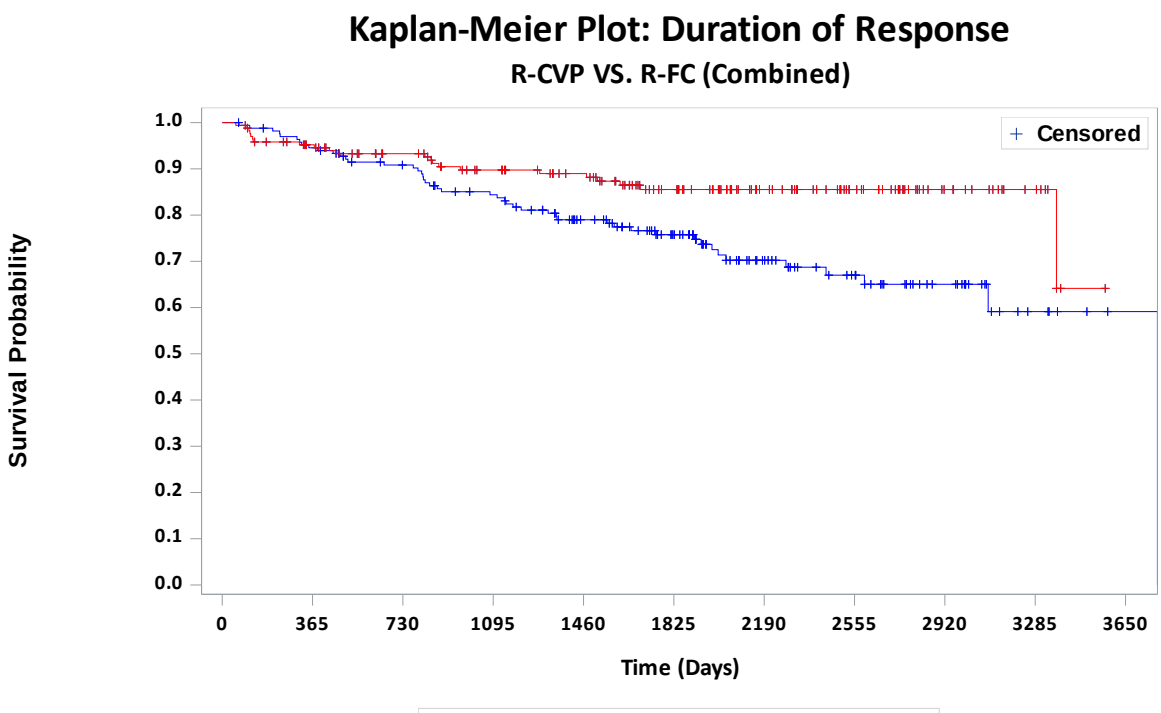
Table 9-1 Cox PH Model Results for Response Duration

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	167	47 (28%)	3779 (3095, 3779)	95% (90%, 97%)	0.48 (0.29, 0.79)	0.004
R-FC (Combined)	169	22 (13%)	NA (3371, NA)	95% (91%, 98%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Duration.sas

Note: Only patients who have experienced a partial or complete response are included in this analysis.

Figure 9-1 Kaplan Meier Plot: Response Duration



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\15 - Response Duration.sas

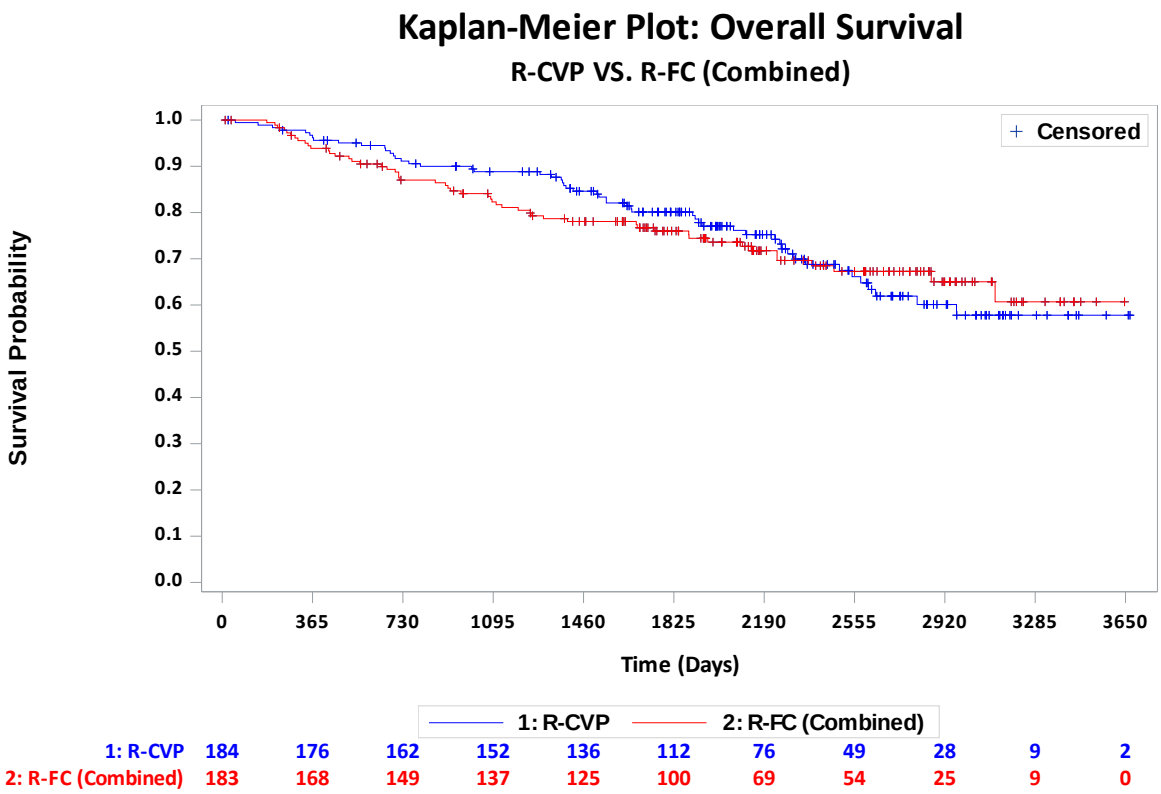
10 Secondary Outcome 3 – Overall Survival

Table 10-1 Cox PH Model Results for Overall Survival

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	53 (29%)	NA (2808, NA)	96% (92%, 98%)	1.04 (0.71, 1.52)	0.842
R-FC (Combined)	183	52 (28%)	NA (3123, NA)	94% (89%, 97%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\16 - Overall Survival.sas

Figure 10-1 Kaplan Meier Plot: Overall Survival



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\16 - Overall Survival.sas

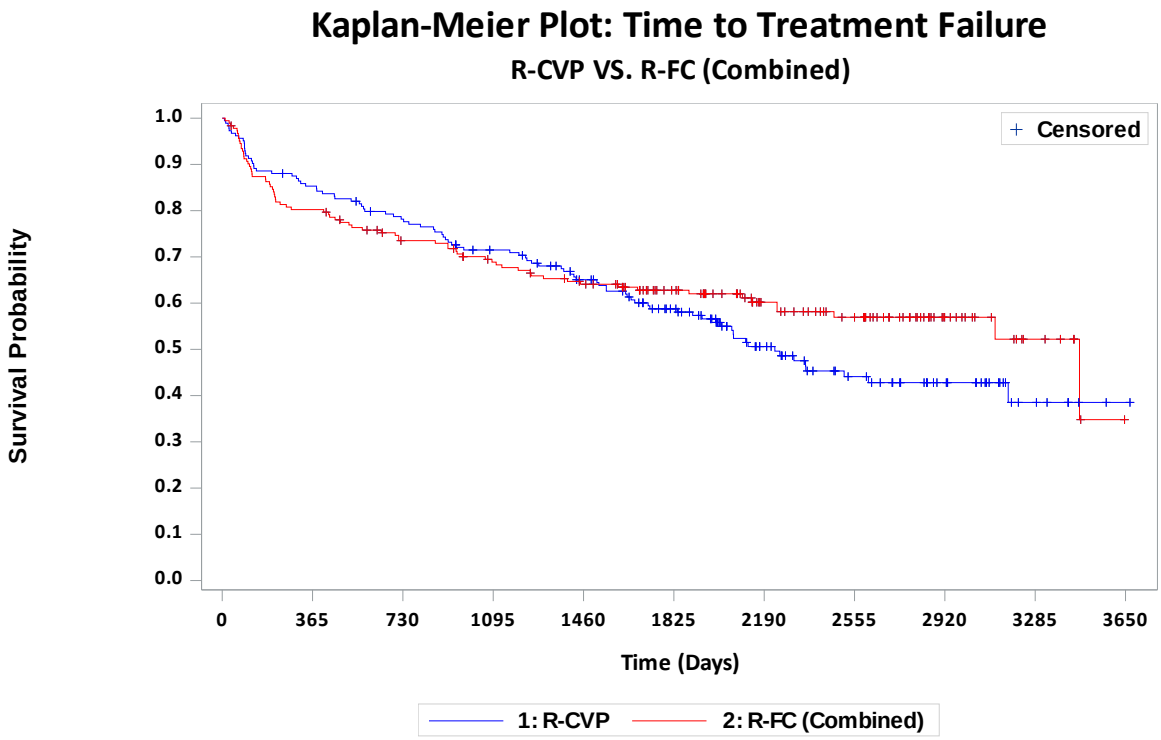
11 Secondary Outcome 4 – Time to Treatment Failure

Table 11-1 Cox PH Model Results for Time to Treatment Failure

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	91 (49%)	2233 (1901, 3176)	85% (79%, 90%)	0.83 (0.61, 1.13)	0.230
R-FC (Combined)	183	74 (40%)	3464 (2472, NA)	80% (74%, 85%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\18 - Time to Treatment Failure.sas

Figure 11-1 Kaplan Meier Plot: Time to Treatment Failure



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\18 - Time to Treatment Failure.sas

12 Secondary Outcome 5 – Time to Next Anti-Lymphoma Treatment

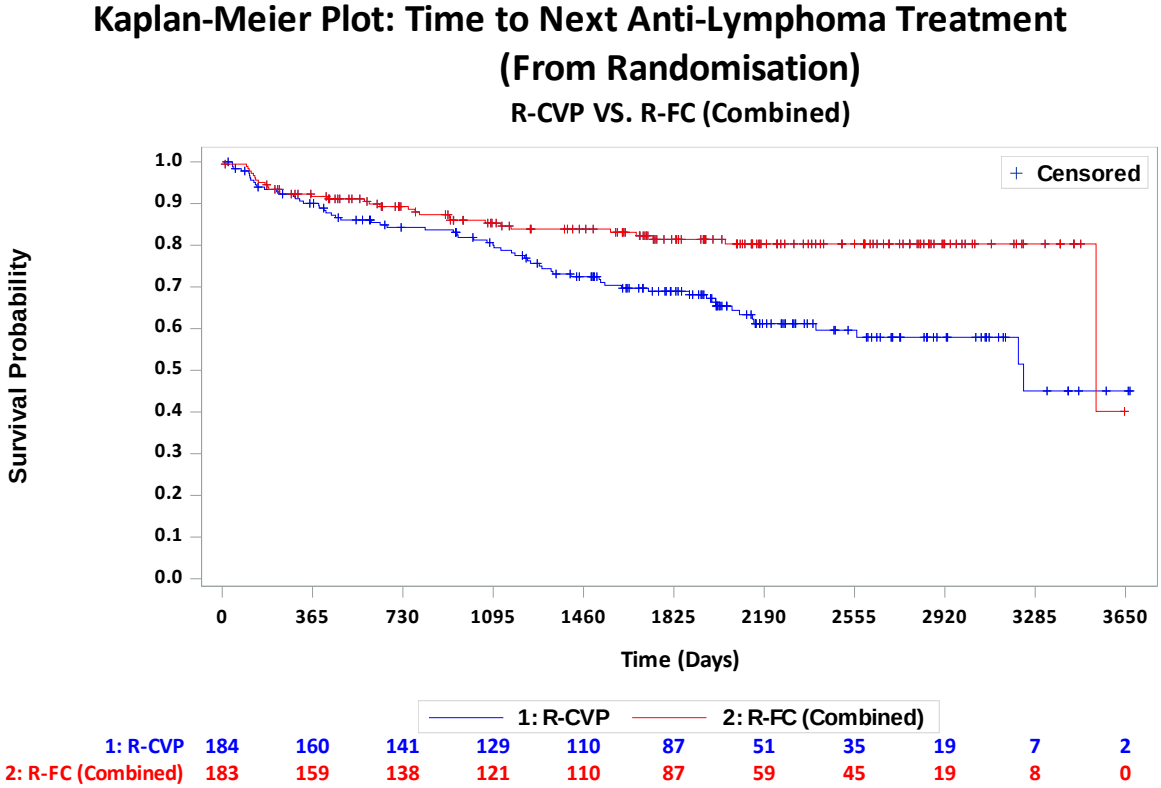
12.1 Time to Next Anti-Lymphoma Treatment From Randomisation

Table 12-1 Cox PH Model Results for Time to Next Anti-Lymphoma Treatment From Randomisation

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	64 (35%)	3238 (2564, NA)	90% (85%, 94%)	0.50 (0.33, 0.76)	0.001
R-FC (Combined)	183	32 (17%)	3531 (3531, NA)	92% (87%, 95%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\18 - Time to Next Anti-Lymphoma Treatment.sas

Figure 12-1 Kaplan Meier Plot: Time to Next Anti-Lymphoma Treatment From Randomisation



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\18 - Time to Next Anti-Lymphoma Treatment.sas

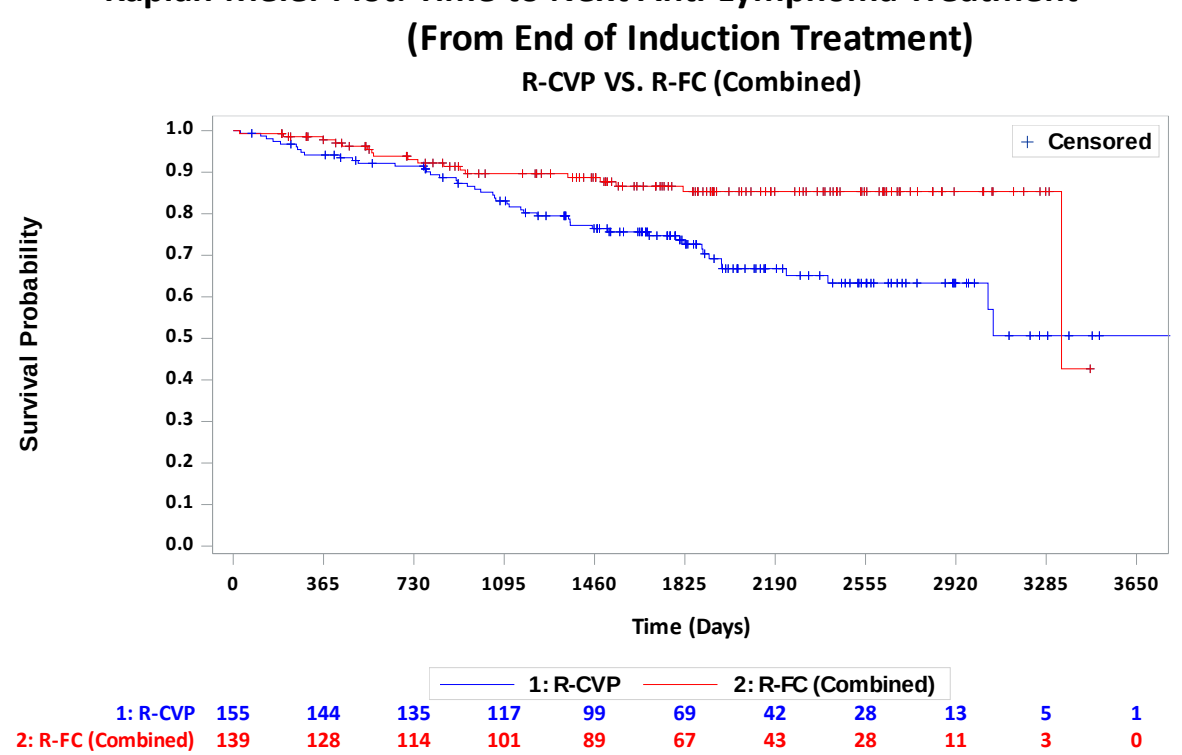
12.2 Time to Next Anti-Lymphoma Treatment From Induction

Table 12-2 Cox PH Model Results for Time to Next Anti-Lymphoma Treatment From Induction

Treatment Arm	No. patients	No. events (%)	Median time in months (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	155	47 (30%)	NA (3050, NA)	94% (89%, 97%)	0.43 (0.25, 0.74)	0.002
R-FC (Combined)	139	18 (13%)	3347 (3347, NA)	98% (93%, 99%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\19 - Time to Next Anti-Lymphoma Treatment.sas
Note: Only patients who completed induction treatment and had a completion date are included in this analysis.

Figure 12-2 Kaplan Meier Plot: Time to Next Anti-Lymphoma Treatment From Induction



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\19 - Time to Next Anti-Lymphoma Treatment.sas

13 Secondary Outcome 6 – Rate of Large Cell Transformation

Table 13-1 Results for the Proportion of Patients Experiencing Large Cell Transformation

Treatment Arm	No. Patients	No. Events	Proportion of Events	p-value*
R-CVP	184	8	4%	0.809
R-FC (Combined)	183	9	5%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\20 - Rate of Large Cell Transformation.sas

Table 13-2 Model Results for Large Cell Transformation

Treatment Arm	Odds Ratio (95% CI)
R-CVP vs. R-FC (Combined)	1.14 (0.43, 3.02)

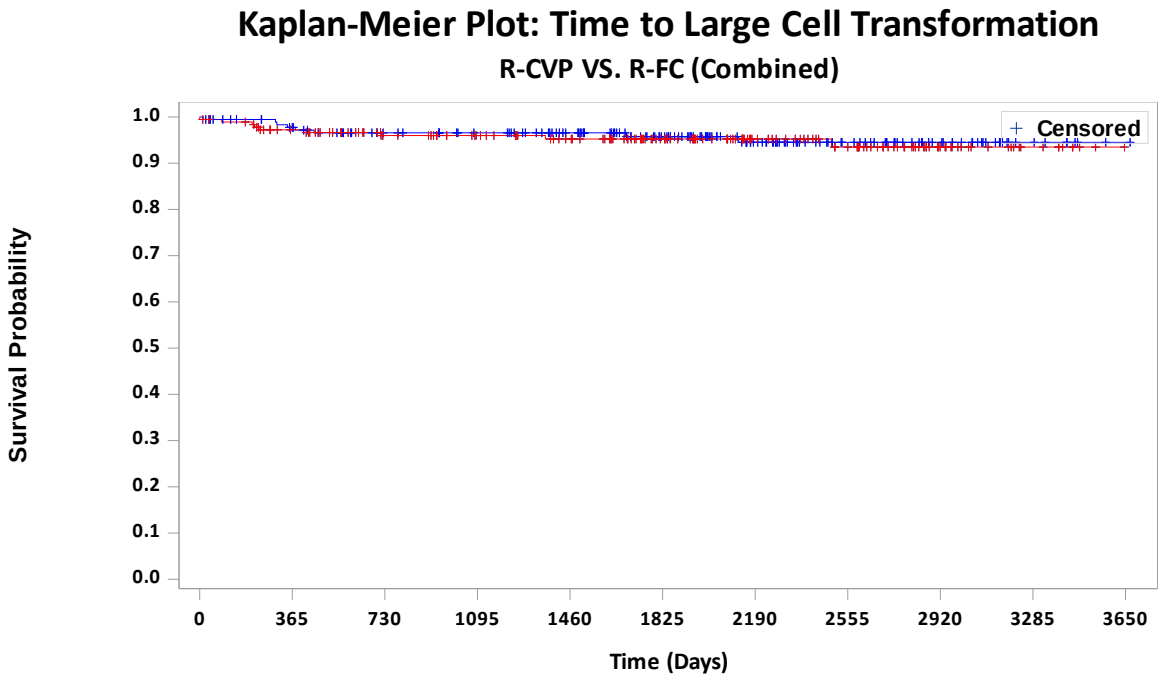
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\20 - Rate of Large Cell Transformation.sas

Table 13-3 Cox PH Model Results for Large Cell Transformation From Randomisation

Treatment Arm	No. patients	No. events (%)	Median time in days (95% CI)	12-month survival rate (95% CI)	Hazard Ratio (95% CI)*	p-value**
R-CVP	184	8 (4%)	NA (NA, NA)	98% (94%, 99%)	1.14 (0.44, 2.95)	0.790
R-FC (Combined)	183	9 (5%)	NA (NA, NA)	97% (93%, 99%)		

*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\20 - Rate of Large Cell Transformation.sas

Figure 13-1 Kaplan Meier Plot: Large Cell Transformation From Randomisation



R-CVP	184	170	155	147	132	106	69	44	26	8	1
R-FC (Combined)	183	166	145	134	122	98	68	52	23	9	0

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\20 - Rate of Large Cell Transformation.sas

14 Secondary Outcome 7 – Response to Second Line Therapy

Evaluable patients for this outcome are based on those who had a response assessment to second line therapy.

Table 14-1 Responses Following Second Line Therapy

Response	R-CVP (N=184)	R-FC Combined (N=183)	Total (N=367)
CR	14 (34%)	6 (38%)	20 (35%)
PR	12 (29%)	6 (38%)	18 (32%)
SD	5 (12%)	0 (0%)	5 (9%)
PD	10 (24%)	4 (25%)	14 (25%)
Total	41	16	57

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

Table 14-2 Complete Response Rates Following Second Line Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Complete Response	Proportion of Events	p-value*
R-CVP	184	41	14	34%	1.000
R-FC (Combined)	183	16	6	38%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

Table 14-3 Partial Response Rates Following Second Line Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Partial Response	Proportion of Events	p-value*
R-CVP	184	41	12	29%	0.545
R-FC (Combined)	183	16	6	38%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

Table 14-4 Stable Disease Rates Following Second Line Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Stable Disease	Proportion of Events	p-value*
R-CVP	184	41	5	12%	0.307
R-FC (Combined)	183	16	0	0%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

Table 14-5 Progressive Disease Rates Following Second Line Therapy

Treatment Arm	No. Patients	No. Evaluable Patients	No. Patients with Progressive Disease	Proportion of Events	p-value*
R-CVP	184	41	10	24%	1.000
R-FC (Combined)	183	16	4	25%	

*Fisher's Exact Test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

Table 14-6 Model Results for Responses Following Second Line Therapy (CR, PR, SD & SD)

Response	Treatment Arm	Odds Ratio (95% CI)
Complete Response	R-CVP vs. R-FC (Combined)	1.16 (0.35, 3.84)
Partial Response	R-CVP vs. R-FC (Combined)	1.45 (0.43, 4.89)
Stable Disease	R-CVP vs. R-FC (Combined)	NA
Progressive Disease	R-CVP vs. R-FC (Combined)	1.03 (0.27, 3.94)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\21 - Response to Second Line Therapy.sas

15 Secondary Outcome 8 – Number of Treatment Cycles Delivered

Table 15-1 Comparison of the Number of Treatment Cycles Completed

Treatment Phase	Statistic	R-CVP (N=184)	R-FC (Combined) (N=183)	p-value*
Induction Phase Cycles	n	184	182	
	Mean (SD)	7.4 (1.6)	7.0 (1.8)	
	Median (IQR)	8.0 (8.0,8.0)	8.0 (7.0,8.0)	0.052
	Range	1, 8	1, 8	
Maintenance Phase Cycles	n	158	146	
	Mean (SD)	10.5 (2.9)	9.7 (3.5)	
	Median (IQR)	12.0 (11.0,12.0)	12.0 (7.0,12.0)	0.009
	Range	1, 12	1, 12	
Total Cycles	n	184	182	
	Mean (SD)	16.4 (5.7)	14.8 (6.2)	
	Median (IQR)	20.0 (14.0,20.0)	18.0 (11.0,20.0)	0.001
	Range	1, 20	1, 20	

*Mann-Whitney U test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\22 - Number of Treatment Cycles Delivered.sas

16 Secondary Outcome 9 – Cumulative Dose of Individual Drugs Administered

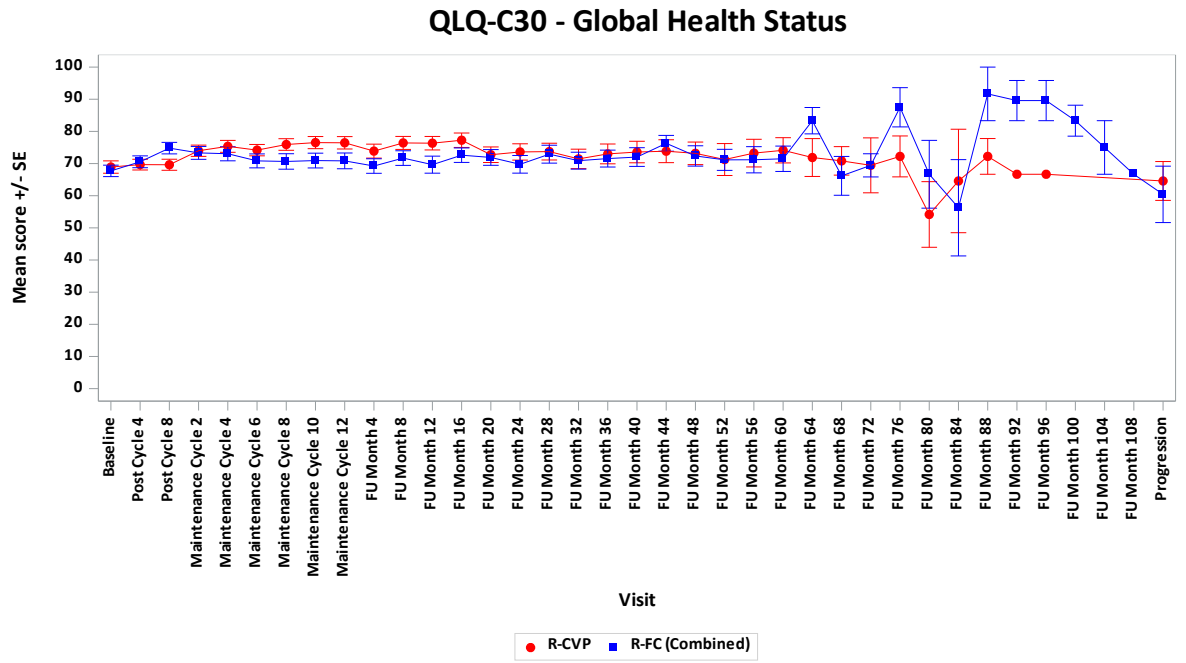
Table 16-1 Comparison of Cumulative Dose Administered

Drug	Route	R-CVP, Median (IQR)	R-FC (Combined), Median (IQR)	p-value*
Rituximab (Induction)	IV	5150.0 (3000,5750)	2600.0 (700.0,4800)	<0.001
	SC	10400.0 (9100,10500)	5600.0 (3850,9800)	<0.001
Rituximab (Maintenance)	IV	8350.0 (7100,8880)	7200.0 (4900,8400)	0.014
	SC	16800.0 (15400,16800)	16800.0 (8400,16800)	0.068
Cyclophosphamide (Induction)	IV	10400.0 (8800,11520)	2400.0 (1350,6000)	<0.001
	PO	NA	3200.0 (2400,4000)	NA

*Mann-Whitney U test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\23 - Cumulative Dose of Individual Drugs Administered.sas

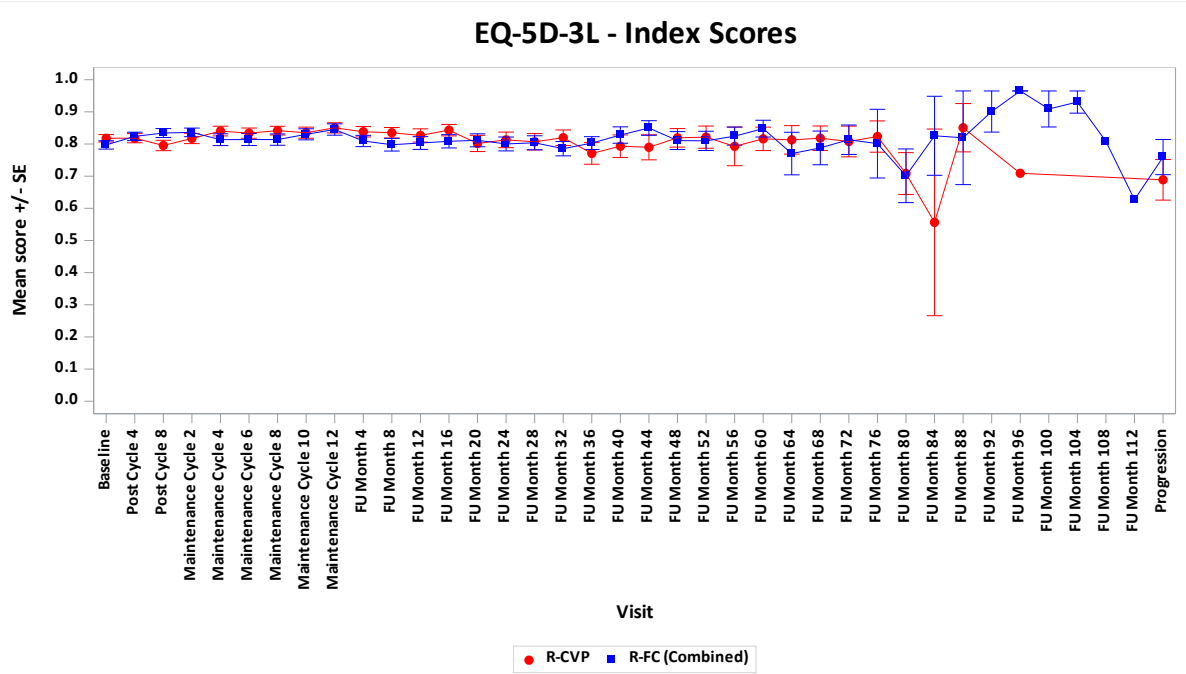
17 Secondary Outcome 10 – Quality of Life

Figure 17-1 EORTC QOL-C30 Global Health Status Over Time



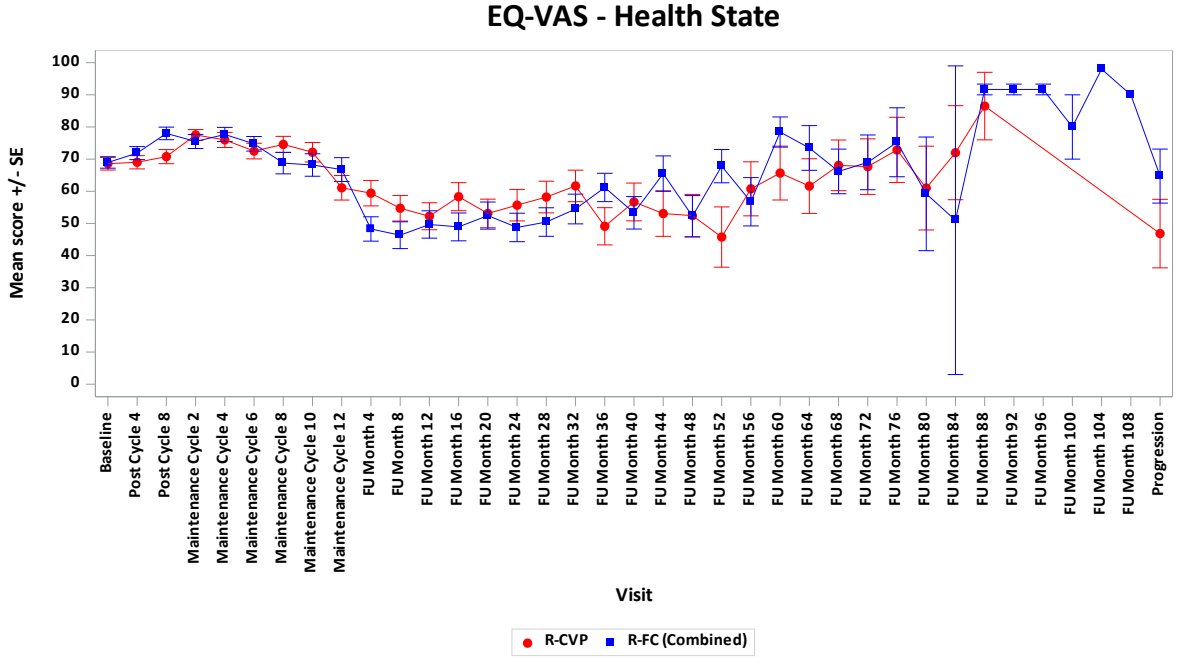
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\24 - Quality of Life.sas

Figure 17-2 EQ-5D Index Score Over Time



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\24 - Quality of Life.sas

Figure 17-3 EQ-VAS Score Over Time



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\24 - Quality of Life.sas

Table 17-1 AUC Measures in EORTC QOL-C30, EQ-5D and EQ-VAS

This analysis has been omitted from v1.0 of the report due to time constraints and will be added in V2.0.

Table 17-2 Joint Longitudinal and Survival Modelling of Qol (EQ-VAS)

This analysis has been omitted from v1.0 of the report due to time constraints and will be added in V2.0.

18 Secondary Outcome 11 – Analysis of Frailty and Comorbidity

18.1 Analysis of Frailty and Comorbidity (Progression Free Survival)

Table 18-1 Cox PH Model Results for Progression Free Survival by Frailty and Comorbidities (Group Comparison)

Frailty/Co-Morbidity	Group	No. patients	No. events	Hazard Ratio (95% CI)*	p-value**
Performance Status	0	174	59	[0 vs. 1] 0.63 (0.45, 0.88)	0.025
	1	170	77	[0 vs. 2] 0.74 (0.35, 1.56)	
	2	23	8	[1 vs. 2] 1.19 (0.57, 2.46)	
Vulnerable Elders Survey-13	<3	150	60	1.26 (0.74, 2.13)	0.392
	≥3	61	18		
Groningen Frailty Index	<4	207	77	0.91 (0.61, 1.35)	0.643
	≥4	98	36		
Timed Up and Go Test	<10	202	84	1.18 (0.76, 1.84)	0.455
	≥10	91	26		

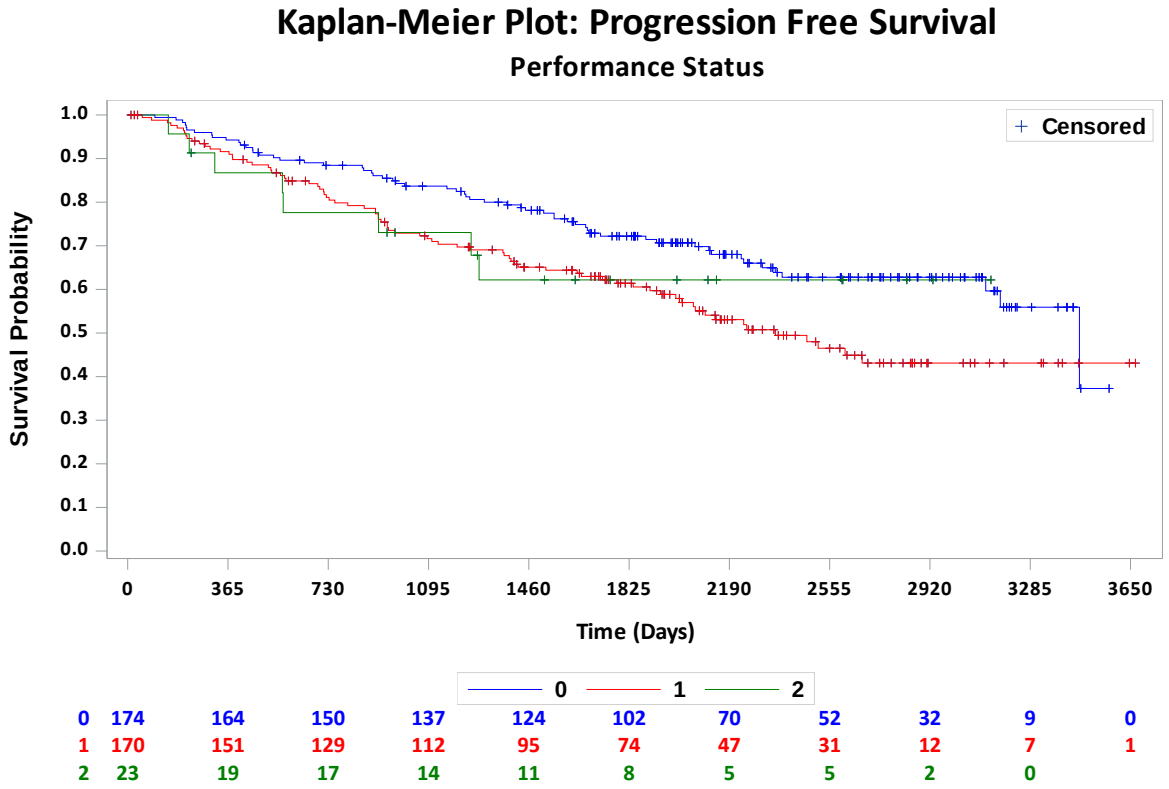
*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Table 18-2 Cox PH Model Results for Progression Free Survival by Frailty and Comorbidities (Arm Comparison)

Frailty/Co-Morbidity	Treatment Arm	No. patients	No. events	Hazard Ratio (95% CI)*	p-value**
Performance Status: 0	R-CVP	93	32	0.96 (0.57, 1.60)	0.875
	R-FC (Combined)	81	27		
Performance Status: 1	R-CVP	77	42	0.65 (0.41, 1.01)	0.055
	R-FC (Combined)	93	35		
Performance Status: 2	R-CVP	14	6	0.54 (0.11, 2.70)	0.450
	R-FC (Combined)	9	2		
Vulnerable Elders Survey-13: <3	R-CVP	77	33	0.87 (0.52, 1.45)	0.597
	R-FC (Combined)	73	27		
Vulnerable Elders Survey-13: ≥3	R-CVP	33	14	0.28 (0.09, 0.86)	0.018
	R-FC (Combined)	28	4		
Groningen Frailty Index: <4	R-CVP	95	37	0.98 (0.63, 1.53)	0.924
	R-FC (Combined)	112	40		
Groningen Frailty Index: ≥4	R-CVP	52	24	0.47 (0.23, 0.94)	0.028
	R-FC (Combined)	46	12		
Timed Up and Go Test: <10	R-CVP	95	42	0.92 (0.60, 1.41)	0.689
	R-FC (Combined)	107	42		
Timed Up and Go Test: ≥10	R-CVP	46	16	0.60 (0.27, 1.32)	0.197
	R-FC (Combined)	45	10		

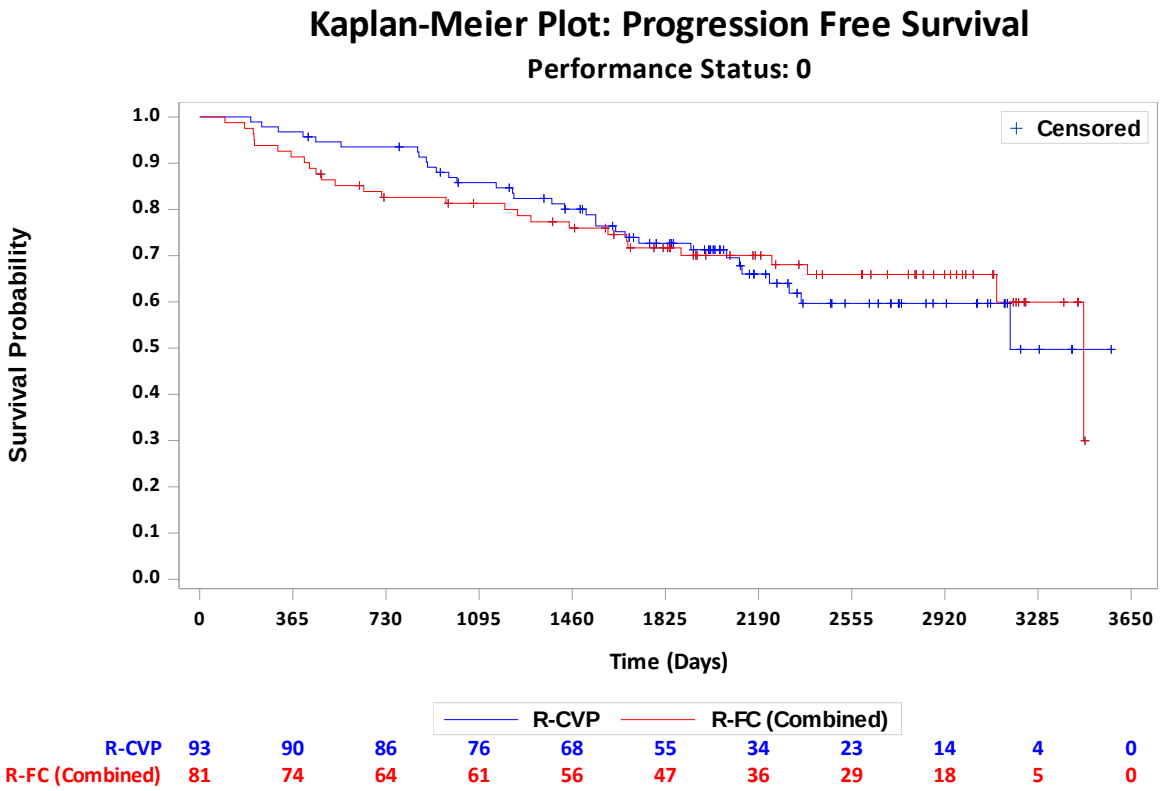
*Cox PH model
**Log rank test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-1 Kaplan Meier Plot: Progression Free Survival by Performance Status (Group Comparison)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

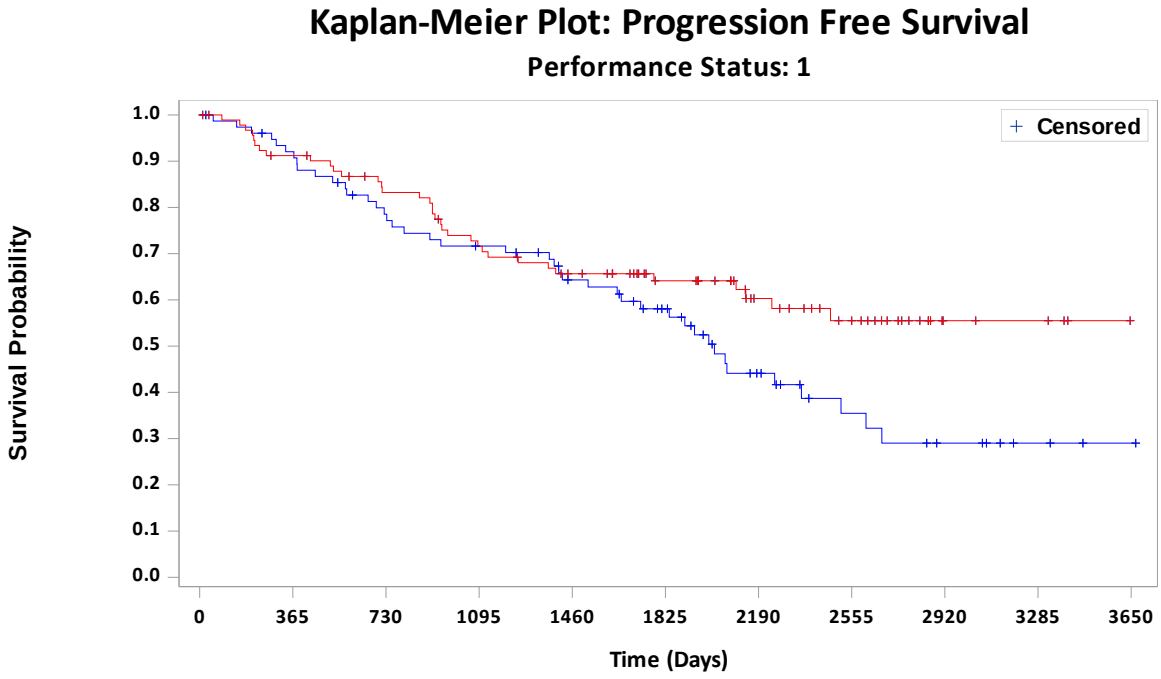
Figure 18-2 Kaplan Meier Plot: Progression Free Survival by Performance Status: 0 (Arm Comparison)



R-CVP	93	90	86	76	68	55	34	23	14	4	0
R-FC (Combined)	81	74	64	61	56	47	36	29	18	5	0

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

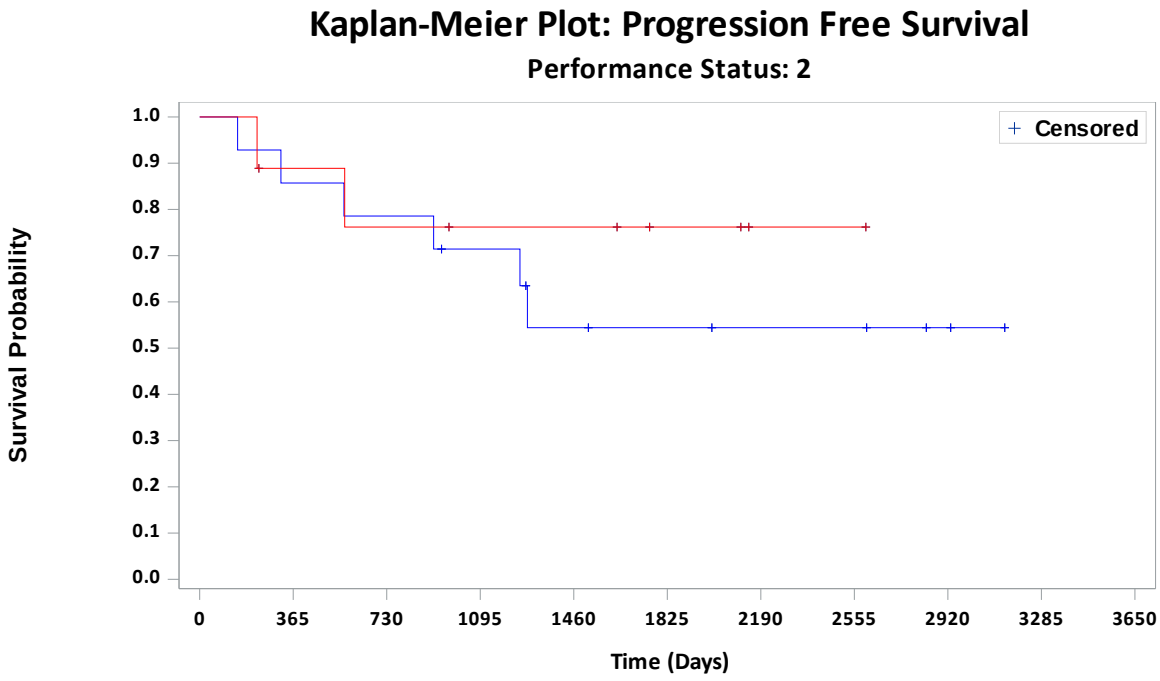
Figure 18-3 Kaplan Meier Plot: Progression Free Survival by Performance Status: 1 (Arm Comparison)



R-CVP	77	69	57	51	42	33	19	11	7	3	1
R-FC (Combined)	93	82	72	61	53	41	28	20	5	4	0

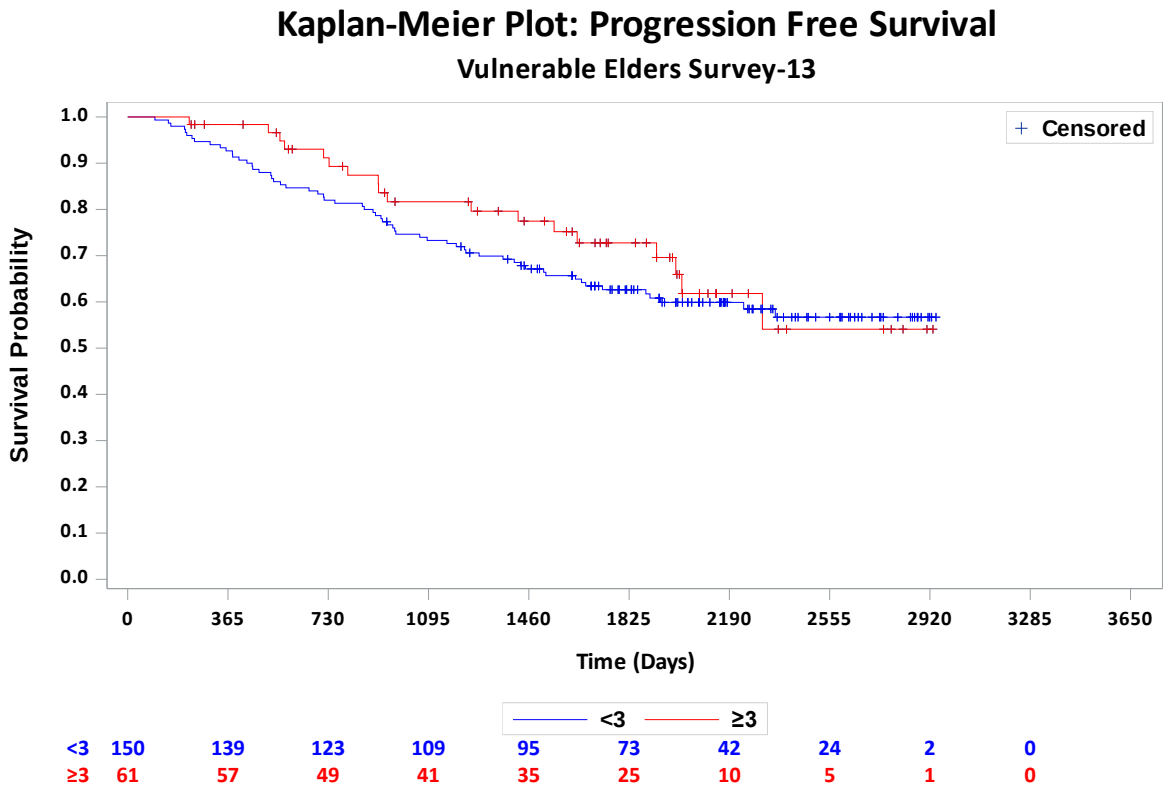
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-4 Kaplan Meier Plot: Progression Free Survival by Performance Status: 2 (Arm Comparison)



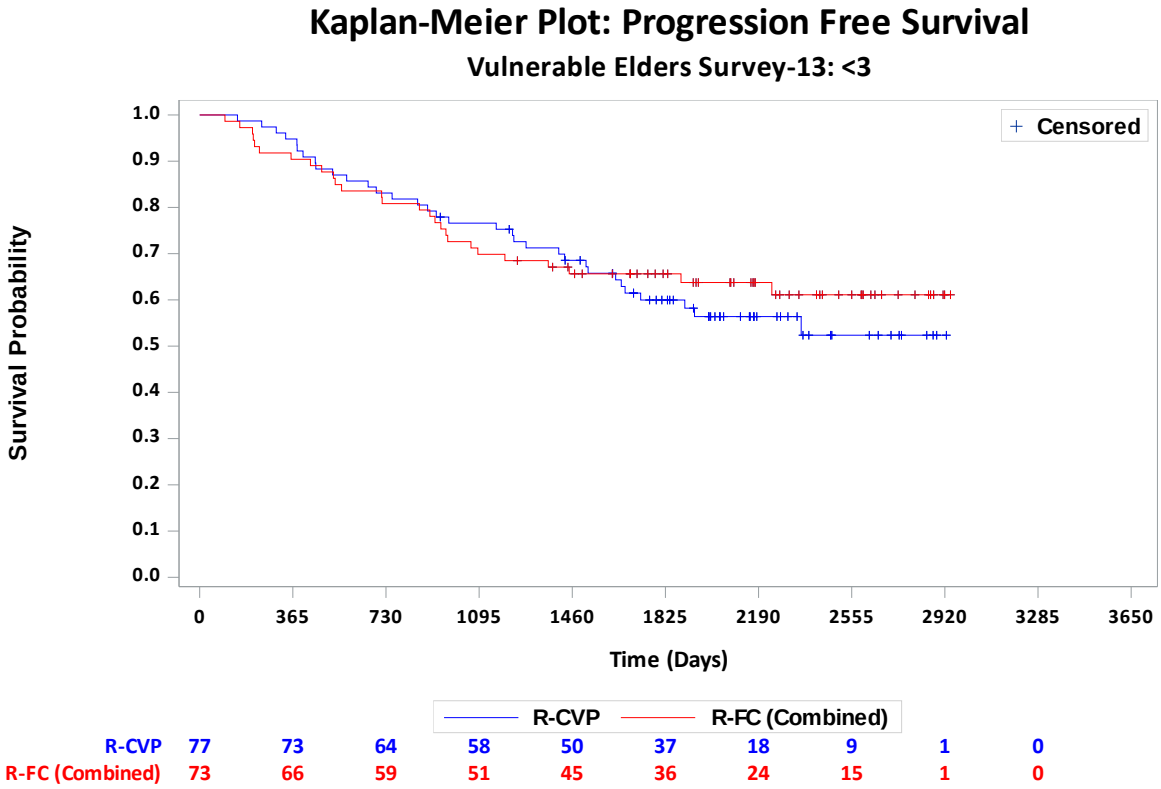
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-5 Kaplan Meier Plot: Progression Free Survival by VES-13 (Group Comparison)



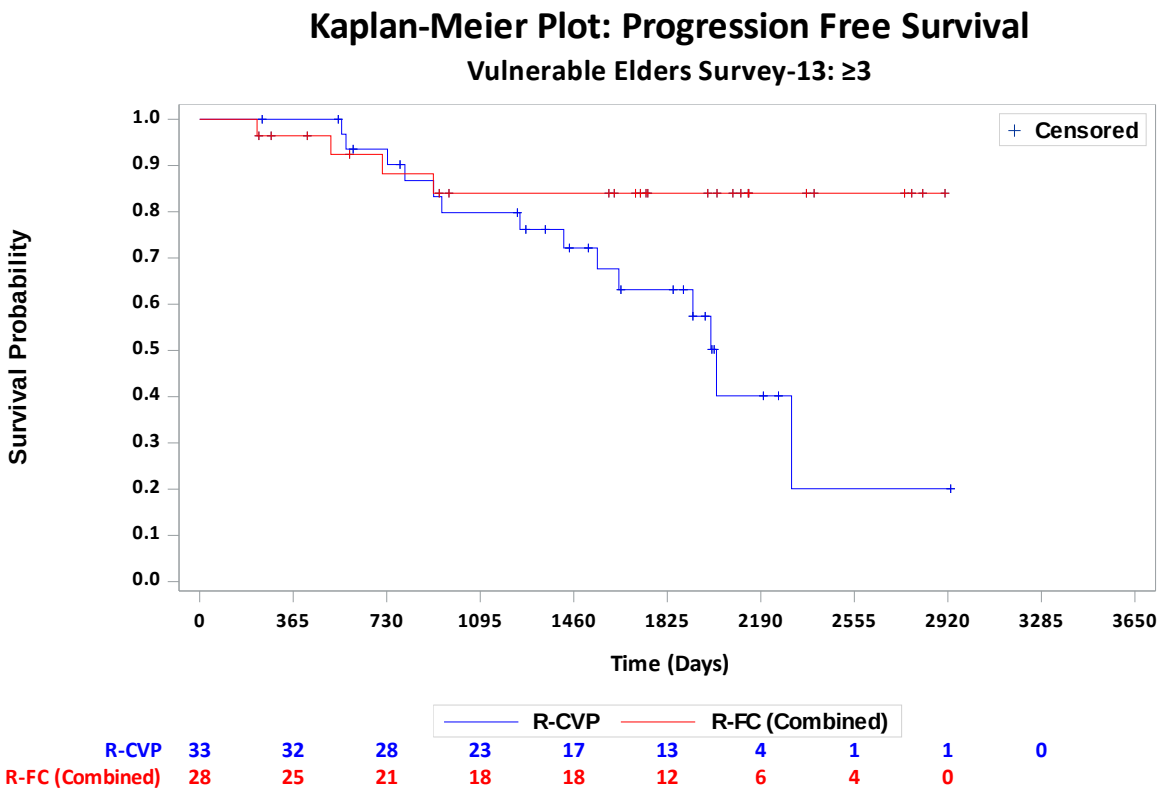
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-6 Kaplan Meier Plot: Progression Free Survival by VES-13: <3 (Arm Comparison)



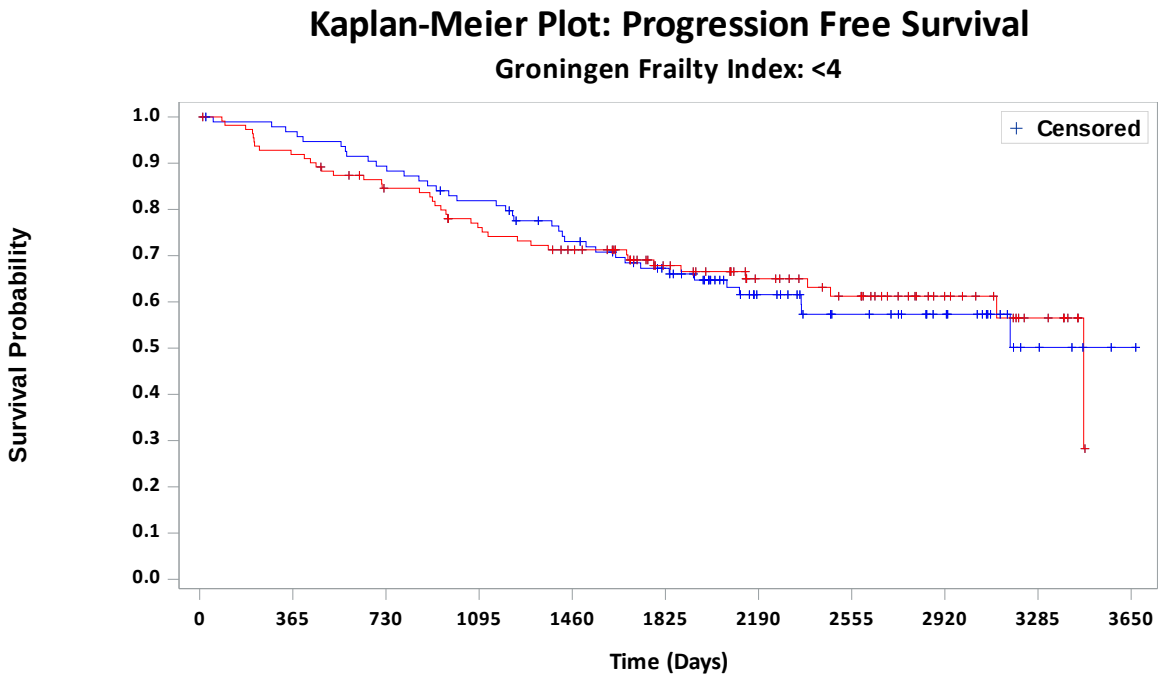
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-7 Kaplan Meier Plot: Progression Free Survival by VES-13: ≥3 (Arm Comparison)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

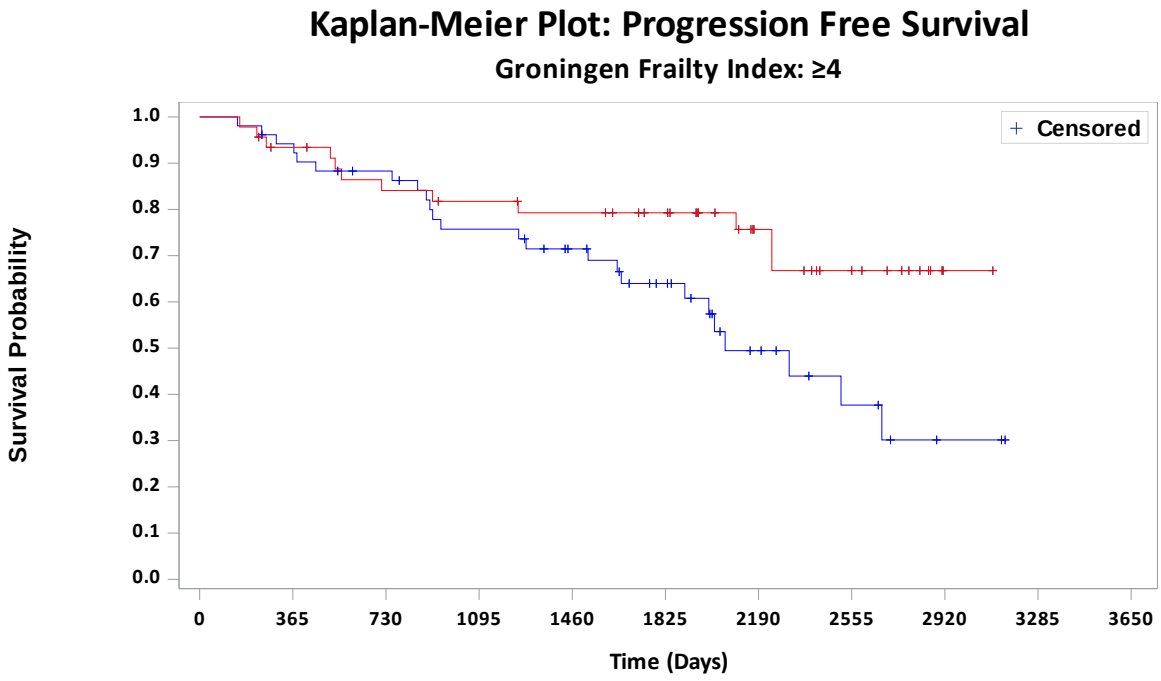
Figure 18-8 Kaplan Meier Plot: Progression Free Survival by GFI: <4 (Arm Comparison)



R-CVP	95	91	84	76	65	55	34	24	17	5	1
R-FC (Combined)	112	102	90	79	71	53	39	31	17	8	0

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

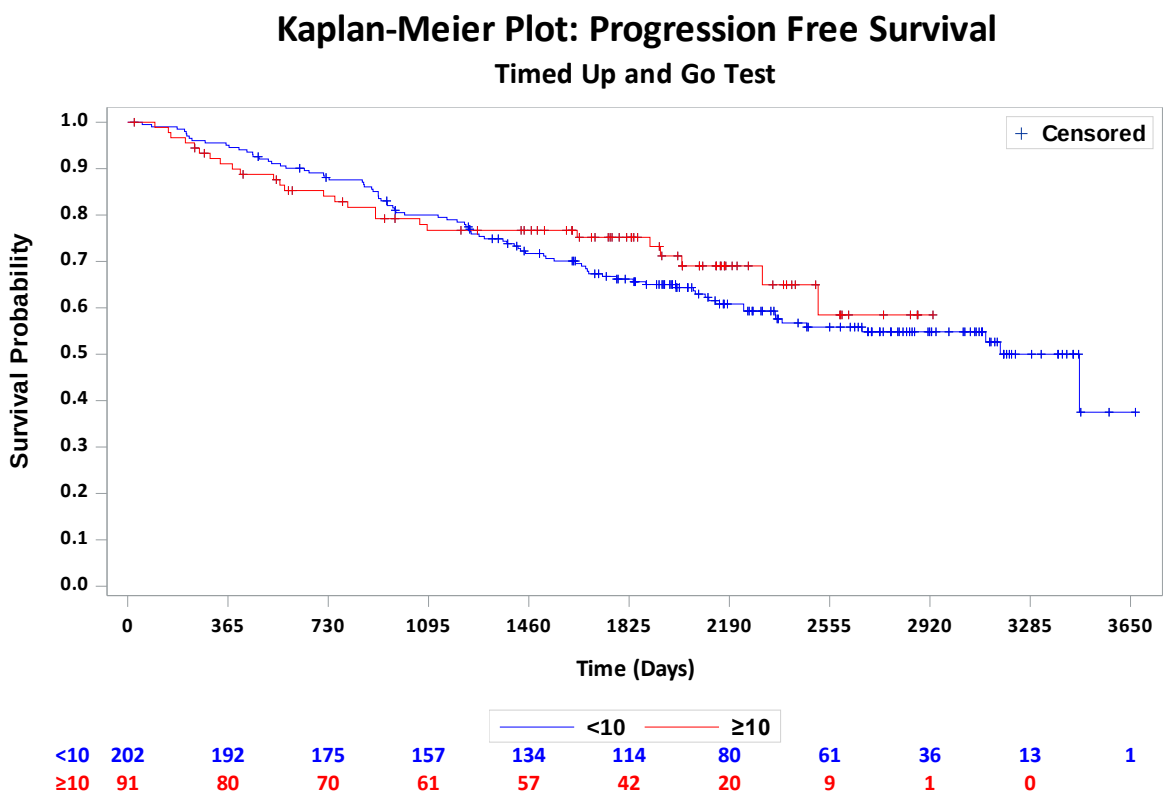
Figure 18-9 Kaplan Meier Plot: Progression Free Survival by GFI: ≥4 (Arm Comparison)



R-CVP	52	48	43	36	30	22	11	6	2	0
R-FC (Combined)	46	41	36	34	32	28	17	11	1	0

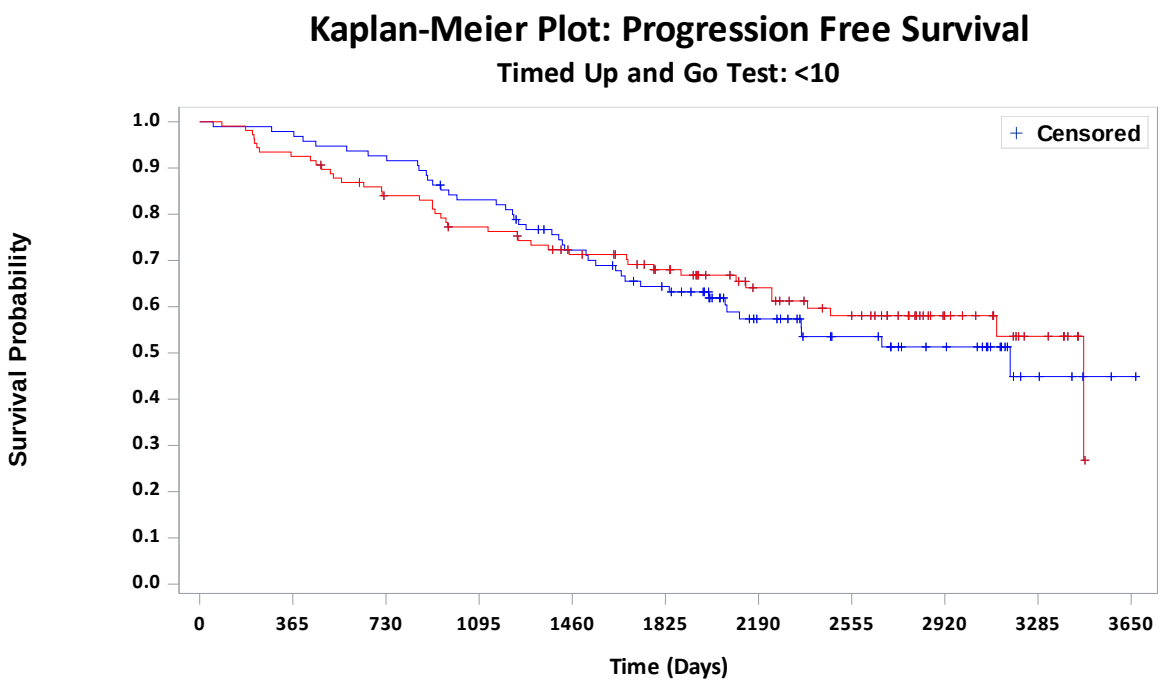
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-10 Kaplan Meier Plot: Progression Free Survival by Timed "Up and Go" Test (Group Comparison)



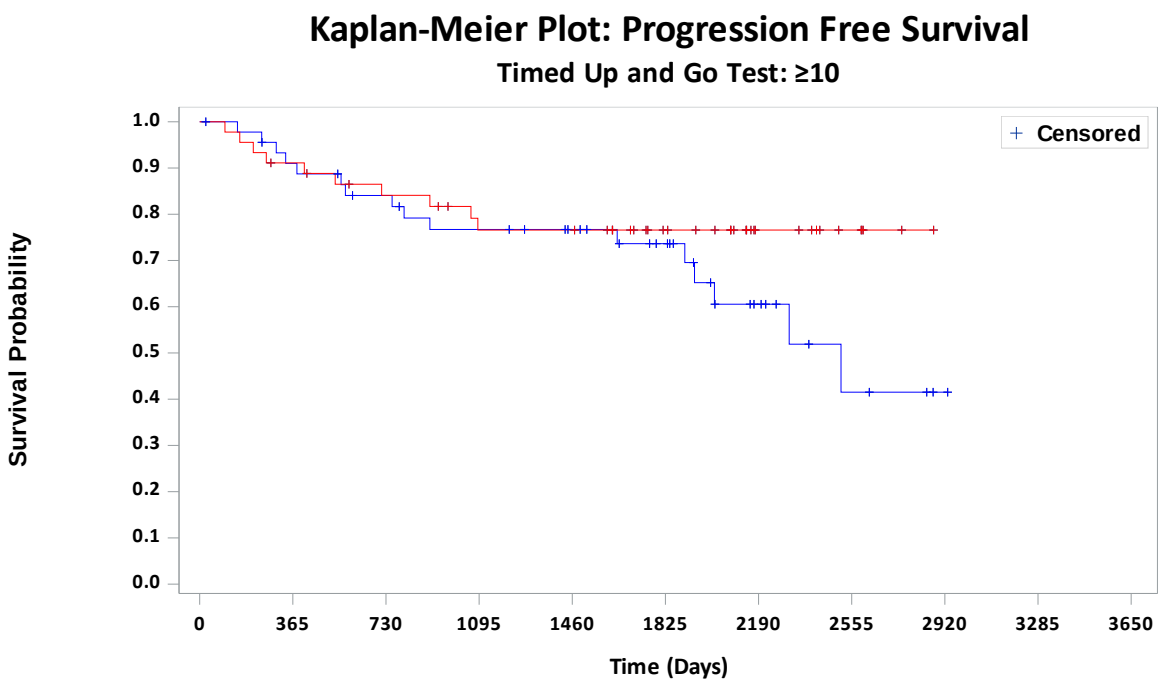
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-11 Kaplan Meier Plot: Progression Free Survival by Timed "Up and Go" Test: <10 (Arm Comparison)



Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

Figure 18-12 Kaplan Meier Plot: Progression Free Survival by Timed "Up and Go" Test: ≥10 (Arm Comparison)



R-CVP	46	40	35	31	27	21	10	4	1	0
R-FC (Combined)	45	40	35	30	30	21	10	5	0	

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5. 12.1 Data and Analysis\Code\25 - Frailty & Co-Morbidity_Progression-Free Survival.sas

18.2 Analysis of Frailty and Comorbidity (Grade 3-4 Infections)

Table 18-3 Proportion of Grade 3-4 Infections by Frailty and Comorbidities (Group Comparison)

Frailty/Comorbidity	Group	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
Performance Status	0	174	40	0 vs. 1: -0.06 (-0.16, 0.03)	0 vs. 1: 0.78 (0.55, 1.12)	0 vs. 1: 0.175
	1	170	50	0 vs. 2: -0.25 (-0.46, -0.03)	0 vs. 2: 0.48 (0.29, 0.80)	0 vs. 2: 0.011
	2	23	11	1 vs. 2: -0.18 (-0.40, 0.03)	1 vs. 2: 0.61 (0.38, 1.00)	1 vs. 2: 0.075
VES-13	<3	150	47	-0.08 (-0.22, 0.06)	0.80 (0.54, 1.18)	0.264
	≥3	61	24			
GFI	<4	207	62	0.02 (-0.08, 0.13)	1.09 (0.74, 1.59)	0.667
	≥4	98	27			
Timed 'Up and Go' Test	<10	202	54	-0.06 (-0.18, 0.05)	0.81 (0.56, 1.18)	0.275
	≥10	91	30			

*Chi-Square test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-4 Model Results for Grade 3-4 Infections (Group Comparison)

Frailty/Comorbidity	Comparison	Odds Ratio (95% CI)
Performance Status	0 vs 1	0.72 (0.44, 1.16)
	0 vs 2	0.33 (0.13, 0.79)
	1 vs 2	0.45 (0.19, 1.10)
VES-13	<3 vs ≤3	0.70 (0.38, 1.31)
GFI	<4 vs ≤4	1.12 (0.66, 1.92)
Timed 'Up and Go' Test	<10 vs ≤10	0.74 (0.43, 1.27)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-5 Proportion of Grade 3-4 Infections by Performance Status (Arm Comparison)

Performance Status	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
0	R-CVP	93	21	0.01 (-0.12, 0.13)	1.04 (0.60, 1.79)	1.000
	R-FC (Combined)	81	19			
1	R-CVP	77	19	0.09 (-0.05, 0.22)	1.35 (0.83, 2.19)	0.287
	R-FC (Combined)	93	31			
2	R-CVP	14	8	-0.24 (-0.64, 0.16)	0.58 (0.21, 1.63)	0.491
	R-FC (Combined)	9	3			

*Chi-Square test
Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-6 Model Results for Grade 3-4 Infections by Performance Status (Arm Comparison)

Performance Status	Comparison	Odds Ratio (95% CI)
0	R-CVP vs. R-FC (Combined)	1.05 (0.52, 2.13)
1	R-CVP vs. R-FC (Combined)	1.53 (0.78, 2.99)
2	R-CVP vs. R-FC (Combined)	0.38 (0.07, 2.15)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-7 Proportion of Grade 3-4 Infections by VES-13 (Arm Comparison)

VES-13	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
<3	R-CVP	77	23	0.03 (-0.12, 0.18)	1.10 (0.69, 1.77)	0.825
	R-FC (Combined)	73	24			
≥3	R-CVP	33	10	0.20 (-0.05, 0.44)	1.65 (0.87, 3.12)	0.191
	R-FC (Combined)	28	14			

*Chi-Square test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-8 Model Results for Grade 3-4 Infections by VES-13 (Arm Comparison)

VES-13	Comparison	Odds Ratio (95% CI)
<3	R-CVP vs. R-FC (Combined)	1.15 (0.58, 2.29)
≥3	R-CVP vs. R-FC (Combined)	2.30 (0.81, 6.56)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-9 Proportion of Grade 3-4 Infections by GFI (Arm Comparison)

GFI	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
<4	R-CVP	95	26	0.05 (-0.08, 0.17)	1.17 (0.77, 1.79)	0.552
	R-FC (Combined)	112	36			
≥4	R-CVP	52	15	-0.03 (-0.20, 0.15)	0.90 (0.47, 1.73)	0.937
	R-FC (Combined)	46	12			

*Chi-Square test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-10 Model Results for Grade 3-4 Infections by GFI (Arm Comparison)

GFI	Comparison	Odds Ratio (95% CI)
<4	R-CVP vs. R-FC (Combined)	1.26 (0.69, 2.29)
≥4	R-CVP vs. R-FC (Combined)	0.87 (0.36, 2.12)

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-11 Proportion of Grade 3-4 Infections by Timed "Up and Go" Test (Arm Comparison)

Timed 'Up and Go' Test	Treatment Arm	Total No. Patients	No. Patients with a Grade 3-4 Infection	Risk Difference (95% CI)	Risk Ratio (95% CI)	p-value*
<10	R-CVP	95	24	0.03 (-0.09, 0.15)	1.11 (0.70, 1.76)	0.775
	R-FC (Combined)	107	30			
≥10	R-CVP	46	13	0.10 (-0.10, 0.29)	1.34 (0.74, 2.42)	0.458
	R-FC (Combined)	45	17			

*Chi-Square test

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\26 - Frailty & Co-Morbidity_Grade 3-4 Infections.sas

Table 18-12 Model Results for Grade 3-4 Infections by Timed "Up and Go" Test (Arm Comparison)

Timed 'Up and Go' Test	Comparison	Odds Ratio (95% CI)
<10	R-CVP vs. R-FC (Combined)	1.15 (0.62, 2.16)
≥10	R-CVP vs. R-FC (Combined)	1.54 (0.64, 3.72)

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19 Safety Analysis

Table 19-1 Summary of Non-Serious Adverse Events by Arm and Overall

		R-FC Combined (N=182)			
Grade	**R-CVP (N=184)**	**R-FC Full (N=52)**	**R-FC Lite (N=130)**	**R-FC (Combined) (N=182)**	**Total (N=366)**
1	1192 (63%)	483 (55%)	812 (58%)	1295 (57%)	2487 (60%)
2	599 (31%)	313 (36%)	468 (34%)	781 (34%)	1380 (33%)
3	92 (5%)	66 (8%)	73 (5%)	139 (6%)	231 (6%)
4	10 (1%)	11 (1%)	19 (1%)	30 (1%)	40 (1%)
Missing	11 (1%)	0 (0%)	25 (2%)	25 (1%)	36 (1%)
Total	1904	873	1397	2270	4174

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\27 - Safety.sas

Table 19-2 Summary of Serious Adverse Events by Arm and Overall

		R-FC Combined (N=182)			
Grade	**R-CVP (N=184)**	**R-FC Full (N=52)**	**R-FC Lite (N=130)**	**R-FC (Combined) (N=182)**	**Total (N=366)**
1	16 (9%)	7 (9%)	13 (8%)	20 (8%)	36 (9%)
2	43 (24%)	17 (21%)	33 (20%)	50 (21%)	93 (22%)
3	89 (50%)	36 (45%)	90 (55%)	126 (52%)	215 (51%)
4	16 (9%)	10 (13%)	11 (7%)	21 (9%)	37 (9%)
5	4 (2%)	5 (6%)	4 (2%)	9 (4%)	13 (3%)
Missing	10 (6%)	5 (6%)	12 (7%)	17 (7%)	27 (6%)
Total	178	80	163	243	421

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\27 - Safety.sas

Table 19-3 Aggregated Serious Adverse Events

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Blood and lymphatic system disorders	Anaemia	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Anaemia	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Febrile neutropenia	R-CVP	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	1 (1)
Blood and lymphatic system disorders	Febrile neutropenia	R-FC Lite	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Lymphadenopathy	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Blood and lymphatic system disorders	Neutropenia	R-CVP	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Neutropenia	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Neutropenia	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Pancytopenia	R-FC Full	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Thrombocytopenia	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Cardiac disorders	Acute myocardial infarction	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Acute myocardial infarction	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Angina pectoris	R-CVP	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Cardiac disorders	Atrial fibrillation	R-CVP	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Cardiac disorders	Bundle branch block left	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Myocardial infarction	R-CVP	0 (0)	0 (0)	1 (1)	2 (3)	0 (0)	0 (0)
Cardiac disorders	Myocardial infarction	R-FC Full	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)
Cardiac disorders	Myocardial infarction	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Myocardial ischaemia	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Cardiac disorders	Pericardial effusion	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Pericarditis	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Tachycardia	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac disorders	Ventricular tachycardia	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Gastrointestinal disorders	Abdominal pain	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Abdominal strangulated hernia	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Ascites	R-FC Lite	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Constipation	R-CVP	0 (0)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Constipation	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Diarrhoea	R-CVP	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Diarrhoea	R-FC Full	1 (1)	2 (2)	2 (3)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Diarrhoea	R-FC Lite	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Diverticulum	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Duodenal ulcer	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Femoral hernia, obstructive	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Intestinal perforation	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Gastrointestinal disorders	Nausea	R-CVP	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Nausea	R-FC Full	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Pancreatitis	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Pancreatitis acute	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Small intestinal obstruction	R-CVP	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Small intestinal obstruction	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Stomatitis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Vomiting	R-FC Lite	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Chest pain	R-CVP	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
General disorders and administration site conditions	Chills	R-FC Lite	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Death	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
General disorders and administration site conditions	Fatigue	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Hernia	R-CVP	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Injection site reaction	R-CVP	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Malaise	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Pyrexia	R-CVP	5 (7)	2 (2)	3 (3)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
General disorders and administration site conditions	Pyrexia	R-FC Full	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Pyrexia	R-FC Lite	4 (4)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	Sudden death	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Hepatobiliary disorders	Cholecystitis acute	R-CVP	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders	Cholecystitis acute	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders	Hepatitis	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Immune system disorders	Anaphylactic reaction	R-CVP	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Immune system disorders	Anaphylactic reaction	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Immune system disorders	Drug hypersensitivity	R-FC Lite	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Immune system disorders	Hypersensitivity	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Immune system disorders	Hypersensitivity	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Infections and infestations	Administration site cellulitis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Anal abscess	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Appendicitis	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Biliary tract infection	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Biliary tract infection	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Cardiac infection	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Cellulitis	R-FC Lite	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Cystitis	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	Cystitis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Infections and infestations	Cytomegalovirus infection	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Cytomegalovirus infection reactivation	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Diverticulitis	R-CVP	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Infections and infestations	Escherichia infection	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Gastroenteritis	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	Gastroenteritis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Gastroenteritis viral	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Gastroenteritis viral	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Gastrointestinal bacterial overgrowth	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Haemophilus infection	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Infections and infestations	Herpes simplex pharyngitis	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Infection	R-CVP	1 (1)	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)
Infections and infestations	Infection	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Infections and infestations	Infection	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Infections and infestations	Influenza	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	Kidney infection	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Lower respiratory tract infection	R-CVP	0 (0)	4 (5)	5 (5)	0 (0)	1 (1)	0 (0)
Infections and infestations	Lower respiratory tract infection	R-FC Full	0 (0)	1 (1)	3 (3)	0 (0)	0 (0)	1 (1)
Infections and infestations	Lower respiratory tract infection	R-FC Lite	0 (0)	5 (6)	12 (14)	0 (0)	1 (1)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Infections and infestations	Neutropenic infection	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Neutropenic sepsis	R-CVP	1 (1)	1 (1)	7 (10)	3 (3)	0 (0)	1 (1)
Infections and infestations	Neutropenic sepsis	R-FC Full	0 (0)	1 (1)	4 (4)	2 (3)	0 (0)	0 (0)
Infections and infestations	Neutropenic sepsis	R-FC Lite	0 (0)	1 (1)	4 (4)	2 (2)	0 (0)	2 (2)
Infections and infestations	Pneumocystis jirovecii pneumonia	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Pneumocystis jirovecii pneumonia	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Pneumocystis jirovecii pneumonia	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Pneumonia	R-CVP	0 (0)	3 (3)	5 (6)	0 (0)	1 (1)	0 (0)
Infections and infestations	Pneumonia	R-FC Full	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Infections and infestations	Pneumonia	R-FC Lite	1 (1)	0 (0)	10 (11)	1 (1)	1 (1)	0 (0)
Infections and infestations	Pneumonia aspiration	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Infections and infestations	Pneumonia pneumococcal	R-CVP	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Infections and infestations	Postoperative wound infection	R-FC Lite	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Infections and infestations	Pyelonephritis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Sepsis	R-CVP	1 (1)	2 (2)	3 (3)	2 (2)	0 (0)	1 (1)
Infections and infestations	Sepsis	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Sepsis	R-FC Lite	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Infections and infestations	Sinusitis	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Tooth abscess	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Infections and infestations	Upper respiratory fungal infection	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Upper respiratory tract infection	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Upper respiratory tract infection	R-FC Full	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	Upper respiratory tract infection	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Urinary tract infection	R-CVP	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	1 (1)
Infections and infestations	Urinary tract infection	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Urinary tract infection	R-FC Lite	0 (0)	0 (0)	4 (4)	0 (0)	0 (0)	0 (0)
Infections and infestations	Urosepsis	R-CVP	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	Urosepsis	R-FC Lite	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Infections and infestations	Viral infection	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations	Viral labyrinthitis	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Fall	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Injury, poisoning and procedural complications	Fall	R-FC Lite	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Femoral neck fracture	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Femur fracture	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Femur fracture	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Injury, poisoning and procedural complications	Humerus fracture	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Infusion related reaction	R-CVP	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Infusion related reaction	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Infusion related reaction	R-FC Lite	1 (1)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	Spinal compression fracture	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	Blood electrolytes abnormal	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	Blood magnesium decreased	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	Clostridium test positive	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Investigations	Liver function test abnormal	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Investigations	Liver function test abnormal	R-FC Full	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Investigations	Lymphocyte count decreased	R-CVP	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Metabolism and nutrition disorders	Cachexia	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	Dehydration	R-FC Full	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	Hyperglycaemia	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	Hyperglycaemia	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Metabolism and nutrition disorders	Hyponatraemia	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	Type 2 diabetes mellitus	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Arthralgia	R-CVP	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Arthritis	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Musculoskeletal and connective tissue disorders	Back pain	R-CVP	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Greater trochanteric pain syndrome	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Interspinous osteoarthritis	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	Osteonecrosis	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma pancreas	R-CVP	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	B-cell lymphoma	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	R-FC Full	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	R-FC Lite	1 (1)	2 (2)	2 (3)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder transitional cell carcinoma	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cervix carcinoma	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Chronic lymphocytic leukaemia transformation	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Chronic lymphocytic leukaemia transformation	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Endometrial adenocarcinoma	R-CVP	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Follicular lymphoma	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Follicular lymphoma	R-FC Full	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer	R-FC Full	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive ductal breast carcinoma	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Invasive lobular breast carcinoma	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung adenocarcinoma	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome	R-FC Full	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Myelodysplastic syndrome	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	R-CVP	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroendocrine carcinoma of the skin	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Oesophageal carcinoma	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma	R-FC Full	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	R-FC Lite	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Renal cell carcinoma	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	R-FC Lite	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of lung	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of skin	R-FC Lite	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Thymoma	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Carotid artery aneurysm	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Cerebrovascular accident	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Nervous system disorders	Dizziness	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Headache	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Loss of consciousness	R-CVP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Nervous system disorders	Peripheral motor neuropathy	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Polyneuropathy	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Presyncope	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Nervous system disorders	Radiculopathy	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Tonic clonic movements	R-CVP	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Transient ischaemic attack	R-CVP	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	Transient ischaemic attack	R-FC Full	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Psychiatric disorders	Confusional state	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	Personality change	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders	Pollakiuria	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders	Ureteric obstruction	R-FC Lite	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive system and breast disorders	Ovarian mass	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Asthma	R-CVP	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Bronchiectasis	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Cough	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	R-FC Full	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
Respiratory, thoracic and mediastinal disorders	Dyspnoea	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	R-FC Full	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	R-FC Lite	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pneumonitis	R-FC Lite	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	R-FC Full	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	R-FC Lite	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pulmonary mass	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	Rash	R-FC Lite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Skin and subcutaneous tissue disorders	Skin lesion	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	Hypotension	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Vascular disorders	Lymphocele	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	Orthostatic hypotension	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	Orthostatic hypotension	R-FC Lite	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)

			Grade [No. Patients (No. Events)]					
SOC Name	**PT Name**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5**	**Missing**
1. Squamous Proliferative lesion - Viral Aetiology 2. Actinic Keratosis	SOC and PT missing therefore AE description shown in SOC	R-CVP	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify. Overall diagnosis of Acute Myeloid Leukaemia with G2 anaemia and G1 fatigue. Bone marrow trephine taken 08/OCT/2014 52% blasts.	SOC and PT missing therefore AE description shown in SOC	R-FC Full	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
metastatic adenocarcinoma of unknown origin	SOC and PT missing therefore AE description shown in SOC	R-CVP	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

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Table 19-4 By-Patient SUSARs Line Listing – R-CVP

SAE Number	Age at Onset	Sex	Randomisation Date	Onset Date	Offset Date	SOC Name	PT Name	Grade	Outcome
194-2-0-5/1	72	Female	19MAR2010	10APR2010	22APR2010	Hepatobiliary disorders	Hepatitis	2	Resolved with sequelae
178-2-0-39/1	70	Female	30NOV2010	13DEC2010	17DEC2010	General disorders and administration site conditions	Pyrexia	1	Resolved
194-2-0-59/4	81	Female	05APR2011	27MAY2011	.	Infections and infestations	Lower respiratory tract infection	5	Death
194-2-0-59/5	81	Female	05APR2011	04APR2011	11APR2011	Infections and infestations	Pneumonia	3	Resolved
155-2-0-64/1	76	Female	13APR2011	28APR2011	03MAY2011	General disorders and administration site conditions	Pyrexia	1	Resolved
155-2-0-64/4	77	Female	13APR2011	24JUL2012	30JUL2012	Infections and infestations	Neutropenic sepsis	4	Resolved with sequelae
338-1-0-119/1	71	Female	09FEB2012	31JAN2014	15SEP2014	Infections and infestations	Anal abscess	3	Not resolved/ongoing
1-2-1-126/1	74	Male	20MAR2012	19MAY2012	21JUN2012	Infections and infestations	Pneumonia	3	Resolved
14-2-0-148/1	75	Male	09JUL2012	01SEP2014	05SEP2014	Respiratory, thoracic and mediastinal disorders	Pulmonary mass	3	Resolved with sequelae
168-1-0-228/3	72	Female	28OCT2013	26JUN2014	.	Infections and infestations	Pneumonia pneumococcal	4	Not resolved/ongoing
82-2-0-256/1	65	Male	21FEB2014	02JUN2014	.	Infections and infestations	Neutropenic sepsis	1	Not resolved/ongoing
142-2-0-308/2	73	Female	15OCT2014	17OCT2016	20OCT2016	Infections and infestations	Gastroenteritis	2	Resolved
194-0-0-327/1	84	Female	12FEB2015	06JUN2015	09JUN2015	Infections and infestations	Pneumonia	3	Not resolved/ongoing
46-2-0-331/1	61	Male	19FEB2015	03MAR2015	17MAR2015	Musculoskeletal and connective tissue disorders	Arthralgia	3	Resolved with sequelae

SAE Number	Age at Onset	Sex	Randomisation Date	Onset Date	Offset Date	SOC Name	PT Name	Grade	Outcome
82-2-0-359/1	77	Female	16OCT2015	02DEC2015	15DEC2015	Injury, poisoning and procedural complications	Fall	Missing	Resolved with sequelae

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Table 19-5 By-Patient SUSARs Line Listing – R-FC Full

SAE Number	Age at Onset	Sex	Randomisation Date	Onset Date	Offset Date	SOC Name	PT Name	Grade	Outcome
194-1-0-6/1	59	Male	30MAR2010	24OCT2010	27OCT2010	Metabolism and nutrition disorders	Type 2 diabetes mellitus	2	Resolved
350-2-0-12/2	69	Female	03JUN2010	04NOV2011	17NOV2011	Infections and infestations	Neutropenic sepsis	4	Resolved
350-2-0-12/3	69	Female	03JUN2010	02DEC2011	15DEC2011	Infections and infestations	Neutropenic sepsis	4	Resolved
350-2-0-12/1	69	Female	03JUN2010	11JUL2011	26JUL2011	Infections and infestations	Pneumocystis jirovecii pneumonia	3	Resolved
114-2-0-18/1	71	Female	07JUL2010	11JUL2010	12JUL2010	General disorders and administration site conditions	Pyrexia	1	Resolved
194-0-0-21/1	58	Male	16AUG2010	13SEP2010	16SEP2010	Metabolism and nutrition disorders	Dehydration	2	Resolved
711-2-0-38/1	72	Male	18NOV2010	14OCT2011	29OCT2011	Infections and infestations	Neutropenic sepsis	3	Resolved
185-1-0-58/2	66	Male	14MAR2011	16JUL2012	23JUL2012	Infections and infestations	Infection	Missing	Resolved with sequelae
350-2-1-76/1	71	Female	24MAY2011	12JUL2012	24AUG2012	Infections and infestations	Gastrointestinal bacterial overgrowth	3	Resolved with sequelae
350-2-1-76/1	70	Female	24MAY2011	26MAY2011	27MAY2011	Gastrointestinal disorders	Nausea	2	Resolved
711-1-0-81/2	68	Male	23JUN2011	28DEC2011	06JAN2012	Infections and infestations	Upper respiratory fungal infection	3	Resolved with sequelae
711-1-0-81/1	68	Male	23JUN2011	14SEP2011	.	Blood and lymphatic system disorders	Pancytopenia	3	Not resolved/ongoing

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Table 19-6 By-Patient SUSARs Line Listing – R-FC Lite

SAE Number	Age at Onset	Sex	Randomisation Date	Onset Date	Offset Date	SOC Name	PT Name	Grade	Outcome
194-2-0-138/1	84	Female	09MAY2012	09JUL2013	01AUG2013	Infections and infestations	Pneumocystis jirovecii pneumonia	3	Resolved
113-2-1-152/1	76	Female	12JUL2012	14JUN2013	26JUN2013	Cardiac disorders	Pericardial effusion	3	Not resolved/ongoing
98-2-0-171/1	73	Male	01NOV2012	17MAR2014	.	Respiratory, thoracic and mediastinal disorders	Pneumonitis	4	Death
132-2-0-179/2	67	Male	18DEC2012	16APR2013	19JUN2013	Gastrointestinal disorders	Ascites	2	Resolved
132-2-0-179/3	67	Male	18DEC2012	03SEP2013	.	Gastrointestinal disorders	Ascites	1	Not resolved/ongoing
132-2-0-179/1	67	Male	18DEC2012	27FEB2013	02MAR2013	Infections and infestations	Upper respiratory tract infection	3	Resolved
46-2-0-181/2	62	Male	04JAN2013	04JUL2015	09JUL2015	Infections and infestations	Pneumonia	3	Resolved
294-1-0-185/1	76	Female	18JAN2013	08OCT2013	17DEC2013	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	3	Resolved with sequelae
49-2-0-190/4	66	Male	12FEB2013	03NOV2013	.	Infections and infestations	Lower respiratory tract infection	3	Not resolved/ongoing
294-1-1-201/2	55	Female	15MAY2013	15JAN2015	27JAN2015	Nervous system disorders	Peripheral motor neuropathy	3	Resolved
120-1-0-221/1	66	Female	23SEP2013	27SEP2013	28SEP2013	Nervous system disorders	Presyncope	Missing	Resolved
338-2-0-224/2	64	Female	17OCT2013	25DEC2013	27DEC2013	Infections and infestations	Cellulitis	3	Not resolved/ongoing
347-2-0-239/1	67	Female	07JAN2014	11MAR2015	.	Infections and infestations	Lower respiratory tract infection	3	Not resolved/ongoing
347-2-0-239/2	67	Female	07JAN2014	14APR2015	.	Infections and infestations	Lower respiratory tract infection	3	Not resolved/ongoing

SAE Number	Age at Onset	Sex	Randomisation Date	Onset Date	Offset Date	SOC Name	PT Name	Grade	Outcome
82-2-0-252/2	68	Female	14FEB2014	10AUG2016	.	Respiratory, thoracic and mediastinal disorders	Bronchiectasis	Missing	Not resolved/ongoing
364-1-0-263/1	66	Male	13MAR2014	16APR2014	17APR2014	Immune system disorders	Drug hypersensitivity	2	Resolved
364-1-0-263/1	68	Male	13MAR2014	23JUL2015	.	Infections and infestations	Lower respiratory tract infection	3	Not resolved/ongoing
142-2-0-269/1	75	Male	29APR2014	01AUG2014	.	Infections and infestations	Sepsis	3	Not resolved/ongoing
102-2-0-274/3	92	Male	20JUN2014	11JAN2017	.	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Second primary malignancy	4	Not resolved/ongoing
183-2-1-306/1	70	Female	08OCT2014	28JUN2016	08JUL2016	Infections and infestations	Gastroenteritis	3	Resolved
132-2-0-307/3	79	Male	14OCT2014	15MAR2016	23APR2017	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	Missing	Death
82-1-0-309/1	74	Male	16OCT2014	22APR2015	28APR2015	Infections and infestations	Neutropenic sepsis	3	Resolved
118-1-0-317/3	77	Female	09JAN2015	06JUL2016	.	Infections and infestations	Neutropenic sepsis	Missing	Missing
711-1-0-326/1	74	Female	05FEB2015	14MAY2015	.	General disorders and administration site conditions	Fatigue	3	Not resolved/ongoing
355-2-0-345/1	82	Female	14MAY2015	05DEC2018	.	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	3	Not resolved/ongoing
349-2-0-367/1	79	Male	21MAR2016	13JUN2017	16JUN2017	Infections and infestations	Tooth abscess	3	Resolved with sequelae

Location of code file: S:\Statistical Documents\Trials\PACIFICO\12. Closed documents\5.12 Final Analysis\5.12.1 Data and Analysis\Code\27 - Safety.sas

20 Final Statistical Analysis Report Lay Summary

This phase III randomised controlled trial (RCT) compared two different chemoimmunotherapy induction regimens in older people with previously untreated, symptomatic, advanced-stage follicular lymphoma. The standard arm consisted of 8 cycles of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP), given every 3 weeks. The experimental arm comprised 4 cycles of rituximab, fludarabine and cyclophosphamide (R-FC) followed by 4 cycles of rituximab alone, given every 4 weeks. Patients who achieved a complete or partial response then received rituximab maintenance every 8 weeks for up to 12 doses. Two key protocol changes were made during the course of the study: (1) rituximab was switched from the intravenous to subcutaneous route of administration (except for the first dose); and (2) the fludarabine and cyclophosphamide components of the R-FC regimen were spread over 4 rather than 3 days with an overall dose reduction of 17.5% and 36%, respectively. Prophylaxis with co-trimoxazole (or equivalent) was mandated in all patients receiving R-FC, together with acyclovir in those with a prior episode of herpes zoster. Patients were followed up for a minimum of 6 months after completion of all treatment, with assessments for response at the end of induction and for progression, toxicity and quality-of-life (QoL) throughout the study. Reporting of serious adverse events (SAEs) was mandated until 28 days after the last day of treatment, except for grade 3-4 infections and neoplasms where reporting requirements were extended to 6 months post treatment and the end of follow-up, respectively.

369 patients were enrolled at 80 UK sites between October 2009 and April 2016, with 185 randomised to R-FC and 184 to R-CVP. Within the R-FC group, 53 patients were allocated to full-dose R-FC (fdR-FC) and 132 to dose-attenuated R-FC (daR-FC). The R-CVP, fdR-FC and daR-FC cohorts were well balanced for age (median 75, 75 and 76.5), sex (female in 54%, 53% and 55%), FLIPI (high in 64%, 68% and 64%) and co-morbidity (CIRS >6 in 19%, 17% and 20%). However, more patients in the fdR-FC group had a WHO performance score of 0 (fully fit) compared to the daR-FC group (64% vs 36%), illustrating a shift in the profile of enrolled patients towards lower fitness levels following the switch from fdR-FC to daR-FC. Following randomisation, one patient was found to be ineligible, and another withdrew consent, leaving 367 patients in the intention-to-treat (ITT) population.

95%, 92% and 89% of patients in R-CVP, fdR-FC and daR-FC cohorts completed the first 4 cycles of induction, while 83%, 74% and 76% completed all 8 cycles. The mean (±SD) number of induction cycles administered in the respective cohorts was 7.4 (1.6), 6.9 (1.9) and 7.1 (1.9), while the total number of cycles administered (including maintenance) was 16.4 (5.7), 14.5 (6.5) and 14.9 (6.1).

The co-primary outcomes were progression-free survival (PFS) and grade 3-4 infections. The probability of being alive and progression free among all 369 patients randomised to R-FC vs R-CVP was 71% vs 72% at 4 years and 61% vs 42% at 8 years, with KM curves diverging after ~4 years. However, the difference did not reach statistical significance irrespective of whether a non-stratified [HR 0.80 (95% CI: 0.58, 1.11); P 0.188] or stratified [0.65 (0.40, 1.05); P=0.077] Cox PH model was used. Since there was evidence of non-proportionality in the Cox model, further analysis was performed using Restricted Mean Survival Time (RMST). However, there was no difference in the RMST ratio [1.05 (95% CI: 0.95, 1.17)].

Subgroup analysis showed broadly similar findings in patients with low, intermediate or high FLIPI scores, and in those with more (CIRS >6) or less (CIRS ≤6) comorbidity. Notably, separation of PFS curves for R-FC vs R-CVP was only evident among the 261 patients who were randomised after the switch from fdR-FC to daR-FC [HR 0.7 (95% CI: 0.46, 1.05); P=0.08], with no discernible difference among the 103 patients who were randomised before this switch [1.03 (95% CI: 0.59, 1.82); P=0.911].

There was no significant difference in the proportion of patients experiencing at least one grade 3-4 infection [risk ratio: 1.11 (95% CI: 0.80, 1.55); P=0.617] or in the occurrence of such infections [odds ratio: 1.16 (95% CI: 0.73, 1.83)]. Subgroup analysis showed broadly similar findings in patients who were randomised before or after the switch from fdR-FC to daR-FC, in those with low, intermediate or high FLIPI scores, and in those with more (CIRS >6) or less (CIRS ≤6) comorbidity.

Secondary outcomes included overall survival (OS), time to next treatment (TNT), high-grade transformation (HGT), anatomical response, response duration and analysis of frailty and comorbidity. There was no difference in OS between R-FC and R-CVP [HR: 1.04 (95% CI: 0.71, 1.52); P=0.842], the probability of remaining alive being 85% vs 78% at 4 years and 65% vs 60% at 8 years. In contrast, TNT was significantly longer for R-FC compared to R-CVP [HR 0.5 (95% CI: 0.33, 0.71); P=0.001], the probability of remaining free of second-line lymphoma treatment being 84% vs 72% at 4 years and 80% vs 58% at 8 years. Rates of HGT were similar for R-FC (5%) and R-CVP (4%).

There was a significant difference in PFS between R-FC and R-CVP by patients classified as ≥3 in the Vulnerable Elders Survey [HR: 0.28 (95% CI: 0.09, 0.86); P=0.018] and ≥4 in the Groningen Frailty Index [HR: 0.47 (95% CI: 0.23, 0.94); P=0.028].

Among the 298 patients who were evaluable for response, overall response (OR) rates for R-FC and R-CVP were 97% vs 99%, respectively, with complete response (CR) rates of 42% vs 39%. Response duration was significantly longer for R-FC compared to R-CVP [HR 0.48 (95% CI: 0.29, 0.79); P=0.004], the probability of remaining progression free being 89% vs 79% at 4 years and 86% vs 65% at 8 years.

Among the 366 patients who received at least one treatment dose, more SAEs of all grades were reported following R-FC compared to R-CVP (243 vs 178). SAE rates for fdR-FC, daR-FC CVP and R-CVP were 1.5, 1.3 and 1.0, respectively, with fatal SAEs occurring in 5/52 (9.6%), 4/130 (3.1%) and 4/178 (2.2%) patients, respectively. The most common SAEs in patients receiving R-FC or R-CVP were infections (102 vs 71) and neoplasms (35 vs 16) which together accounted for 53% of all SAEs. The most common infections were lower respiratory (43 vs 22) and neutropenic sepsis (18 vs 16), while the most common neoplasms were non-melanoma skin cancers (16 vs 1). Regarding SAEs of special interest, there were three reports of Pneumocystis jirovecii pneumonia (one each with fdR-FC, daR-FC and R-CVP), two of cytomegalovirus reactivation (both with fdR-FC), and five of myelodysplasia (three with fdR-FC, one each with daR-FC and R-CVP). Regarding supportive care, red-cell transfusions were administered to 3% patients in the R-CVP cohort, 13% in the fdR-FC cohort and 8% in the daR-FC cohort. The corresponding rates for immunoglobulin infusions were 1%, 6% and 5%, while those for granulocyte colony stimulating factor (G-CSF) administration were 21%, 34% and 34%.

QoL scores obtained with EORTC QLQ-C30, EQ-5D-3L and EQ-VAS questionnaires were similar for R-CVP and R-FC. This suggests that any reduction in QoL due to the higher toxicity of R-FC compared to R-CVP was balanced by an improvement in QoL due to the longer remissions obtained.

Conclusion: R-FC was superior to R-CVP in terms of TNT, response duration and long-term QoL. R-FC was also associated with greater supportive care requirements and more SAEs, especially lower respiratory infections and non-melanoma skin cancers. Despite having a lower level of fitness, patients in the daR-FC cohort experienced significantly fewer SAEs compared to the fdR-FC cohort, with a fatal SAE rate only 1% higher than for R-CVP. Failure of the longer TNT associated with R-FC to translate into a statistically significant PFS advantage may be explained by the relatively high background death rate in this elderly population with a commensurate narrowing of the difference in proportional hazard. This, together with the effectiveness of subsequent therapies, may also explain the lack of a demonstrable OS advantage. In summary, daR-FC is a highly effective treatment option in follicular lymphoma with an acceptable safety profile, even in an elderly population. The flattening of KM plots

for TNT and response duration after ~5 years is unexpected and indicates that responses induced by R-FC may be extremely durable, potentially amounting to a function cure, in a significant proportion of patients.