The CAPER study: A Phase Ib clinical trial of Cyclophosphamide And Pembrolizumab in metastatic Renal cell carcinoma (CAPER Trial)

2018-004314-17

Trial registration No.: ISRCTN 95900287

Final Statistical Analysis Report

Version 1.0 01/05/2024

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Jessica Green Ella Brayshaw	Ella Brayshaw	Dr Ashley Jones
Title	Trial Statistician	Trial Statistician	Lead Statistician
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3 Recruitment

3.1 Screening summary

Table 3-1 Screening summary by centre

Centre (code)	Assessed for eligibility [N] N	Eligible [a] n (%)	Ineligible [b] n (%)	Not registered [c] n (%)	Registered [d] n (%)
Addenbrooke's Hospital (Cambridge) (2)	3	3 (100%)	0 (0%)	1 (33.3%)	2 (66.7%)
The Christie (Manchester) (1)	7	7 (100%)	0 (0%)	0 (0%)	7 (100%)
TOTAL	**10**	**10 (100%)**	**0 (0%)**	**1 (10%)**	**9 (90%)**

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Table 3-2 Calculating percentages for Table 3-1

Percentages	Equation
Percent eligible	a/N
Percent ineligible	b/N
Percent not registered	c/a
Percent registered	d/a

Table 3-3 Reasons for ineligibility

Not applicable. No patients assessed for eligibility were ineligible.

Table 3-4 Reasons for not being registered

Centre (code)	No. not registered	Reason for not being registered:
		R1 n (%)
Addenbrooke's Hospital (Cambridge) (2)	1	1 (100%)
TOTAL	**1**	**1 (100%)**

Note: percentages will be calculated using [a] as the denominator
R1= Went out of trial window due to CAPER lab closure over Christmas

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3.2 Registration

Table 3-5 Registration details for recruiting centres

Centre (code)	Date of centre opening	Date of first registration	Date of last registration	Date centre closed	Total number registered
The Christie (Manchester) (1)	26/01/2021	19/05/2021	05/07/2022	28/04/2023	7
Addenbrooke's Hospital (Cambridge) (2)	29/04/2021	26/05/2021	08/11/2022	28/04/2023	2
Western General Hospital (Edinburgh) (3)	22/10/2021	N/A	N/A	28/04/2023	0
Royal Marsden Hospital (London) (4)	17/06/2021	N/A	N/A	28/04/2023	0
TOTAL					**9**

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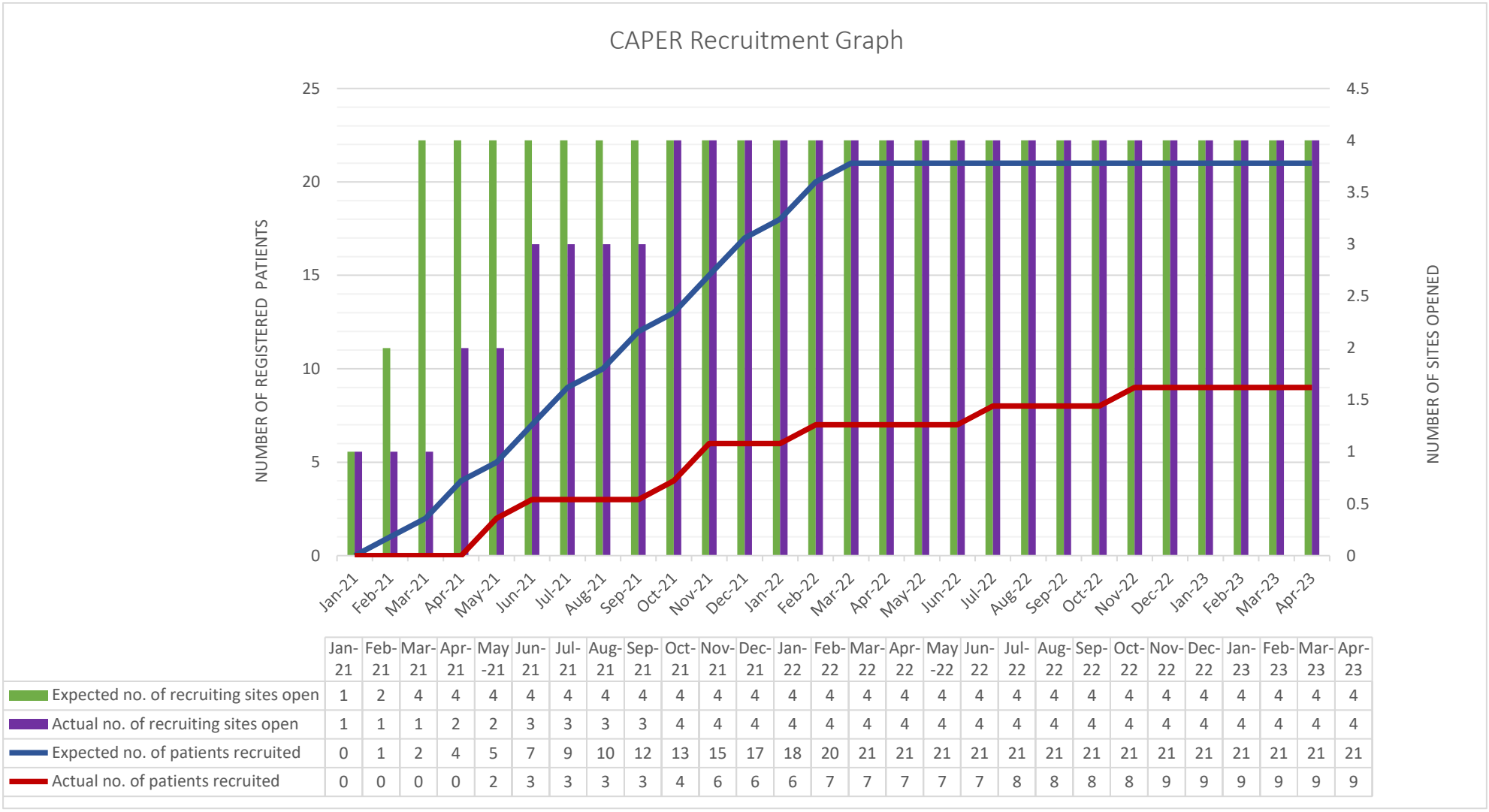
3.3 Recruitment graph

Figure 3-1 Recruitment graph



	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23
Expected no. of recruiting sites open	1	2	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Actual no. of recruiting sites open	1	1	1	2	2	3	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Expected no. of patients recruited	0	1	2	4	5	7	9	10	12	13	15	17	18	20	21	21	21	21	21	21	21	21	21	21	21	21	21	21
Actual no. of patients recruited	0	0	0	0	2	3	3	3	3	4	6	6	6	7	7	7	7	7	8	8	8	8	9	9	9	9	9	9

4 Serious breaches

There have been no serious breaches.

5 Completeness of follow-up

Figure 4-1 CONSORT flow diagram

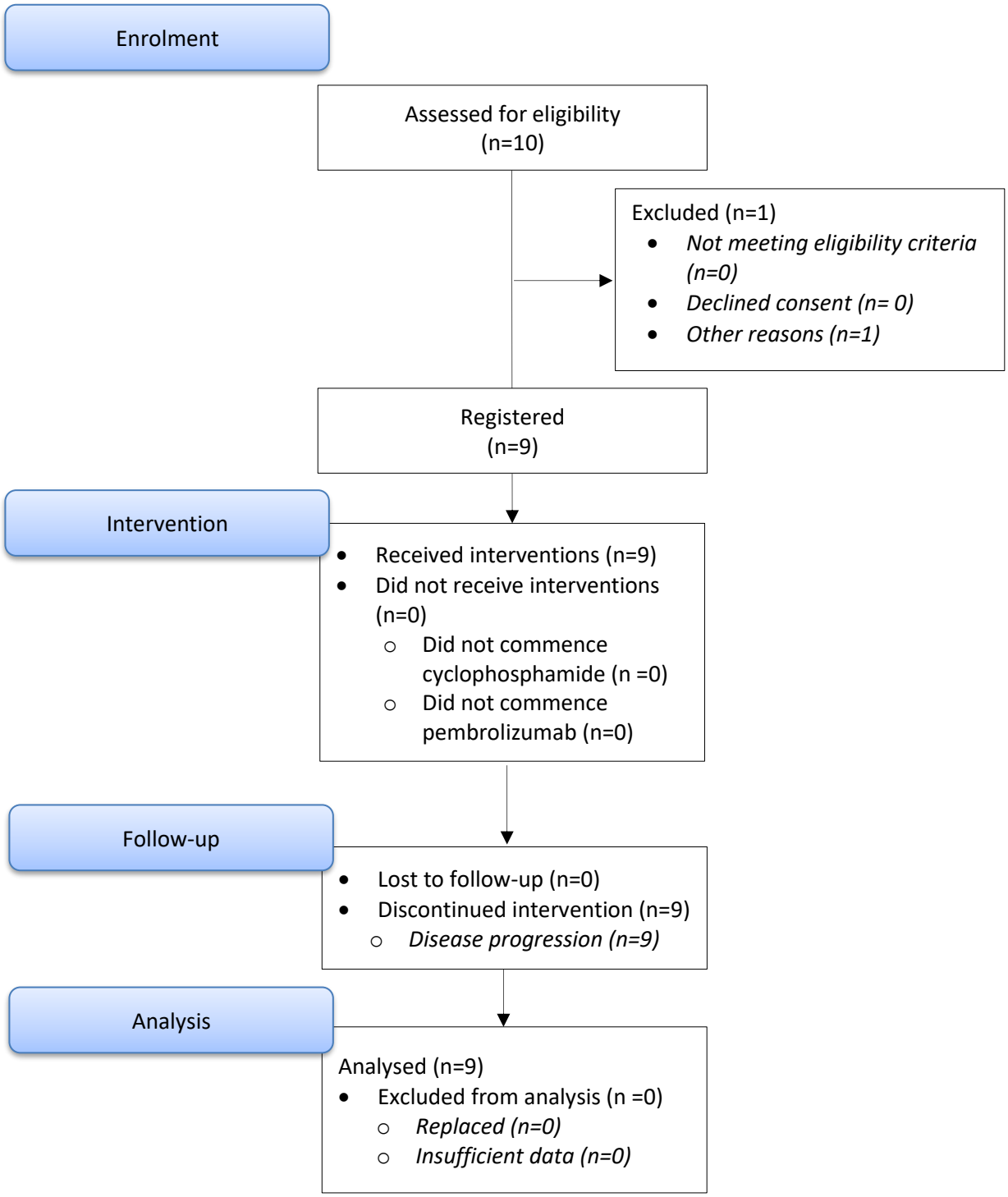


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Table 5-1 Details of participants who were withdrawn and replaced

Not applicable. No participants were withdrawn and replaced.

Table 5-2 Reasons for discontinuation of treatment or withdrawal from follow-up

Discontinuation number	Type of discontinuation	Time to discontinuation of treatment (days)	Time to withdrawal from follow-up (days)	Reason for discontinuation of treatment	Reason for withdrawal from follow-up
1	Treatment	127	N/A	Disease Progression	N/A
2	Treatment	80	N/A	Disease Progression	N/A
3	Treatment	104	N/A	Disease Progression	N/A
4	Treatment	492	N/A	Disease Progression	N/A
5	Treatment	63	N/A	Disease Progression	N/A
6	Treatment	135	N/A	Disease Progression	N/A
7	Treatment	260	N/A	Disease Progression	N/A
8	Treatment	23	N/A	Disease Progression	N/A
9	Treatment	79	N/A	Disease Progression	N/A

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Table 5-3 Summary of discontinuations of treatment and withdrawals from follow-up

		Total
Discontinued treatment		9 (100.0%)
Reason for discontinuation	Disease Progression	9 (100.0%)
Withdrew from follow-up		0 (0.0%)
Reasons for withdrawal	Withdrawal of consent	0 (0.0%)
	Loss to follow-up	0 (0.0%)

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6 Baseline characteristics

Table 6-1 Demographic details

		Total
Age (years)	n	9
	Mean (SD)	64.1 (9.0)
	Median (IQR)	67.0 (61.0, 71.0)
	Range	(48.0, 75.0)
Age (years): n (%)		(N=9)
	18 to 64 years	4 (44.4)
	65 to 84 years	5 (55.6)
Gender: n (%)		(N=9)
	Male	7 (77.8)
	Female	2 (22.2)
Ethnicity: n (%)		(N=9)
	White: British	7 (77.8)
	Any other White background	1 (11.1)
	Asian or Asian British: Indian	1 (11.1)
Ethnicity (reduced): n (%)		(N=9)
	White	8 (88.9)
	Asian or Asian British	1 (11.1)
Smoking status: n (%)		(N=9)
	Current smoker	1 (11.1)
	Ex-smoker	6 (66.7)
	Never smoked	2 (22.2)
Number of years smoking	n	7
	Mean (SD)	21.1 (14.2)
	Median (IQR)	20.0 (10.0, 30.0)
	Range	(5.0, 45.0)
Number of cigarettes/day	n	7
	Mean (SD)	12.4 (9.9)
	Median (IQR)	10.0 (4.0, 20.0)
	Range	(4.0, 30.0)
Alcohol status: n (%)		(N=9)
	Regular	2 (22.2)
	Sporadic	4 (44.4)
	None	3 (33.3)

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Table 6-2 Baseline vital signs

		Total
Height (cm)	n	9
	Mean (SD)	169.8 (9.8)
	Median (IQR)	170.0 (162.0, 176.0)
	Range	(156.0, 182.0)
Weight (kg)	n	9
	Mean (SD)	84.5 (19.2)
	Median (IQR)	81.5 (73.9, 91.3)
	Range	(60.0, 124.0)
Systolic blood pressure (mmHg)	n	9
	Mean (SD)	132.7 (8.0)
	Median (IQR)	136.0 (123.0, 139.0)
	Range	(122.0, 142.0)
Diastolic blood pressure (mmHg)	n	9
	Mean (SD)	75.1 (5.8)
	Median (IQR)	76.0 (71.0, 77.0)
	Range	(67.0, 84.0)
Temperature (°C)	n	9
	Mean (SD)	36.5 (0.5)
	Median (IQR)	36.5 (36.2, 37.0)
	Range	(35.5, 37.1)
Respiratory rate (breaths per minute)	n	9
	Mean (SD)	15.9 (2.3)
	Median (IQR)	16.0 (14.0, 18.0)
	Range	(12.0, 19.0)
Pulse rate (beats per minute)	n	9
	Mean (SD)	81.0 (9.8)
	Median (IQR)	80.0 (78.0, 84.0)
	Range	(66.0, 98.0)
Oxygen saturation (%)	n	9
	Mean (SD)	97.3 (1.5)
	Median (IQR)	97.0 (97.0, 98.0)
	Range	(95.0, 100.0)

ECOG performance status: n (%)		(N=9)
	0	6 (66.7)
	1	3 (33.3)
Physical exam (abnormal sites)[a]: n (%)		(N=9)
	General appearance	1 (11.1)
	Skin	1 (11.1)
	Extremities	1 (11.1)
	Cardiovascular	0 (0.0)
	Respiratory	0 (0.0)
	Gastrointestinal	0 (0.0)
	Neurological	0 (0.0)
	Musculoskeletal	0 (0.0)
	Other	1 (11.1)

[a] *More than one site could be marked as abnormal.*

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Table 6-3 Baseline haematological data

		Total
Haemoglobin (g/L)	n	9
	Mean (SD)	135.3 (7.5)
	Median (IQR)	138.0 (132.0, 142.0)
	Range	(123.0, 143.0)
White blood cell count (x10^9/L)	n	9
	Mean (SD)	9.5 (1.5)
	Median (IQR)	9.1 (8.6, 10.9)
	Range	(7.4, 11.6)
Platelets (x10^9/L)	n	9
	Mean (SD)	295.4 (79.3)
	Median (IQR)	286.0 (268.0, 369.0)
	Range	(173.0, 402.0)
Red blood cell count (x10^9/L)	n	9
	Mean (SD)	4.9 (0.4)
	Median (IQR)	4.8 (4.5, 5.0)
	Range	(4.5, 5.4)
Haematocrit (L/L)	n	9
	Mean (SD)	0.4 (0.0)

	Median (IQR)	0.4 (0.4, 0.4)
	Range	(0.4, 0.4)
Absolute neutrophil count (x10^9/L)	n	9
	Mean (SD)	6.8 (1.4)
	Median (IQR)	6.4 (5.8, 8.2)
	Range	(4.9, 8.4)
Eosinophils (x10^9/L)	n	9
	Mean (SD)	0.2 (0.1)
	Median (IQR)	0.2 (0.2, 0.2)
	Range	(0.1, 0.4)
Basophils (x10^9/L)	n	9
	Mean (SD)	0.0 (0.0)
	Median (IQR)	0.0 (0.0, 0.0)
	Range	(0.0, 0.1)
Lymphocytes (x10^9/L)	n	9
	Mean (SD)	1.8 (0.4)
	Median (IQR)	2.0 (1.6, 2.0)
	Range	(1.1, 2.3)
Monocyte levels (x10^9/L)	n	9
	Mean (SD)	0.5 (0.2)
	Median (IQR)	0.5 (0.3, 0.7)
	Range	(0.3, 0.7)
Prothrombin time (seconds)	n	9
	Mean (SD)	11.7 (0.9)
	Median (IQR)	11.5 (11.1, 11.9)
	Range	(10.7, 13.5)
Activated Partial Thromboplastin Time (seconds)	n	9
	Mean (SD)	26.9 (3.5)
	Median (IQR)	26.2 (24.8, 29.4)
	Range	(20.9, 32.2)
INR	n	9
	Mean (SD)	1.0 (0.1)
	Median (IQR)	1.0 (1.0, 1.0)
	Range	(0.9, 1.2)

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Table 6-4 Baseline biochemistry data

		Total
Sodium (mmol/L)	n	9
	Mean (SD)	136.9 (2.0)
	Median (IQR)	137.0 (136.0, 138.0)
	Range	(133.0, 139.0)
Potassium (mmol/L)	n	9
	Mean (SD)	4.6 (0.4)
	Median (IQR)	4.5 (4.2, 4.9)
	Range	(4.1, 5.1)
Urea (mmol/L)	n	9
	Mean (SD)	6.5 (3.0)
	Median (IQR)	5.9 (5.1, 6.7)
	Range	(3.7, 14.0)
Creatinine (µmol/L)	n	9
	Mean (SD)	98.4 (22.7)
	Median (IQR)	109.0 (74.0, 114.0)
	Range	(65.0, 120.0)
GFR (ml/min)	n	9
	Mean (SD)	68.0 (21.5)
	Median (IQR)	58.0 (54.0, 87.5)
	Range	(44.0, 101.0)
	Missing	1
Calcium – unadjusted (mmol/L)	n	9
	Mean (SD)	2.4 (0.2)
	Median (IQR)	2.3 (2.3, 2.5)
	Range	(2.2, 2.6)
Magnesium (mmol/L)	n	9
	Mean (SD)	0.8 (0.1)
	Median (IQR)	0.8 (0.8, 0.9)
	Range	(0.6, 0.9)
Phosphate (mmol/L)	n	9
	Mean (SD)	1.1 (0.2)
	Median (IQR)	1.0 (1.0, 1.2)
	Range	(0.9, 1.3)
Bilirubin (µmol/L)	n	9

	Mean (SD)	7.4 (4.0)
	Median (IQR)	6.0 (5.0, 8.0)
	Range	(5.0, 17.0)
Alkaline phosphatase (IU/L)	n	9
	Mean (SD)	98.9 (23.4)
	Median (IQR)	98.0 (93.0, 103.0)
	Range	(56.0, 148.0)
Alanine aminotransferase (ul/L)	n	9
	Mean (SD)	25.2 (17.6)
	Median (IQR)	21.0 (14.0, 30.0)
	Range	(9.0, 68.0)
Lactate dehydrogenase (IU/L)	n	9
	Mean (SD)	183.1 (31.9)
	Median (IQR)	183.0 (163.0, 195.0)
	Range	(133.0, 246.0)
Total protein (g/L)	n	9
	Mean (SD)	70.1 (3.1)
	Median (IQR)	69.0 (69.0, 73.0)
	Range	(65.0, 74.0)
Albumin (g/L)	n	9
	Mean (SD)	42.2 (3.6)
	Median (IQR)	44.0 (41.0, 44.0)
	Range	(34.0, 46.0)
Glucose (mmol/L)	n	9
	Mean (SD)	9.2 (5.8)
	Median (IQR)	6.1 (5.4, 16.0)
	Range	(2.8, 17.3)

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Table 6-5 Baseline thyroid function

		Total
Free T4 (mmol/L)	n	9
	Mean (SD)	16.4 (3.1)
	Median (IQR)	15.1 (14.0, 19.4)
	Range	(12.0, 21.0)
	n	9

Thyroid stimulating hormone (mIU/L)	Mean (SD)	2.6 (1.4)
	Median (IQR)	2.0 (1.7, 4.1)
	Range	(1.0, 4.5)

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Table 6-6 Baseline urinalysis

		Total
Specific gravity	n	9
	Mean (SD)	114.2 (339.7)
	Median (IQR)	1.0 (1.0, 1.0)
	Range	(1.0, 1020.0)
pH	n	9
	Mean (SD)	6.0 (0.6)
	Median (IQR)	6.0 (6.0, 6.0)
	Range	(5.0, 7.0)
Protein: n (%)		(N=9)
	Negative	9 (100)
Glucose: n (%)		(N=9)
	Negative	6 (66.7)
	Positive	3 (33.3)
Blood: n (%)		(N=9)
	Negative	4 (44.4)
	Trace	4 (44.4)
	Positive	1 (11.1)
Nitrites: n (%)		(N=9)
	Negative	9 (100)

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Table 6-7 Baseline disease factors

		Total
Time from initial diagnosis to registration (days)	n	9
	Mean (SD)	2589.6 (1630.3)
	Median (IQR)	2389.0 (1138.0, 3715.0)
	Range	(587.0, 5153.0)
	n	9

Time from metastatic disease confirmation to registration (days)	Mean (SD)	1728.9 (1344.8)
	Median (IQR)	1138.0 (916.0, 2649.0)
	Range	(573.0, 4562.0)
Site(s) of metastases[1]: n (%)		(N=9)
	Bone	2 (22.2)
	Liver	2 (22.2)
	Lymph Nodes	2 (22.2)
	Lungs	5 (55.6)
	Other	6 (66.7)
Presence of sarcomatoid component: n (%)		(N=9)
	Yes	1 (11.1)
	No	7 (77.8)
	Missing	1 (11.1)
Percentage that is sarcomatoid component (%)	n	1
	Mean (SD)	-
	Median (IQR)	-
	Range	-
	Not known	1
Current TNM Stage: n (%)		(N=9)
	TX/NX/M1	1 (11.1)
	TX/N0/M1	2 (22.2)
	TX/N1/M1	2 (22.2)
	T1/N0/M1	1 (11.1)
	T3/NX/M1	1 (11.1)
	T4/N0/M1	1 (11.1)
	T4/N1/M1	1 (11.1)
Fuhrman Grade: n (%)		(N=9)
	2	1 (11.1)
	3	3 (33.3)
	4	4 (44.4)
	Missing	1 (11.1)
IMDC prognostic group classification: n (%)		(N=9)
	0	2 (22.2)
	1	2 (22.2)
	2	4 (44.4)
	3	1 (11.1)

Sum of lesion diameter (mm)	n	9
	Mean (SD)	94.7 (58.5)
	Median (IQR)	89.0 (62.0, 100.0)
	Range	(32.0, 232.0)

[1] *It is possible for the same participants to have metastases in more than one location.*

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Table 6-8 Previous treatment for RCC

		Total
Surgery for RCC: n (%)		(N=9)
	Yes	7 (77.8)
	No	2 (22.2)
Operation for RCC: n (%)		(N=7)
	Nephrectomy	6 (85.7)
	Metastasectomy	2 (28.6)
Site of operation for RCC: n (%)		(N=7)
	Kidney	3 (42.9)
	Bilateral adrenal glands	1 (14.3)
	Kidney and adrenal gland	1 (14.3)
	Left kidney	1 (14.3)
	Right forearm	1 (14.3)
	Right kidney	1 (14.3)
Radiotherapy for RCC: n (%)		(N=9)
	Yes	1 (11.1)
	No	8 (88.9)
Radiotherapy treatment site: n (%)		(N=1)
	Right 8th rib lesion	1 (100)
Systemic therapy for RCC: n (%)		(N=9)
	Yes	9 (100)
Drug received for systemic therapy: n (%)		(N=9)
	Nivolumab	8 (88.9)
	Ipilimumab	4 (44.4)
	Pazopanib	4 (44.4)
	Avelumab	1 (11.1)
	Axitinib	1 (11.1)
	High dose IL-2	1 (11.1)
	Sunitinib	1 (11.1)

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Table 6-9 Medical history (all conditions within bolded lines are for the same patient)

Condition number	Condition	Status	CTCAE grade of AE	Treatment ongoing
1-1	Hypertension	Continuing	2	Yes
1-2	Thromboembolic event	Continuing	N/A	Yes
2-1	Breast cancer	Resolved/ Asymptomatic	N/A	No
2-2	Total right knee replacement	Resolved/ Asymptomatic	N/A	No
2-3	Constipation	Continuing	2	Yes
2-4	Hypothyroidism	Resolved/ Asymptomatic	N/A	No
2-5	Pancreatitis	Resolved/ Asymptomatic	N/A	No
2-6	Gastroesophageal reflux disease	Continuing	1	Yes
2-7	Pain	Continuing	1	Yes
2-8	Bruising	Continuing	1	Yes
2-9	Thromboembolic event	Resolved/ Asymptomatic	N/A	No
2-10	Dyspnea	Continuing	1	Yes
2-11	Generalized muscle weakness	Continuing	1	Yes
2-12	Low bone density	Continuing	2	Yes
2-13	White coat hypertension	Continuing	1	Yes
3-1	Gastroesophageal reflux disease	Continuing	1	Yes
3-2	Insomnia	Continuing	1	Yes
3-3	Fatigue	Continuing	1	Yes
3-4	Flank pain	Continuing	1	Yes
3-5	Hypertension	Continuing	1	Yes
3-6	Anxiety	Continuing	1	Yes
3-7	Pruritus	Continuing	1	Yes
3-8	Anorexia	Resolved/ Asymptomatic	1	No
4-1	Groin Abscess	Resolved/ Asymptomatic	2	No

4-2	Hypertension	Continuing	2	Yes
4-3	Pain	Continuing	1	Yes
4-4	Type 1 Diabetes Mellitus	Continuing	2	Yes
4-5	High Blood Pressure	Continuing	2	Yes
5-1	Hypertension	Continuing	2	Yes
5-2	Atrial fibrillation	Continuing	2	Yes
5-3	Hypothyroidism	Continuing	2	Yes
6-1	Hypertension	Continuing	2	Yes
6-2	Myocardial infarction	Resolved/ Asymptomatic	3	No
6-3	Hypoadrenalism	Continuing	2	Yes
6-4	Hyperthyroidism	Continuing	2	Yes
7-1	Hypertension	Continuing	1	Yes
7-2	Abdominal pain	Continuing	1	Yes
7-3	Glaucoma	Continuing	1	Yes
8-1	Dizziness	Continuing	1	Yes
9-1	Nasal polypectomy	Resolved/ Asymptomatic	N/A	No

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Table 6-10 Baseline concomitant medication (all medications within bolded lines are for the same patient)

Concomitant medication number	Generic drug name	Indication	Dose (with units, frequency, route)	Treatment ongoing at start of treatment
1-1	Ramipril	Hypertension	10 mg/ Daily/ Po	Yes
1-2	Dalteparin	Pulmonary Embolus	15000 iu/ Daily/ SC	No
1-3	Rivaroxaban	Pulmonary embolism	15 mg/ Daily/ Po	No
1-4	Rivaroxaban	Pulmonary embolism	20 mg/ Daily/ Po	Yes
1-5	Ibuprofen	Chest discomfort	400 mg/ prn/ Po	No
1-6	Paracetamol	Chest discomfort	1 g/ prn/ Po	Yes
1-7	Lansoprazole	Stomach prophylaxis	30 mg/ Daily/ Po	Yes
1-8	Naproxen	Chest discomfort	500 mg/ bd/ Po	Yes
1-9	Naproxen	Chest discomfort	500 mg/ bd/ Po	Yes
1-10	Amoxicillin	Dental abscess	500 mg/ tid/ Po	No
1-11	Amoxicillin	Dental abscess	500 mg/ tid/ Po	No
2-1	Cosmocol	Constipation	2 sachets/ Daily/ Po	Yes
2-2	Lansoprazole	Gastro-oesophageal reflux disease	30 mg/ Daily/ Po	Yes
2-3	Metoclopramide	Gastro-oesophageal reflux disease	10 mg/ tid/ Po	Yes
2-4	Paracetamol	Pain	1 g/ prn/ Po	Yes
2-5	Fludrocortisone	Post-adrenalectomy	0.15 mg/ Daily/ Po	Yes
2-6	Prednisolone	Post-adrenalectomy	7.5 mg/ Daily/ Po	Yes
2-7	Alendronate	Low bone density	70 mg/ Daily/ Po	Yes
2-8	Senna	Constipation	1.5 tablets/ Daily/ Po	Yes
2-9	Lidocaine and hydrocortisone mouthwash	Mucositis	10 ml/ qid/ Other	Yes
2-10	Dexamethasone	Abdominal bloating	4 mg/ Daily/ Po	Yes
3-1	Bendruflume thiazide	Hypertension	2.5 mg/ Daily/ Po	Yes
3-2	Fluoxetine	Stress	20 mg/ Daily/ Po	Yes
3-3	Lansoprazole	Gastro oesophageal reflux	30 mg/ bd/ Po	Yes
3-4	Amitriptyline	Insomnia and pain	10 mg/ Daily/ Po	Yes
3-5	Metformin slow release	Diabetes	500 mg/ bd/ Po	Yes
3-6	Doxazosin	Hypertension	1 mg/ Daily/ Po	Yes
3-7	Diprobase	Rash	1 app/ prn/ Top	Yes
3-8	Gliclazide	Diabetes	80 mg/ bd/ Po	Yes

3-9	Dermovate	Pruritis	1 app/ prn/ Top	Yes
3-10	E45 cream	Pruritis	1 app/ prn/ Top	Yes
3-11	Sitagliptin	Diabetes	50 mg/ Daily/ Po	Yes
3-12	Pexofenadine	Pruritis	60 mg/ bd/ Po	Yes
3-13	Doxycycline	Lower respiratory tract infection	100 mg/ bd/ Po	No
3-14	Metoclopramide	Nausea	10 mg/ tid/ Po	Yes
3-15	Hydrocortisone	Rash	1 appt/ prn/ Po	Yes
3-16	Fexofenadine cream	Pruritis	60 mg/ tid/ Po	Yes
3-17	Fucidin	Pruritis	1 app/ tid/ Top	Yes
3-18	Insulin(levemir)	Diabetes	8 units/ Daily/ SC	Yes
4-1	Usinopril	High blood pressure	30 mg/ Daily/ Po	Yes
4-2	Metformin	Diabetes	500 mg/ bd/ Po	Yes
4-3	Novorapid	Diabetes	8 units/ prn/ SC	Yes
4-4	Atorvastatin	High cholesterol	40 mg/ Daily/ Po	Yes
4-5	Co codamol 30/500	Left sided abdominal pain	1-2 tabs/ prn/ Po	Yes
4-6	Tresiba	Diabetes	30 mg/ Daily/ SC	No
4-7	Metoclopramide	Nausea	10 mg/ prn/ Po	Yes
4-8	Tresiba	Diabetes	23 units/ Daily/ SC	Yes
4-9	Flucloxacillin	Abscess Left Buttock	250 mg/ tid/ Po	Yes
4-10	Amoxicillin	Lower respiratory tract infection	500 mg/ tid/ Po	No
4-11	Betnovate	Rash	n/a n/a/ bd/ Top	No
4-12	Co-amoxiclav	UTI	625 mg/ tid/ Po	No
4-13	Co-codamol	Flank pain/UTI	30 mg/ tid/ Po	No
4-14	Flucoxacillin	L buttock abscess	500 mg/ qid/ Po	No
4-15	Flucoxacillin	L buttock abscess	500 mg/ qid/ Po	No
4-16	Flucoxacillin	L buttock abscess	500 mg/ qid/ Po	No
4-17	Novorapid	Diabetes	12 units/ prn/ SC	Yes
5-1	Metformin	Diabetes	1 g/ Daily/ Po	Yes
5-2	Lansoprazole	Preventative	15 mg/ bd/ Po	Yes
5-3	Linagliptin	Diabetes	5 mg/ Daily/ Po	Yes
5-4	Bisoprolol	Hypertension	5 mg/ bd/ Po	Yes
5-5	Levothyroxine	Hypothyroidsm	75 mcg/ Daily/ Po	Yes
5-6	Loratidine	Prevention of rhinitis	10 mg/ Daily/ Po	Yes
5-7	Rivarxaban	Atrial fibrillation	20 mg/ Daily/ Po	Yes
5-8	Atorvastatin	Preventative	20 mg/ Daily/ Po	Yes

5-9	Digoxin	Atrial fibrillation	62.5 micrgrams/ Daily/ Po	Yes
5-10	Humulin insulin	Diabetes	* / Daily/ SC	Yes
5-11	Gliclazide	Diabetes	160 mg/ bd/ Po	Yes
5-12	Calcichew-D3	Calcium/vitamin D deficiency	1 tablet/ Daily/ Po	Yes
5-13	Terbinifine cream 1%	Fungal nail	1 application/ bd/ Top	Yes
6-1	GTN Spray	Myocardial Infarction	1 / prn/ Inhal	Yes
6-2	Aspirin	Prevention	75 mg/ Daily/ Po	Yes
6-3	Hydrocortisone	Hypothyroidism	10 mg/ bd/ Po	Yes
6-4	Levothyroxine	Hypothyroidism	50 mcg/ Daily/ Po	Yes
6-5	Loratadine	Nasal Congestion	* / Daily/ Po	Yes
6-6	Dymista Nasal Spray	Nasal Congestion	2 / bd/ Inhal	Yes
6-7	Lansaprazole	Gastric Protection	30 mg/ Daily/ Po	Yes
6-8	Tazocin	Urinary tract infection	4.5 g/ prn/ IV	No
6-9	Cefalexin	Urinary tract infection	500 mg/ tid/ Po	No
6-10	Paracetamol	Loin discomfort	1 g/ prn/ Po	Yes
6-11	Nitrofurantoin	Urinary tract infection	100 mg/ bd/ Po	No
6-12	Nitrofurantoin	Loin discomfort	100 mg/ bd/ Po	No
6-13	Calcichew	Hypocalcaemia	500 mg/ bd/ Po	Yes
6-14	Co-amoxyiclav	UTI and sinusitis	625 mg/ tid/ Po	Yes
7-1	Ramipril	Hypertension	5 MG/ Daily/ Po	Yes
7-2	Atorvastatin	Hypercholasteremia	20 mg/ Daily/ Po	Yes
7-3	Levothyroxine	Hypothyroidism	100 mg/ Daily/ Po	Yes
7-4	Adcal D3	Bone protection	1 tablet/ Daily/ Po	Yes
7-5	Denosumab	Bone protection	120 mg/ qod/ SC	Yes
7-6	Monopost	Glaucoma	1 drop/ Daily/ Po	Yes
7-7	Paracetamol	Neckpain	1 g/ prn/ Po	Yes
7-8	Covid vaccine	Vaccination	1 dose/ #/ IM	No
7-9	Lansoprazole	Leg pain	18 mg/ Daily/ Po	Yes
7-10	Pregabalin	Leg pain	50 mg/ Daily/ Po	Yes
7-11	Naproxen	Leg pain	500 mg/ bd/ Po	Yes
7-12	Diazepam	Leg pain	2 mg/ tid/ Po	Yes
8-1	Tamsulosin	Benign prostatic hyperplasia	400 mcg/ Daily/ Po	Yes
8-2	Finasteride	Benign prostatic hyperplasia	5 mg/ Daily/ Po	Yes
8-3	Omeprazole	Gastric protection	20 mg/ Daily/ Po	Yes

8-4	Dexamethasone	Brain metastases	16 mg/ bd/ Po	Yes
9-1	Hydrocortisone	Physiological replacement	10 mg/ Daily/ Po	Yes
9-2	Hydrocortisone	Physiological replacement	20 mg/ Daily/ Po	Yes

* Dose missing
# Frequency missing

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\11 - Concomitant Medications V1.0.sas"

7 Study population

Table 7-1 Datasets analysed

Population	Total
Screened	10
Registered	9
Intention-to-treat	9 (100.0%)
Safety	9 (100.0%)

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8 Protocol deviations

Table 8-1 Line listing of protocol deviations (all deviations within bolded lines are for the same patient)

Deviation number	Deviation type	Deviation details
1-1	Major: Safety	Safety follow up not performed within 30 days
1-2	Minor: translational	Sample 6 (streck tube) for patient [ID redacted] cycle 12 was missed in error
2-1	Minor: translational	Patient [ID redacted], biopsy at cycle 2 was taken after pembrolizumab administration due to an out-of-range INR value
3-1	Major: Treatment regime	Cyclophosphamide compliance was not checked
3-2	Major: Treatment regime	Cyclophosphamide compliance was not checked
3-3	Major: Administration of wrong treatment or incorrect dose etc	Patient [ID redacted] missed 1 cyclophosphamide dose in error prior to cycle 5
3-4	Major: Other - IMP Issue	Patient [ID redacted], cycle 7 was outside of protocol defined +/- 3-day window. Cycle 6 pembrolizumab administration was on [Date redacted] and cycle 7 was on [Date redacted]
3-5	Major: Patient Management/Assessment - Patient examination/Test	Patient [ID redacted], pulse and O2 saturation at safety follow are not available for patient therefore can't confirm if performed.

4-1	Major: Patient Management/Assessment - Blood Results	Patient [ID redacted] cycle 4 no glucose result available therefore can't confirm test was performed
5-1	Major: Safety	SAEs not monitored as per protocol
5-2	Major: Safety	AESIs not reported as per protocol
5-3	Major: Patient Management/Assessment - Patient examination/Test	Patient [ID redacted], all haematology, biochemistry and thyroid tests were not tested during safety follow up
6-1	Major: Safety	Safety follow up not performed within 30 days
6-2	Major: Safety	SAEs not monitored as per protocol
6-3	Major: Safety	AESIs not reported as per protocol
7-1	Major: Treatment regime	Cyclophosphamide compliance was not checked
7-2	Minor: translational	Site asked whether cycle 1 bloods could be omitted for patient [ID redacted] due to scheduling difficulties as patient can only come in on Friday and this would mean research blood samples would not be able to be processed. CI was informed and approved as these are duplicate baseline
7-3	Minor: translational	Site contacted as site as patient [ID redacted] cycle 3 research blood samples would not be collected due to scheduling issues and patient only being able to attend on a Friday. This would mean that research bloods would not be able to be processed
7-4	Minor: translational	Cycle 5 research bloods were not collected for patient [ID redacted] as patient was having cataract surgery
7-5	Minor: Patient examination/test	For patient [ID redacted], Physical Examinations for cycle 1, cycle 2, cycle 3, cycle 4, cycle 5, cycle 6 and follow up were not completed. AE assessments were completed.
7-6	Minor: translational	End of treatment/discontinuation research blood samples were not taken for patient [ID redacted]
7-7	Minor: Patient examination/test	During the early discontinuation visit the urinalysis and temperature for vital signs were not performed for patient [ID redacted]

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\22b - Protocol Deviations V1.0.sas"

Table 8-2 Summary of protocol deviations

	Events n	**Patients n (%)**
Protocol deviation	22	7 (77.8%)
Major deviation	14	6 (66.7%)
Safety	6	3 (33.3%)
Deviation from patient management	3	3 (33.3%)

	Events n	Patients n (%)
Treatment regime	3	2 (22.2%)
Received wrong treatment/incorrect dose	1	1 (11.1%)
Other	1	1 (11.1%)
Minor deviation	8	3 (33.3%)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\22b - Protocol Deviations V1.0.sas"

9 Compliance with intervention

Table 9-1 Reasons treatment(s) not commenced

Not applicable. All participants commenced treatment.

Table 9-2 Reasons for premature discontinuation of intervention

Premature discontinuation number	Treatment(s) discontinued	Cyclophosphamide		Pembrolizumab	
		Number of cycles completed	Reason for discontinuing	Number of cycles completed	Reason for discontinuing
1	Cyclophosphamide and Pembrolizumab	5	Disease Progression	4	Disease Progression
2	Cyclophosphamide and Pembrolizumab	24	Disease Progression	23	Disease Progression
3	Cyclophosphamide and Pembrolizumab	4	Disease Progression	3	Disease Progression
4	Cyclophosphamide and Pembrolizumab	7	Disease Progression	6	Disease Progression
5	Cyclophosphamide and Pembrolizumab	13	Disease Progression	12	Disease Progression
6	Cyclophosphamide and Pembrolizumab	2	NON treatment-related event	1	NON treatment-related event
7	Cyclophosphamide and Pembrolizumab	4	Disease Progression	3	Disease Progression
8	Cyclophosphamide and Pembrolizumab	6	Disease Progression	5	Disease Progression
9	Cyclophosphamide and Pembrolizumab	4	Disease Progression	3	Disease Progression

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\13 - Compliance with Intervention V2.0.sas"

Table 9-3 Details of missed cyclophosphamide doses (all cycles within bolded lines are for the same patient)

Missed cyclophosphamide dose number	Cycle number	Number of tablets missed	Reason for missed doses
1-1	4	14	Progressive disease
2-1	5	4	Hospitalisation
2-2	6	1	Patient error
2-3	7	15	Progressive disease
3-1	13	15	Progressive disease
4-1	2	7	Disease progression
5-1	4	14	Potential disease progression

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\13 - Compliance with Intervention V2.0.sas

Table 9-4 Details of modified pembrolizumab infusions (all cycles within bolded lines are for the same patient)

Modified pembrolizumab infusion number	Cycle number	Dose (mg)	Dose interrupted?	Reason for dose interruption	Dose delayed?	Reason for dose delay	Length of dose delay (days)
1-1	19	200	No	N/A	Yes	Patient holiday	7
2-1	6	200	No	N/A	Yes	Patient was on holiday	7
3-1	2	200	No	N/A	Yes	Deferred two weeks due to holiday	14

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Table 9-5 Summary of treatment received

	Total
Cyclophosphamide	
Participants who completed at least one cycle	9 (100%)
Cycles completed	(N = 9)
N	9
Mean (SD)	7.7 (6.9)
Median (IQR)	5.0 (4.0, 7.0)
Range	(2.0, 24.0)
Participants who missed at least one tablet	5 (55.6%)

Cycles with missed tablets		(N = 5)
	N	5
	Mean (SD)	1.4 (0.9)
	Median (IQR)	1.0 (1.0, 1.0)
	Range	(1.0, 3.0)
Tablets/cycle missed		(N = 7)
	N	7
	Mean (SD)	10.0 (5.9)
	Median (IQR)	14.0 (4.0, 15.0)
	Range	(1.0, 15.0)
Pembrolizumab		
Participants who completed at least one cycle		9 (100%)
Cycles completed		(N = 9)
	N	9
	Mean (SD)	6.7 (6.9)
	Median (IQR)	4.0 (3.0, 6.0)
	Range	(1.0, 23.0)
Participants who received <200mg in at least one cycle		0 (0%)
Cycles with dose <200mg		(N = 0)
	N	-
	Mean (SD)	-
	Median (IQR)	-
	Range	-
Dose/cycle (where dose <200mg)		(N = 0)
	N	-
	Mean (SD)	-
	Median (IQR)	-
	Range	-
Participants whose dose was interrupted in at least one cycle		0 (0%)
Cycles with dose interrupted		(N = 0)
	N	-
	Mean (SD)	-
	Median (IQR)	-
	Range	-

Participants whose dose was delayed in at least one cycle		3 (5%)
Cycles with dose delayed		(N = 3)
	N	3
	Mean (SD)	1.0 (0)
	Median (IQR)	1.0 (1.0, 1.0)
	Range	(1.0, 1.0)
Days/delay		(N = 3)
	N	3
	Mean (SD)	9.3 (4)
	Median (IQR)	7.0 (7.0, 14.0)
	Range	(7.0, 14.0)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\13 - Compliance with Intervention V2.0.sas

10 Outcome Data

10.1 Primary outcome – Objective response as per RECIST

10.1.1 Primary analysis

Table 10-1 Best overall response by participant

Response number	Best response	Time until best response first achieved (days)
1	Stable Disease (SD)	59
2	Stable Disease (SD)	63
3	Stable Disease (SD)	64
4	Stable Disease (SD)	64
5	Stable Disease (SD)	64
6	Stable Disease (SD)	64
7	Progressive Disease (PD)	36
8	Progressive Disease (PD)	62
9	Progressive Disease (PD)	78

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\14 - PO Objective Response as per RECIST V1.0.sas"

Table 10-2 Summary of best overall responses

Outcome	Total
Progressive Disease (PD)	3 (33.3%)
Stable Disease (SD)	6 (66.7%)

Partial Response (PR)	0 (0.0%)
Complete Response (CR)	0 (0.0%)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\14 - PO Objective Response as per RECIST V1.0.sas"

Table 10-3 Duration of stable disease

		Total
Stable disease duration[1] (days)	n	6
	Mean (SD)	203.0 (159.0)
	Median (IQR)	130.0 (120.0, 253.0)
	Range	(80.0, 505.0)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\26 - Stable Disease Duration V1.0.sas"

Table 10-4 Objective response rate

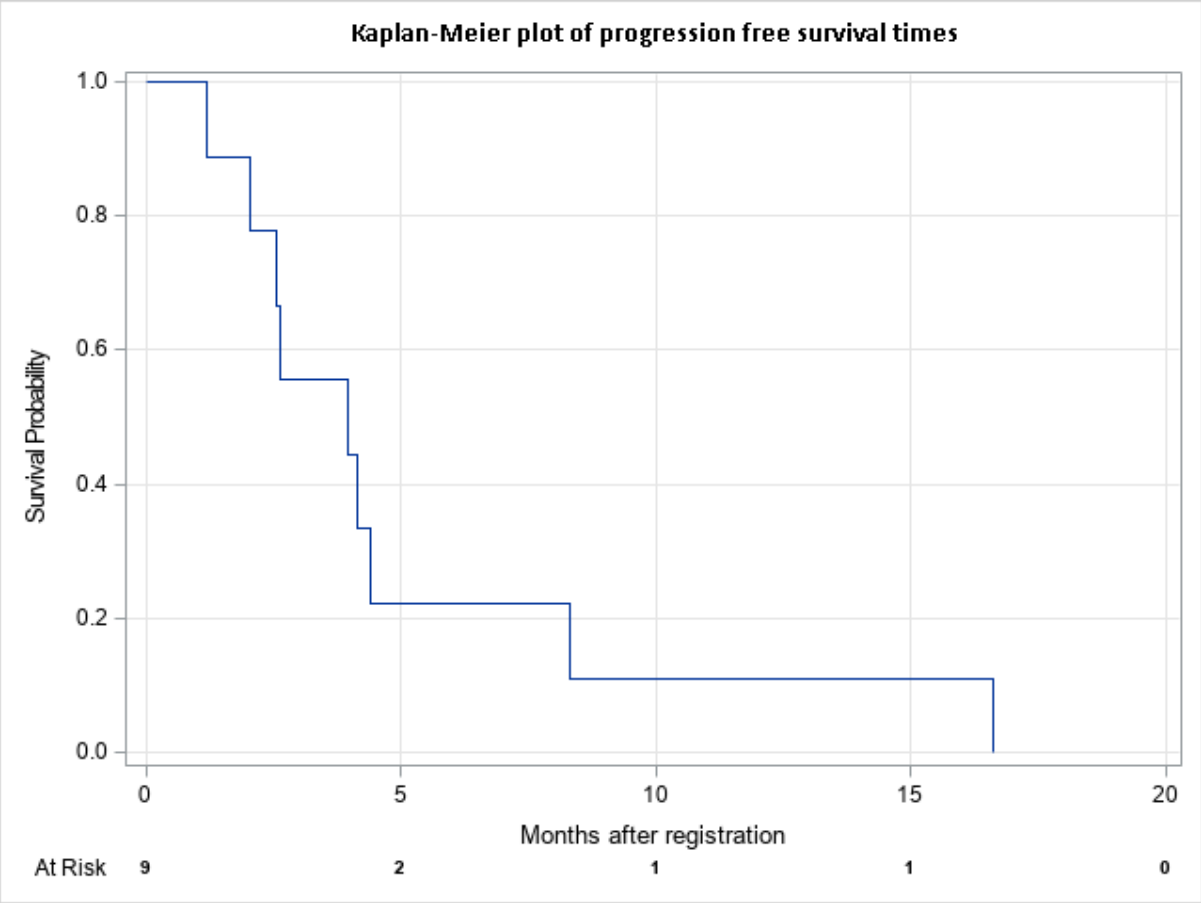
Number of participants registered and not replaced	**Number achieving objective response (OR)**	**OR rate (80% CI)**
9	0	0.0 (N/A)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\14 - PO Objective Response as per RECIST V1.0.sas"

[1] For one patient, their first follow-up scan response was stable disease. However, they had declined clinically so they were removed from treatment and did not have any further follow-up scans. The date they were taken off treatment (date of clinical progressive disease) has been taken as their date of progressive disease.

10.2 Secondary outcome 1 – Progression free survival

Figure 10-1 Kaplan Meier plot of progression free survival times



Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\16 - SO1 Progression Free Survival V2.0.sas"

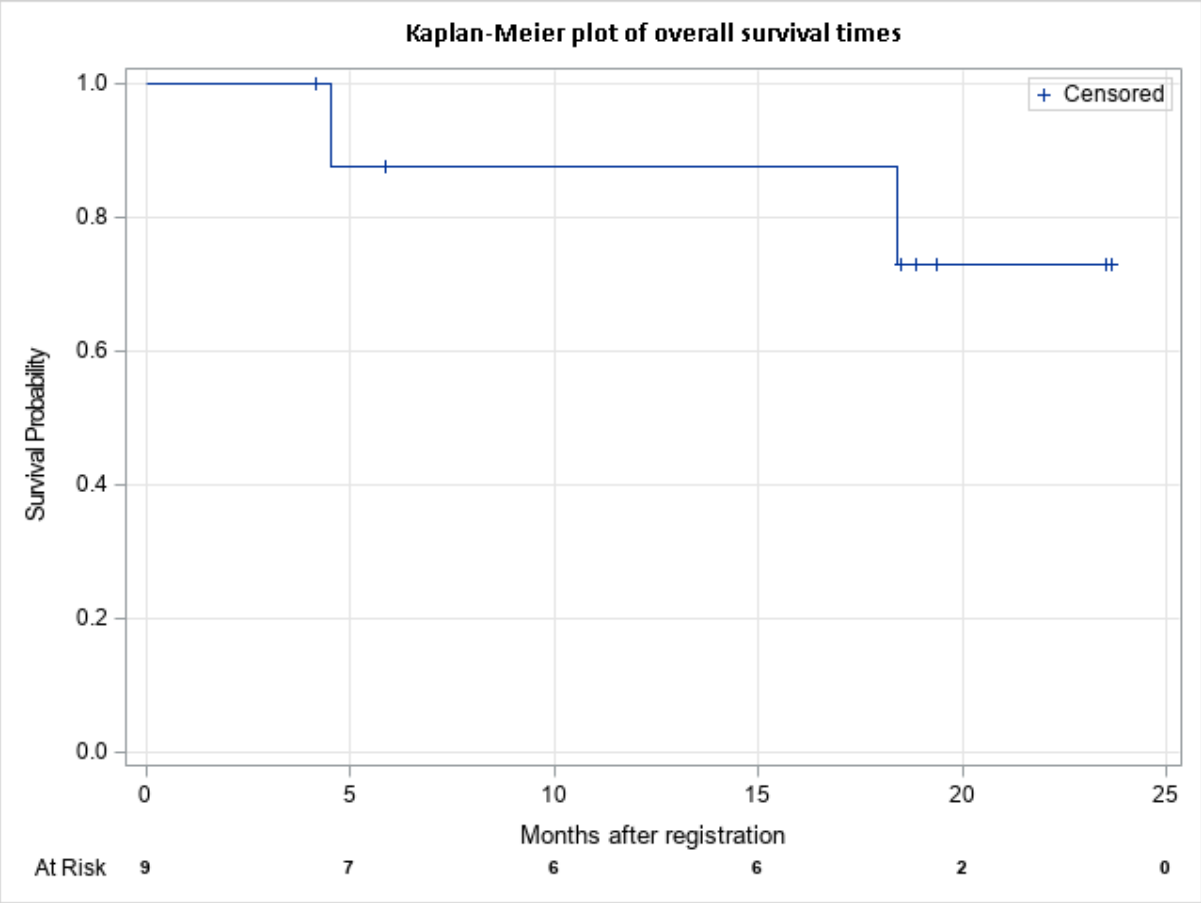
Table 10-5 Progression free survival times

Number of ppts registered and not replaced	Number of ppts who progressed[1]	Median progression free survival time (95% CI)	12-month progression free survival (95% CI)
9	9	3.9 (1.2, 8.3)	0.1 (0.0, 0.4)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\16 - SO1 Progression Free Survival V2.0.sas"

10.3 Secondary outcome 2 – Overall survival

Figure 10-2 Kaplan Meier plot of overall survival times



Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\17 - SO2 Overall Survival V1.0.sas"

Table 10-6 Overall survival times

Number of ppts registered and not replaced	Number of ppts who died	Median survival time in months (95% CI)	12-month survival (95% CI)
9	2	NA (4.5, NA)	0.9 (0.4, 1.0)

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\17 - SO2 Overall Survival V1.0.sas"

10.4 Secondary outcome 3 - Safety and tolerability

Table 10-7 Summary of SAEs and Grade 3+ toxicities

	Events **n**	**Patients** **n (%)**
SAEs	2	2 (22.2%)
Grade 3+ toxicities	0	0 (0.0%)
TOTAL	**2**	**2 (22.2%)**

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\20 - SO3 Safety and Tolerability V1.0.sas"

11 Safety Data

11.1 Non-serious adverse events

Table 11-1 Non-serious adverse events by CTCAE grade

CTCAE grade v5	Events n	Patients n (%)
1	40	8 (88.9%)
2	12	7 (77.8%)
3	0	0 (0.0)
4	0	0 (0.0)
5	0	0 (0.0)
TOTAL	**52**	**9 (100.0%)**

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\19b - Adverse Events V2.0.sas"

Table 11-2 Non-serious adverse events grouped by system organ class and preferred term by CTACE grade

System Organ Class	Preferred Term	CTCAE grade v5	Events n	Patients n (%)
Gastrointestinal disorders	Abdominal distension	1	1	0 (0.0%)
		2	1	1 (11.1%)
	Frequent bowel movements	1	1	1 (11.1%)
	Nausea	1	4	3 (33.3%)
		2	1	1 (11.1%)
	Chest discomfort	1	1	1 (11.1%)

General disorders and administration site conditions	Fatigue	1	4	3 (33.3%)
		2	1	1 (11.1%)
	Mucosal inflammation	1	1	1 (11.1%)
Infections and infestations	Abscess limb	1	1	0 (0.0%)
		2	1	1 (11.1%)
	COVID-19	1	1	1 (11.1%)
	Infection	2	1	1 (11.1%)
	Lower respiratory tract infection	1	1	1 (11.1%)
		2	1	1 (11.1%)
	Onychomycosis	1	1	1 (11.1%)
	Tooth abscess	2	1	1 (11.1%)
	Urinary tract infection	2	2	2 (22.2%)
Injury, poisoning and procedural complications	Procedural pain	1	2	1 (11.1%)
Investigations	Biopsy	1	2	2 (22.2%)
Metabolism and nutrition disorders	Decreased appetite	1	2	2 (22.2%)
	Hypercalcaemia	1	1	1 (11.1%)
	Hypocalcaemia	1	1	1 (11.1%)
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1 (11.1%)
	Back pain	1	2	2 (22.2%)
	Musculoskeletal pain	1	1	1 (11.1%)
	Neck pain	1	1	1 (11.1%)
		2	1	1 (11.1%)
Nervous system disorders	Hemiparesis	2	1	1 (11.1%)

	Neuralgia	1	1	1 (11.1%)
Psychiatric disorders	Affect lability	1	1	1 (11.1%)
	Insomnia	1	1	1 (11.1%)
	Irritability	1	1	1 (11.1%)
Respiratory, thoracic and mediastinal disorders	Cough	1	1	0 (0.0%)
		2	1	1 (11.1%)
	Epistaxis	1	1	1 (11.1%)
	Haemoptysis	1	1	1 (11.1%)
	Nasal congestion	1	1	1 (11.1%)
Skin and subcutaneous tissue disorders	Pruritus	1	2	1 (11.1%)
	Rash	1	1	1 (11.1%)
	TOTAL	**1**	**40**	**2 (22.2%)**
		2	**12**	**7 (77.8%)**

Note: Where patients have experienced more than one adverse event and more than one CTCAE grade for a preferred term, they have been reported in the most severe category for the patients column.

Created using: "S:\Statistical Documents\Trials\CAPER\Closed\Final Analysis\Version 1.0\Programs\25 - AE Summaries V1.0.sas"

Table 11-3 Line listing of all non-serious adverse events (all events within bolded lines are for the same patient, related events are given in bold)

AE number	System Organ Class	Preferred Term	Description	CTCAE grade v5	Relationship to pembrolizumab	Relationship to cyclophosphamide	Outcome
1-1	**General disorders and administration site conditions**	**Fatigue**	**Intermittent fatigue**	**1**	**Probable**	**Probable**	**Not resolved / ongoing**

1-2	Metabolism and nutrition disorders	Hypercalcaemia	Hypercalcaemia	1	Not related	Not related	Not resolved / ongoing
1-3	General disorders and administration site conditions	Chest discomfort	Chest discomfort	1	Not related	Not related	Not resolved / ongoing
1-4	Infections and infestations	Tooth abscess	Dental abscess	2	Not related	Not related	Not resolved / ongoing
2-1	**General disorders and administration site conditions**	**Fatigue**	**Fatigue**	**1**	**Not related**	**Probable**	**Change in severity**
2-2	**Gastrointestinal disorders**	**Nausea**	**Nausea**	**2**	**Not related**	**Probable**	**Resolved**
2-3	Respiratory, thoracic and mediastinal disorders	Epistaxis	Epistaxis	1	Unlikely	Unlikely	Resolved
2-4	**General disorders and administration site conditions**	**Mucosal inflammation**	**Mucositis**	**1**	**Unlikely**	**Probable**	**Resolved**
2-5	**Gastrointestinal disorders**	**Abdominal distension**	**Abdominal bloating**	**1**	**Possible**	**Unlikely**	**Change in severity**
2-6	**Gastrointestinal disorders**	**Frequent bowel movements**	**Increased stool frequency**	**1**	**Possible**	**Unlikely**	**Resolved**
2-7	**General disorders and administration site conditions**	**Fatigue**	**Fatigue**	**2**	**Not related**	**Probable**	**Not resolved / ongoing**
2-8	**Gastrointestinal disorders**	**Abdominal distension**	**Abdominal bloating**	**2**	**Possible**	**Unlikely**	**Not resolved / ongoing**

3-1	Infections and infestations	Lower respiratory tract infection	Lower respiratory tract infection	2	Not related	Not related	Resolved
3-2	Gastrointestinal disorders	Nausea	Nausea	1	Not related	Not related	Resolved
3-3	**Skin and subcutaneous tissue disorders**	**Pruritus**	**Pruritis**	**1**	**Possible**	**Not related**	**Not resolved / ongoing**
3-4	**Skin and subcutaneous tissue disorders**	**Pruritus**	**Pruritis**	**1**	**Probable**	**Not related**	**Not resolved / ongoing**
3-5	**Metabolism and nutrition disorders**	**Decreased appetite**	**Reduced appetite**	**1**	**Probable**	**Not related**	**Not resolved / ongoing**
3-6	Psychiatric disorders	Affect lability	Emotional Lability	1	Not related	Not related	Not resolved / ongoing
3-7	Psychiatric disorders	Insomnia	Insomnia	1	Not related	Not related	Not resolved / ongoing
3-8	Psychiatric disorders	Irritability	Irritability	1	Not related	Not related	Not resolved / ongoing
4-1	**Gastrointestinal disorders**	**Nausea**	**Nausea**	**1**	**Not related**	**Highly probable**	**Resolved**
4-2	Injury, poisoning and procedural complications	Procedural pain	Pain at site of biopsy	1	Not related	Not related	Resolved
4-3	Gastrointestinal disorders	Nausea	Intermittent nausea	1	Not related	Not related	Resolved
4-4	Injury, poisoning and procedural complications	Procedural pain	Pain at site of biopsy	1	Not related	Not related	Resolved

4-5	Infections and infestations	Abscess limb	Abscess (left buttock)	1	Not related	Not related	Resolved
4-6	Infections and infestations	Lower respiratory tract infection	Lower respiratory tract infection	1	Not related	Not related	Resolved
4-7	Skin and subcutaneous tissue disorders	Rash	Rash	1	Not related	Not related	Resolved
4-8	Infections and infestations	Urinary tract infection	UTI / flank pain	2	Not related	Not related	Resolved
4-9	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Buttock pain (abscess)	1	Not related	Not related	Resolved with sequelae
4-10	Musculoskeletal and connective tissue disorders	Neck pain	Neck muscle ache	1	Not related	Not related	Resolved
4-11	Metabolism and nutrition disorders	Decreased appetite	Anorexia	1	Not related	Not related	Resolved
4-12	Infections and infestations	Abscess limb	Buttock abscess	2	Not related	Not related	Resolved
5-1	Infections and infestations	Onychomycosis	Fungal nail infection	1	Not related	Not related	Lost to follow up
5-2	Investigations	Biopsy	Protocol required biopsy	1	Not related	Not related	Resolved
6-1	Respiratory, thoracic and mediastinal disorders	Nasal congestion	Nasal congestion	1	Not related	Not related	Not resolved / ongoing
6-2	Musculoskeletal and connective tissue disorders	Back pain	Loin discomfort	1	Not related	Not related	Resolved

6-3	Infections and infestations	Urinary tract infection	Urinary tract infection	2	Not related	Not related	Resolved
6-4	General disorders and administration site conditions	Fatigue	Fatigue	1	Not related	Not related	Not resolved / ongoing
6-5	Metabolism and nutrition disorders	Hypocalcaemia	Hypocalcaemia	1	Not related	Not related	Not resolved / ongoing
6-6	Infections and infestations	Infection	Infection	2	Not related	Not related	Resolved
7-1	Respiratory, thoracic and mediastinal disorders	Cough	Cough	1	Not related	Not related	Resolved
7-2	**Gastrointestinal disorders**	**Nausea**	**Nausea (intermittent)**	**1**	**Not related**	**Highly probable**	**Not resolved / ongoing**
7-3	Respiratory, thoracic and mediastinal disorders	Cough	Cough	2	Not related	Not related	Not resolved / ongoing
7-4	Musculoskeletal and connective tissue disorders	Arthralgia	Knee pain	1	Not related	Not related	Resolved
7-5	Musculoskeletal and connective tissue disorders	Neck pain	Neck pain	2	Not related	Not related	Resolved
7-6	Respiratory, thoracic and mediastinal disorders	Haemoptysis	Heamoptysis	1	Not related	Not related	Resolved

7-7	Nervous system disorders	Neuralgia	Neuropathic leg pain	1	Not related	Not related	Not resolved / ongoing
8-1	Nervous system disorders	Hemiparesis	Left sided weakness	2	Not related	Not related	Not resolved / ongoing
9-1	Infections and infestations	COVID-19	COVID-19 infection	1	Not related	Not related	Resolved
9-2	Investigations	Biopsy	Abdomen biopsy	1	Not related	Not related	Resolved
9-3	Musculoskeletal and connective tissue disorders	Back pain	Back pain	1	Not related	Not related	Not resolved / ongoing
9-4	General disorders and administration site conditions	Fatigue	Fatigue	1	Not related	Not related	Not resolved / ongoing

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11.2 Serious adverse events

Table 11-4 Line listing of serious adverse events (all events within bolded lines are for the same patient, related events are given in bold)

SAE number	Diagnosis	Onset date	Reason for seriousness	CTCAE grade v5	MedDRA		Cyclophosphamide			Pembrolizumab			Most likely cause, if unrelated (PI assessment)	Outcome
							Relatedness			Relatedness				
					SOC	PT	Site assessment	MR assessment	Expectedness	Site assessment	MR assessment	Expectedness		
1-1	**Urinary tract infection**	**23/01/2022**	**Required hospitalisation**	**3**	**Infections and infestations**	**Urinary tract infection**	**Unrelated**	**Possibly**	**Expected**	**Unrelated**	**Unrelated**	**N/A**	**Patient's original condition**	**Resolved**
2-1	Pneumonia	03/04/2022	Required hospitalisation	3	Infections and infestations	Pneumonia	Unrelated	Unlikely	N/A	Unrelated	Unrelated	N/A	Patient's original condition	Resolved

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Table 11-5 Summary of SAEs

	Events n	Patients n (%)
TOTAL	**2**	**2 (22.2%)**
CTCAE grade		
1	0	0 (0.0)
2	0	0 (0.0)
3	2	2 (22.2%)
4	0	0 (0.0)
5	0	0 (0.0)
Infections and infestations		
Pneumonia	1	1 (11.1%)

	Urinary tract infection	1	1 (11.1%)
	TOTAL	2	2 (22.2%)
Reason for seriousness			
	Death	0	0 (0.0)
	Life-threatening	0	0 (0.0)
	Required hospitalisation	2	2 (22.2%)
	Prolonged hospitalisation	0	0 (0.0)
	Resulted in persistent/significant disability/incapacity	0	0 (0.0)
	Congenital anomaly or birth defect	0	0 (0.0)
	Other important medical event	0	0 (0.0)
AESIs			(N=9)
	New cancer not the condition under summary	0	0 (0.0)
	Overdose of study medication	0	0 (0.0)
	Elevated AST/ALT and elevated bilirubin and ALP less than 2xULN	0	0 (0.0)

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12 Lay Summary of Study Results

The CAPER trial aimed to study whether an old-fashioned tablet chemotherapy drug called Cyclophosphamide could help to improve the chances of a patient benefiting from modern drugs that try to boost the immune system to help fight cancer (called immunotherapy). 9 patients with incurable kidney cancer were recruited and all patients had previously received immunotherapy treatment and it had stopped working. Patients received 3 weeks of oral cyclophosphamide (taken as a daily tablet) initially before continuing this treatment alongside an immunotherapy drip called Pembrolizumab (intravenous treatment given every 3 weeks). The original plan for the trial was to recruit 21 patients but the trial was stopped early after 9 patients had been enrolled due to slow recruitment.

Amongst the 9 patients, 7 were men and the average age was 64. 6 patients had previously undergone surgery to remove the primary tumour on the kidney. 3 patients did not appear to derive any benefit from the treatment given within the trial, with growth of the cancer on the first CT scan in the trial. 6 patients had evidence of some benefit with the cancer being held stable for a period of time. The average length of time that the cancer was held stable amongst these 6 patients was for 203 days. 1 patient experienced the cancer being held stable for 505 days. None of the patients experienced shrinkage of the tumour in response to the trial treatment. The trial treatment was not associated with any unexpected or worrying side-effects – 8 out of 9 patients had mild (grade 1) or moderate (grade 2) side effects but no patients had any severe side-effects.

Biopsy samples from the tumour and extra blood samples were collected from patients during their participation in the trial. Work is now ongoing to look at these samples to see if it is possible to identify any features that may predict why some patients seemed to have a beneficial effect from the treatment and others didn't.

13 Mapping between report shell and SAP

This report has been created following the CAPER Statistical Analysis Plan V2.0 (dated 31/08/2023).

The following table lists changes from the SAP that are applicable to multiple items within the report.

Section/subsection of SAP	Changes from SAP
N/A	• In all line listings from Section 5 onwards, site/centre columns have been removed to prevent identifiability due to the small number of patients. • In all line listings when the same patient could appear across multiple rows, all information relating to the same patient has been presented within bolded lines. • A column specifying a number for each row has been added to each line listing to make the rows easier to identify.

	• The SAP does not specify how many decimal places to present to and the shell has inconsistent decimal places. To make it consistent everything has been presented to one decimal place.

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Table 13-1 Mapping between report shell and SAP

Section/subsection of SAP	**Item within report**	**Additional details (if required)**
Section 19: Disposition of patients	Figure 5-1: CONOSRT flow diagram	Changes from shell: In Figure 5-1, the reasons for discontinuing intervention have been changed to match the reasons on the CRF.
Section 19.1: Screening, eligibility and recruitment	Table 3-1: Screening summary by centre; Table 3-2: Calculating percentages for Table 3-1; Table 3-3: Reasons for ineligibility; Table 3-4: Reasons for not being registered; Table 3-5: Registration details for recruiting centres	Changes from shell: In Table 3-5, the Hospital name column has been removed as it is the same as the centre column.
Section 19.2: Post registration discontinuations	Table 5-1: Details of participants who were withdrawn and replaced; Table 5-2: Reasons for discontinuation of treatment or withdrawal from follow-up; Table 5-3: Summary of discontinuations of treatment and withdrawals from follow-up	Changes from shell: In Table 5-3, reasons for discontinuation have been changed to match those on the CRF.
Section 20: Protocol deviations	Table 8-1: Line listing of protocol deviations; Table 8-2: Summary of protocol deviations	Changes from shell: In Table 8-2, there are additional deviation types to reflect those that have been derived from the data based on the monitoring plan.
Section 22: Analysis datasets	Table 7-1: Datasets analysed	
Section 23: Baseline characteristics	Table 6-1: Demographic details; Table 6-2: Baseline vital signs; Table 6-3: Baseline haematological data; Table 6-4: Baseline biochemistry data; Table 6-5: Baseline thyroid function; Table 6-6: Baseline urinalysis; Table 6-7: Baseline disease factors; Table 6-8: Previous treatment for RCC; Table 6-9: Medical history; Table 6-10: Baseline concomitant medication;	Changes from shell: • In Tables 6-6, 6-7 and 6-8, n (%) has been added to the categorical variables to make it clear what is being presented. • In Table 6-7, days has been added to time from metastatic disease confirmation to registration to make it clear that the summary is in days.

Section 24: Compliance with interventions	Table 9-1: Reasons treatment(s) not commenced; Table 9-2: Reasons for premature discontinuation of intervention; Table 9-3: Details of missed cyclophosphamide doses; Table 9-4: Details of modified pembrolizumab infusions; Table 9-5: Summary of treatment received	
Section 25.2.2: Primary outcome	Table 10-1: Best overall response by participant; Table 10-2: Summary of best overall responses; Table 10-3: Duration of Stable Disease; Table 10-4 Objective response rate	Changes from shell: Table 10-4 added ad hoc following request by CI
Section 25.2.3.1: Progression free survival	Figure 10-1: Kaplan Meier plot of progression free survival times; Table 10-5: Progression free survival times	
Section 25.2.3.2: Overall survival	Figure 10-2: Kaplan Meier plot of overall survival times; Table 10-6: Overall survival times	
Section 25.2.3.3: Safety and tolerability	Table 10-7: Summary of SAEs and Grade 3+ toxicities	
Section 26: Safety evaluations	Table 11-1: Non-serious adverse events by CTCAE grade; Table 11-2 Non-serious adverse events grouped by system organ classed and preferred term by CTCAE grade; Table 11-3: Line listing of all non-serious adverse events; Table 11-4: Line listing of all SAES; Table 11-5: Summary of SAEs	Changes from shell: • Table 11-2 has been added ad hoc following request from CI to present toxicities in the format required for manuscripts. • In Table 11-3, an additional column has been added for the SOC and PT terms as adverse events have been Meddra coded in the database since V2.0 of the SAP was approved. An additional column has also been added for CTCAE grade so the line listing corresponds with the other non-serious AE tables. • In Table 11-3 and Table 11-4, related events have been bolded to make them easier to see.

14 Version history

Table 14-1 Version history

Updated shell version no.	Shell section changed	Description of change	Date changed	Initials
2.0	6	In vital signs table, blood pressure has been split into systolic and diastolic	31/08/2023	JG
2.0	11.2	Reason for seriousness and Meddra SOC and PT have been added to SAE line listing. Meddra SOC and PT term have been added to summary of SAEs table.	31/08/2023	RK