EORTC
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The future of cancer therapy

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Short Study Report for Regulatory Bodies

Name of Sponsor/Company: **EORTC**	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of the finished product: Opdivo and Yervoy	Volume:	
Name of Active Ingredient: Nivolumab, Ipilimumab	Page	
Title of the Study	Phase II trial in inoperable oesophageal cancer evaluating the feasibility of the combination of definitive chemoradiation with the immune checkpoint blockers Nivolumab +/- Ipilimumab (CRUCIAL) EudraCT:2018-000053-53 NCT03437200	
Investigators & Study Centres	Here is the list of sites which enrolled patients: Pr. Eric Deutsch, Gustave Roussy, 114 Rue Edouard Vaillant, 94805 Villejuif, France Dr. Jean-Priac Prevost, Centre Pierre Curie, 2 Rue Delbecque, 62660 Beuvry, France	
Publication (reference)	There was no publication for this study which was closed for poor accrual with a small number of patients registered.	
Phase of development	Phase 2	

Institution Name	Registration
Centre Pierre Curie	1
Gustave Roussy (CLCC)	7
Total	8

Studied period	Date of first enrolment: 24/06/2019 Date of last enrolment: 29/07/2020 Clinical cut-off date: 06/10/2022 Date of global end of Study: 06/10/2022
Substantial changes to the protocol	**Protocol v2.0 and PISIC v2.0:** amendment submitted in September 2018 taking into account several requests from competent authorities such as adaptation of in/exclusion criteria, updates in the IB/SmPC and toxicity management. **Protocol v3.0 and PISIC v3.0:** amendment triggered by requirement of German CA and updated information contained in the latest Nivolumab SmPC, as well as updates for contraceptive methods and protocol clarifications. **Protocol v4.0 and PISIC v4.0:** amendment triggered by updated information in the SmPCs of Ipilimumab and Nivolumab
Objective(s)	The primary objective of the trial is to assess the feasibility and the safety of the addition of immunotherapy with PD-1 antibody nivolumab +/- CTLA-4 antibody ipilimumab to concomitant chemoradiotherapy (CRT) in inoperable patients with early or locally advanced oesophageal cancer and to select the more promising experimental arm among the two possible combinations in terms of activity (based on PFS at 12 months according to RECIST v1.1) for further evaluation in a phase III trial. The secondary objectives will aim to evaluate: • progression-free survival • failure-free survival • pattern of first cause of progression (including incidence of distant metastasis) • overall survival.
Methodology	This is a phase 2, randomized, open label, multicentric study of nivolumab plus ipilimumab or nivolumab alone in combination with oxaliplatin plus fluorouracil plus radiotherapy in patients with early or locally advanced oesophageal cancer.

	After signing the informed consent form and upon confirmation of the patients' eligibility, patients will be randomized 1:1 to either the nivolumab-CRT arm (arm A) or the nivolumab-plus-ipilimumab-CRT arm (arm B). **Progression under nivolumab +/- ipilimumab treatment** If radiologic imaging shows progression of disease according to RECIST 1.1 before completing 1 year of treatment BUT the patient appears to have a clinical benefit as defined hereunder*, the patient can continue nivolumab +/- ipilimumab. A new tumor assessment will be repeated ≥ 4 weeks after the initial disease progression (but no longer than 8 weeks later), in order to determine whether progression is confirmed according to iRECIST (iCPD), which would terminate the trial treatment. If progression is not confirmed and the patient appears to have clinical benefit*, the patient can continue nivolumab +/- ipilimumab until iCPD. Note: patients who continue treatment beyond initial progression as per RECIST 1.1 will be considered to have had progressive disease for the primary endpoint at the time of the initial progression event and it must be recorded as such on the eCRF. ***Clinical benefit definition:** • investigator-assessed clinical benefit; • Tolerance of study drug(s); • Stable performance status; • Absence of rapid progression of disease. End of Study was defined as the time when all the following criteria have been satisfied: 1.At least 100 days after the end of the protocol treatment of the last patient and 2.Provided all patients have finished protocol specific procedures, not being otherwise part of the standard clinical practice and 3.Provided the trial is mature for the analysis of the primary endpoint as defined in the protocol and 4.The database has been fully cleaned and frozen for this analysis.
Number of patients Number planned (Statistical design)	A separate A-Hern design will be applied to each experimental arm in order to test if a 45% PFS rate at 12 months (H0) can be rejected. If both experimental arms pass the test, a play-the winner selection strategy according to Sargent and Goldberg will be applied to select the superior experimental arm to be tested in a further phase III trial. A one-sided type I error of 5% will be spent for the A-Hern test in each experimental arm. Using exact binomial distributions, this is computed those 54 patients and at least 31 patients alive and progression free at 12 months per arm would be required in each experimental arm to reject a 45% PFS rate at 12

Number analyzed	months (H0) with 90% power under the assumption of a 65% PFS rate at 12 months (H1). In case both experimental arms are found active, 3 more patients alive and progression free at 12 months in one experimental arm compared to the other will be required to recommend formally this experimental arm for further investigation in future phase III. Accounting for a maximum of +/-15% patients lost to follow-up at 12 months, ineligible after medical review or did not start study treatment, a total of 130 patients needs to be randomized. The study was prematurely closed to recruitment due to poor accrual. Only 8 patients were randomized in the study. The efficacy analyses were conducted on 6 patients (per protocol population) and the safety analyses on 7 patients (safety population).

Diagnosis and main criteria for inclusion	• Histologically proven oesophageal squamous cell carcinoma or adenocarcinoma
	• Both early stage and locally advanced tumor patients (according to TNM staging version 8):
	  • Any stage III or any stage IVA
	  • Stage IIA and IIB, only if not operable after complete work up
	  • If squamous cell carcinoma, T1 N1 M0, only if not operable after complete work up
	• If squamous cell carcinoma, T1 N1 M0, only if not operable after complete work up
	• Patient eligible for definitive chemoradiation and not considered for primary surgery after multidisciplinary meeting decision or patient refuses to undergo surgery
	• Prior surgery, other than surgery for primary tumor, is allowed if completed at least 4 weeks before randomization
	• Subject must be previously untreated with systemic treatment given as primary therapy for advanced or metastatic disease
	• At least one measurable lesion by CT scan or MRI based on RECIST version 1.1 with radiographic tumor assessment performed within 28 days prior to randomization.
	• Availability of adequate tissue for immunohistochemical staining
	• Age ≥ 18 years
	• WHO performance status 0 or 1
	• Adequate organ function within 14 days prior to randomization:
	  • White blood cell count (WBC) ≥ 2.0 x 10^9/L (≥ 2000 per mm^3)
	  • Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
	  • Platelet count ≥ 100 x 10^9/L (≥ 100,000 per mm^3)
	  • Haemoglobin ≥ 9.0 g/dL (≥ 5.59 mmol/l)
	  • Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) or direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 x ULN.
	  • AST (SGOT) and ALT (SGPT) ≤ 2.5 x institutional upper limit of normal

	• Lipase < 2.0 x the ULN and no radiologic or clinical evidence of pancreatitis • Potassium within normal ranges as per local lab values • Measured/calculated creatinine clearance ≥ 60 mL/min (according to Cockcroft-Gault); • International Normalized Ratio (INR) and/or Prothrombin Time (PT) and additionally Partial Thromboplastin Time (PTT) must be within the normal ranges as per institution's standard. **Note:** Patients receiving anticoagulant therapy (have to be shifted to Low molecular weight heparin (LMWH) before treatment start as Warfarin and related 4-hydroxycoumarin-containing molecules are not permitted) are eligible if their PTT and PT or INR is within the recommended range for the desired level of anticoagulation. • Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 72 hours prior to randomization. • Patients of childbearing / reproductive potential should use highly effective birth control measures, during the study treatment period and for at least 6months for a woman and 7 months for a man after the last study treatment For sites and countries where applicable (e.g., Germany, etc.), please refer to Clinical Trial Facilitation Group (CTFG) guidelines for further recommendation. • Female patients who are breast feeding should discontinue nursing prior to the first dose of study medication and must not be breast feeding during the trial treatment and for a period of at least 6 months following the last administration of trial drug(s). • Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. • Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations **Exclusion criteria** • Cancer of cervical oesophagus (15 to 19 cm from dental ridge) • Known Her2 positive adenocarcinoma • Weight loss > 15 % over the last 3 months without improvement after nutritional support • Patient with cardiac dysfunction e.g., symptomatic congestive heart failure, uncontrolled hypertension, myocardial infarction within 6 months prior to randomization, clinically significant active heart disease • Mean resting corrected QT interval (QTc) >450 msec for men and >470 msec for women, obtained from 3 ECGs using local clinic ECG machine derived QTcF value • Personal or family history of congenital long QT syndrome • Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), hepatitis B or hepatitis C. • Any prior treatment for advanced disease including treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1(PD-L1), anti-PD-L2, anti-cytotoxic T lymphocyte associated

	antigen-4 (anti-CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • Live vaccines within 30 days prior to the first dose of study therapy. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, BCG, and typhoid vaccine • Known history of solid organ/tissue or allogeneic stem cell transplant • History of hypersensitivity to study drugs or any excipient (refer to SmPCs for ipilimumab, nivolumab, 5-FU and oxaliplatin) • Known dihydropyrimidine dehydrogenase (DPD) deficiency (testing not required). In case of specific recommendations due to institutional and/or national guidelines please proceed accordingly • Current participation or treatment with an investigational agent or use of an investigational agent within 4 weeks of the first dose of study treatment • Serious comorbidity or life expectancy less than one year • Contraindication to chemoradiation therapy • Treatment history of radiotherapy • Child-Pugh B/C and patients with history of acute or chronic pancreatitis • Patient with Type I diabetes mellitus, or skin disorders (such as vitiligo, psoriasis, or alopecia) except if not requiring systemic treatment or with hyperthyroidism or hypothyroidism except if the patient is stable on hormone replacement. • Active infection requiring therapy • Known severe systemic autoimmune disease affecting the lungs or the bowel • Known interstitial lung disease • Known contraindication to CT scans with IV contrast • Chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 15 days prior to enrolment (corticosteroid use as premedication for IV contrast allergies/reactions is allowed; daily prednisone at doses up to 10 mg or equivalent doses of any other corticosteroid is allowed as an example of replacement therapy) • Ongoing or concomitant use of the antiviral drug sorivudine or its chemically related analogs, such as brivudine • Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. • Autoimmune paraneoplastic syndrome requiring immunosuppressive or dedicated treatment. A specific attention should be given in order to detect any minor myasthenia signs at enrolment; acetylcholine receptor antibodies will be systematically tested when symptoms are suggestive of a myasthenia. • History of any other hematologic or primary solid tumor malignancy, unlessen remission for at least 5 years. A pT1-2 prostatic cancer Gleason score < 6, superficial bladder cancer, non-melanomatous skin cancer or carcinoma in situ of the cervix is eligible.

	• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
Treatment Test product. Dose and mode of administration Duration of treatment	In the induction phase, all patients will receive standard fractionation radiation therapy (RT) scheme: 50Gy in 25 fractions over 5 weeks (i.e., 2Gy per fraction), concurrently with 3 cycles of 2 weeks of FOLFOX (oxaliplatin 85 mg/m2, folinic acid 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and in fusional fluorouracil 1600 mg/m^2 over 48 h), followed by 3 cycles of 2 weeks of FOLFOX without RT. • Arm A: Induction phase: Nivolumab will be administered IV at a dose of 240 mg on days 1, 15, 29,43,57 and 71 followed by a maintenance phase (to start on day 85) of Nivolumab IV 240 mg q2 weekly for up to 1 year (26 cycles). • Arm B: Same as Arm A + induction phase: Ipilimumab will be administered IV at a dose of 1 mg/kg q6 weekly for up to 1 year (26 cycles of nivolumab and 8 cycles of ipilimumab).
Reference therapy, dose and mode of administration	NA
Criteria for evaluation Safety	**Progression-free survival** will be measured from the date of treatment start to the date of first occurrence of any of the following events: any locoregional progression/recurrence or distant progression according to RECIST 1.1 or death due to any cause. **Failure-free survival** will be measured from the date of treatment start to the date of first occurrence of any of the following events (any locoregional progression/recurrence or distant progression according to RECIST 1.1, death due to any cause, but also protocol treatment stopped due to toxicity or initiation of other anticancer treatment). **Overall survival** will be measured from the date of randomization to the date of death whatever the cause of death. Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).
Statistical analyses	Due to the premature closure of the study recruitment and the very low number of patients registered, the statistical analyses as described in the protocol cannot be performed. Data reporting is therefore purely descriptive. Efficacy data will be reported in the per-protocol population i.e., all eligible patients who started protocol treatment as allocated. A patient is considered eligible if he/she did not have any deviation from the study entry criteria listed in **diagnosis and main criteria for inclusion**. Safety data will be reported in the safety population i.e., all patients who received at least one administration of the protocol treatment as allocated.

Summary of Results	Out of the 8 patients, 3 patients were randomized to Arm A (nivolumab-CRT arm) and 5 to Arm B (nivolumab-plus-ipilimumab-CRT arm). One patient in Arm A never started treatment because of renal failure. One additional patient in Arm A was excluded from the per protocol population due to not fulfilling eligibility criteria (T3N2M1, UICC stage IVb). The following table presents treatment exposure of the 6 patients of the per protocol population i.e. maximum number of cycles from each treatment (FOLFOX, ipilimumab, nivolumab), the total number of fractions for radiotherapy.

Treatment arm	FOLFOX cycles	Number of fractions	Nivolumab cycles	Ipilimumab cycles
ArmA	6	25	26	
ArmB	6	23	3	1
ArmB	6	27	13*	5
ArmB	6	25	19	7
ArmB	6	19	16	6
ArmB	6	25	7	3

**For this patient, 15 cycles of nivolumab were documented in the database but total number of cycles administered was 13 as the 2nd and the 3rd cycle was withheld due to toxicity.*

The one patient who started CTR+nivolumab completed their protocol treatment (26 cycles of nivolumab, 6 cycles of FOLFOX, 25 fractions of RT).

All 5 patients in Arm B (CTR+nivolumab+ipilimumab) discontinued protocol treatment. One patient discontinued protocol treatment due to toxicity (cutaneous toxicity grade III due to nivolumab treatment) and the other 4 patients due to progression of disease/relapse/death.

At the end of the follow-up period (median follow-up of 15.4 months), one patient (out of one) in Arm A died due to progression of disease. Two patients (out of 5) in Arm B died due to progression of disease. One patient (out of 5) in Arm B had progression but is still alive. The two other patients (out of 5) in Arm B were still alive without progression at the end of their follow up of respectively 65 days (consent withdrawal) and 231 days.

The following table presents baseline characteristics of all randomized patients:

	Total **N (%)**
Age of the patient at randomization	Median=64 Range= 47-68
T category (TNM staging version 8)	
T3	7 (87.5)
T4	1 (12.5)
N category (TNM staging version 8)	
N1	3 (37.5)
N2	5 (62.5)

N category (TNM staging version 8)		
M0	7	(87.5)
M1	1	(12.5)
Clinical TNM stage (version 8)		
Stage III	6	(75.0)
Stage IVa	1	(12.5)
Stage IVb	1	(12.5)
Primary tumor location		
Upper thoracic	4	(50.0)
Middle thoracic	3	(37.5)
Lower thoracic	1	(12.5)
WHO performance status		
0	5	(62.5)
1	3	(37.5)
Sex		
Female	4	(50.0)
Male	4	(50.0)

The following table displays the number of patients in the safety population with major deviations:

Safety population	Treatment arm CRT+nivolumab (N=2) N (%)	CRT+nivolumab +ipilimumab (N=5) N (%)	Total (N=7) N (%)
Any deviation			
Yes	2 (100.0%)	5 (100.0%)	7 (100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any Major Deviation			
Yes	2 (100.0%)	5 (100.0%)	7 (100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major deviation safety assessment			
Yes	2 (100.0%)	5 (100.0%)	7 (100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major deviation Drug/systemic treatment			
Yes	1 (50.0%)	1 (20.0%)	2 (28.6%)
No	1 (50.0%)	4 (80.0%)	5 (71.4%)

The following table presents the best overall response according to RECIST 1.1 in the per protocol population:

Conclusions	<table><tr><th></th><th>Treatment arm CRT+nivolumab (N=1) N (%)</th><th>CRT+nivolumab +ipilimumab (N=5) N (%)</th><th>Total (N=6) N (%)</th></tr><tr><td>Complete response (CR)</td><td>0 (0.0)</td><td>1 (20.0)</td><td>1 (16.7)</td></tr><tr><td>Stable disease (SD)</td><td>1 (100.0)</td><td>1 (20.0)</td><td>2 (33.3)</td></tr><tr><td>Progressive disease (PD)</td><td>0 (0.0)</td><td>2 (40.0)</td><td>2 (33.3)</td></tr><tr><td>Not evaluable for response</td><td>0 (0.0)</td><td>1* (20.0)</td><td>1 (16.7)</td></tr></table> *For this patient, treatment duration was less than 3 months and the frequency of scans to be provided was every 3 months within the 1st year. The graphs for progression free survival and overall survival are presented in Appendix D . There were 6 out of 7 patients in the safety population with grade 3 treatment-related AE. No grade 5 treatment-related AEs were reported. The detailed tables for adverse events (AEs) and related adverse events are presented in Appendix A. The reporting of serious adverse events (SAEs) can be found in Appendix B and C. **No conclusions regarding the feasibility, safety and efficacy of the addition of immunotherapy with PD-1 antibody nivolumab +/- CTLA-4 antibody ipilimumab to concomitant chemoradiotherapy (CRT) in this setting can be drawn based on this database.**
Date of Report	No final analysis report will be generated for this study due to premature closure of the study (poor accrual). The current report serves as study report. **Date of short report:** 08/11/2022

Appendix A: All Adverse Events

	Standard treatment/CTR+nivolumab (Safety pop:N=2)						Experimental treatment/CRT+nivolumab+ipilimumab (Safety pop:N=5)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1
System Organ Class + Preferred term	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
PATIENTS' WORST GRADE		1	1		1	2			5		5	5
BLOOD AND LYMPHATIC SYSTEM												
Anemia							1 (20)					1 (20)
CARDIAC DISORDERS												
Palpitations								1 (20)				1 (20)
ENDOCRINE DISORDERS												
Hyperthyroidism								1 (20)	1 (20)		1 (20)	2 (40)
Hypothyroidism								1 (20)				1 (20)
GASTROINTESTINAL DISORDERS												
Constipation	1 (50)					1 (50)						
Diarrhea							1 (20)					1 (20)
Dysphagia		1 (50)	1 (50)		1 (50)	2 (100)	1 (20)	1 (20)	1 (20)		1 (20)	3 (60)
Esophagitis			1 (50)		1 (50)	1 (50)	1 (20)	2 (40)				3 (60)
Mucositis Oral							1 (20)					1 (20)
Nausea	2 (100)					2 (100)						
Vomiting	2 (100)					2 (100)						
GENERAL DISORDERS AND												
Chills	1 (50)					1 (50)						
Fatigue		2 (100)				2 (100)	1 (20)	1 (20)				2 (40)
Fever	1 (50)					1 (50)		1 (20)				1 (20)
Infusion Related Reaction							1 (20)					1 (20)
INVESTIGATIONS												
Lymphocyte Count Decreased								1 (20)	1 (20)		1 (20)	2 (40)
Neutrophil Count Decreased									4 (80)		4 (80)	4 (80)
Platelet Count Decreased							1 (20)	1 (20)				2 (40)
Serum Amylase Increased									1 (20)		1 (20)	1 (20)
Weight Loss		1 (50)				1 (50)		1 (20)				1 (20)
White Blood Cell Decreased									1 (20)		1 (20)	1 (20)
METABOLISM AND NUTRITION												
Anorexia	1 (50)					1 (50)						
MUSCULOSKELETAL AND CONNECTIVE												
Myalgia							1 (20)					1 (20)
NERVOUS SYSTEM DISORDERS												
Paresthesia							1 (20)					1 (20)
Peripheral Sensory Neuropathy	1 (50)					1 (50)						
RESPIRATORY, THORACIC AND												
Dyspnea							2 (40)					2 (40)
SKIN AND SUBCUTANEOUS TISSUE												

	Standard treatment/CTR+nivolumab (Safety pop:N=2)						Experimental treatment/CRT+nivolumab+ipilimumab (Safety pop:N=5)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1
System Organ Class + Preferred term	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Dry Skin							1 (20)					1 (20)
Rash Maculo-Papular	1 (50)					1 (50)			1 (20)		1 (20)	1 (20)

Adverse Events assessed as treatment-related by the investigator

System Organ Class + Preferred term	Standard treatment/CTR+nivolumab (Safety pop:N=2)						Experimental treatment/CRT+nivolumab+ipilimumab (Safety pop:N=5)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade ≥1
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PATIENTS' WORST GRADE		1 (50.0)	1 (50.0)		1	2			5		5	5
ENDOCRINE DISORDERS												
Hyperthyroidism								1 (20)	1 (20)		1 (20)	2 (40)
Hypothyroidism								1 (20)				1 (20)
GASTROINTESTINAL DISORDERS												
Diarrhea							1 (20)					1 (20)
Dysphagia			1 (50)		1 (50)	1 (50)	1 (20)	1 (20)	1 (20)		1 (20)	3 (60)
Esophagitis			1 (50)		1 (50)	1 (50)	1 (20)	2 (40)				3 (60)
Mucositis Oral							1 (20)					1 (20)
Nausea	1 (50)					1 (50)						
Vomiting	2 (100)					2 (100)						
GENERAL DISORDERS AND												
Chills	1 (50)					1 (50)						
Fatigue		2 (100)				2 (100)	1 (20)	1 (20)				2 (40)
Fever	1 (50)					1 (50)		1 (20)				1 (20)
Infusion Related Reaction							1 (20)					1 (20)
INVESTIGATIONS												
Lymphocyte Count Decreased								1 (20)	1 (20)		1 (20)	2 (40)
Neutrophil Count Decreased									4 (80)		4 (80)	4 (80)
Platelet Count Decreased							1 (20)	1 (20)				2 (40)
Weight Loss								1 (20)				1 (20)
White Blood Cell Decreased									1 (20)		1 (20)	1 (20)
MUSCULOSKELETAL AND CONNECTIVE												

System Organ Class + Preferred term	Standard treatment/CTR+nivolumab (Safety pop:N=2)						Experimental treatment/CRT+nivolumab+ipilimumab (Safety pop:N=5)					
	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade ≥3 N (%)	Grade ≥1 N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade ≥3 N (%)	Grade ≥1 N (%)
Myalgia							1 (20)					1 (20)
NERVOUS SYSTEM DISORDERS												
Paresthesia							1 (20)					1 (20)
Peripheral Sensory Neuropathy	1 (50)					1 (50)						
RESPIRATORY, THORACIC AND												
Dyspnea							1 (20)					1 (20)
SKIN AND SUBCUTANEOUS TISSUE												
Dry Skin							1 (20)					1 (20)
Rash Maculo-Papular	1 (50)					1 (50)			1 (20)		1 (20)	1 (20)

Appendix B: Cumulative Summary Tabulation of Serious Adverse Events (SAE)

SOC	PT	Arm B
Cardiac disorders	Palpitations	1
Endocrine disorders	Hyperthyroidism	1
Gastrointestinal disorders	Dysphagia	2
General disorders and administration site conditions	General physical health deterioration	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
Grand Total		6

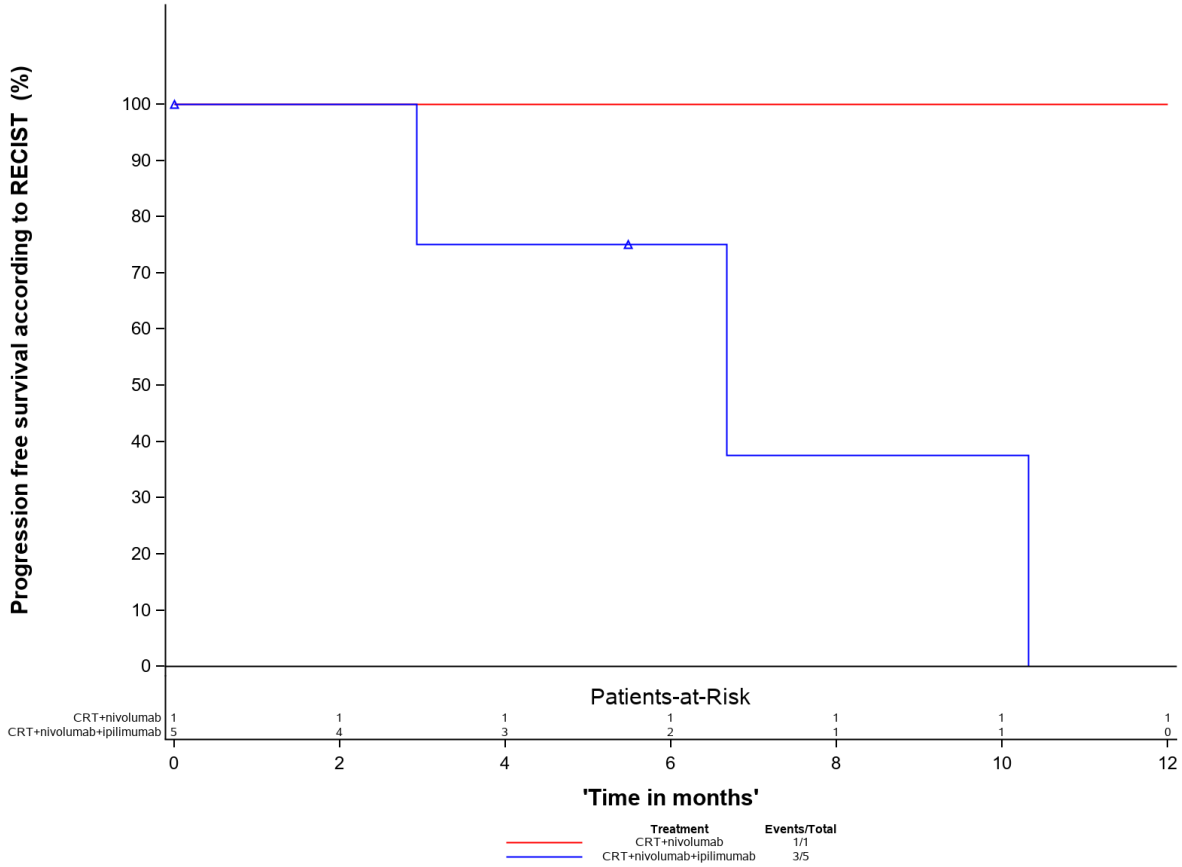
PT=Preferred term, **SOC**=system organ class

Appendix C: Cumulative Summary Tabulations of Serious Adverse Reactions (SAR)

SOC	PT	Arm B
Endocrine disorders	Hyperthyroidism	1
Gastrointestinal disorders	Dysphagia	2
Grand Total		3

PT=Preferred term, **SOC**=system organ class

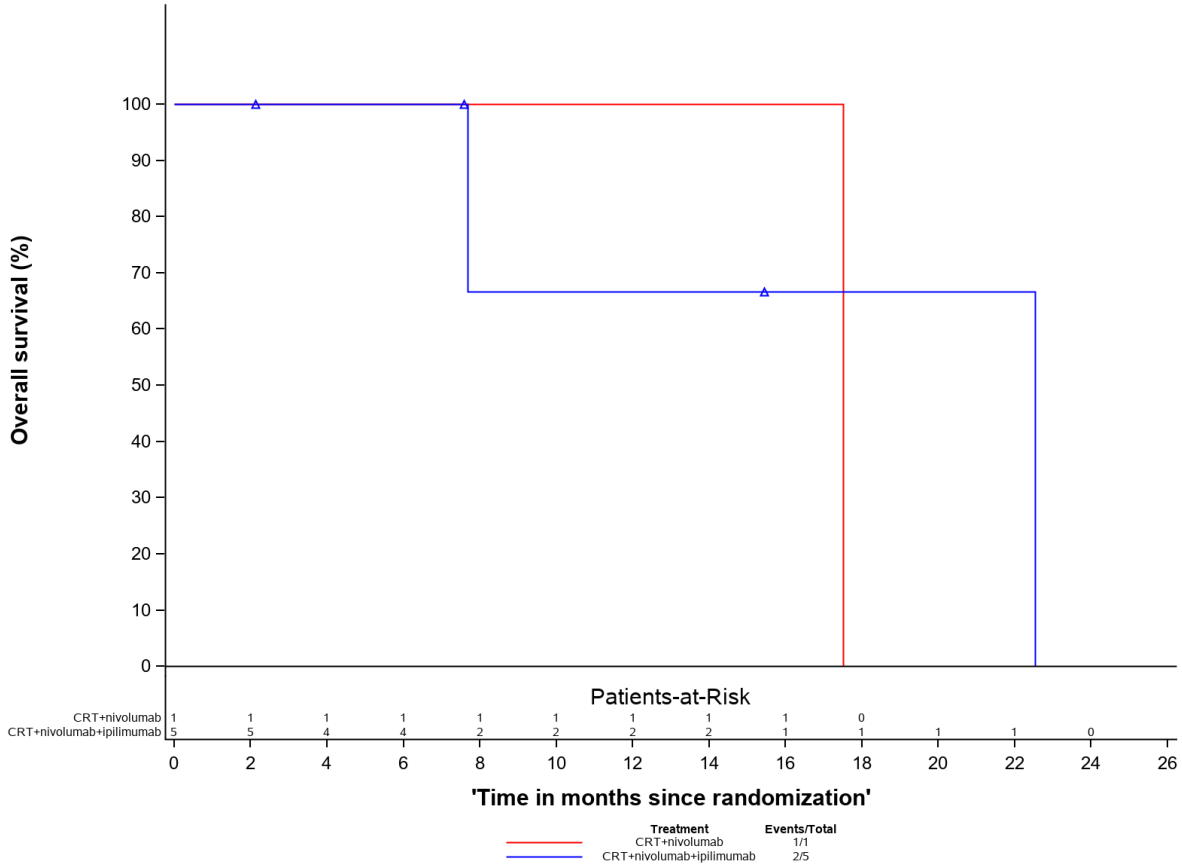
Appendix D: Graphs PFS and OS



Progression free survival Kaplan-Meier curves of progression-free survival in per protocol population per treatment arm.

	Event/Total	Median (95% CI)[KM]
Treatment		
CRT+nivolumab	1/1	17.3 (NE-NE)
CRT+nivolumab+ipilimumab	3/5	6.7 (2.9-NE)

[KM]Kaplan-Meier method;



Overall survival Kaplan-Meier curves of overall survival in per protocol population per treatment arm.

	Event/Total	Median (95% CI)[KM]
Treatment		
CRT+nivolumab	1/1	17.5 (NE-NE)
CRT+nivolumab+ipilimumab	2/5	22.5 (7.7-NE)

[KM]Kaplan-Meier method;