	EUROPEAN COMMISSION RE SEARCH AND INNOVATION DG	Periodic Report

Project No: 257144

Project Acronym: ARTFORCE

Project Full Name: Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment outcomE

Periodic Report

Period covered: from 01/10/2015 **to** 30/09/2017

Start date of project: 01/04/2011

Project coordinator name:
Prof. Harry Bartelink

Version: 1

Date of preparation: 23/10/2017

Date of submission (SESAM):

Project coordinator organisation name:
STICHTING HET NEDERLANDS KANKER IN STITUUT - ANTONI VAN LEEUWENHOEK ZIEK ENHUIS

Periodic Report

PROJECT PERIODIC REPORT

Grant Agreement number:	257144
Project acronym:	ARTFORCE
Project title:	Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment out comE
Funding Scheme:	FP7-CP-FP
Date of latest version of Annex I against which the assessment will be made:	03/02/2017
Period number:	4th
Period covered - start date:	01/10/2015
Period covered - end date:	30/09/2017
Name of the scientific representative of the project's coordinator and organisation:	Prof. Harry Bartelink STICHTING HET NEDER LANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS
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Declaration by the scientific representative of the project coordinator (1)

I, Prof. Harry Bartelink STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS , as scientific representative of the coordinator of the project ARTFORCE and in line with the obligations as stated in Article II.2.3 of the Grant Agreement declare that:

The project has achieved most of its objectives and technical goals for the period with relatively minor devi ations.

The attached periodic report represents an accurate description of the work carried out in this project for this re porting period.

The public website is up to date.

To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 6) and if applicable with the certificate on financial statement.

All beneficiaries, in particular non-profit public bodies, secondary and higher education establishments, re search organisations and SMEs, have declared to have verified their legal status. Any changes have been repor ted under section 5 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name	Prof. Harry Bartelink STICHTING HET NEDER LANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS
Date	

This declaration was visaed electronically byH.G.A.M. VAN LUENEN(ECAS user name nlueneva) on

1. Publishable summary

Summary description of project context and objectives

The ARTFORCE project introduces very sophisticated tools to improve treatment outcome of pa tients with advanced tumours by enabling tailored irradiation of the most active parts of the tumour. Furthermore, the work carried out in this project aims to improve quality of life by withholding inef fective, toxic treatments and to decrease community costs by targeting expensive treatments to those who will benefit. To this end, treatment-specific tumour response predictors are developed for patient selection, i.e. genetic predictors for cisplatin and radiation sensitivity as well as functional and ana tomical imaging predictors early during the treatment. Also a major aim is to improve the overall level of radiation oncology in Europe by introducing methods for fully-controlled image guided adap ted radiotherapy to personalize the very intensive and aggressive treatment for lung and head & neck cancer.

Description of work performed and main results

Within the ARTFORCE project there are several interlinked work packages.
In work package 2 (Adaptive radiotherapy (RT) to account for anatomical changes) the database of delivered dose of patients participating in clinical trials was further developed and supported already research for work package 5 and 7. Cross validation of accumulated dose and in-vivo dosimetry showed that both methods have in common that there are only small deviations between the planned and delivered dose to the target volumes. However, in the presence of anatomical changes, the in-vivo dosimetry based method exhibits a 5-fold over-estimation of the dosimetric changes as a func tion of volume changes. 4D inverse planning, aimed at incorporation of the time dependency of the delivered dose into the adaptive treatment planning optimization process, has led to a decision rule for adaptive radiotherapy. This decision rule, based on daily dose accumulation predictions, pre defines deviations in dose-volume histogram-parameters early in treatment with high accuracy.
In work package 3 (Biological adaptive treatment planning in the presence of advanced techniques) it was shown that already in the second week of treatment it is now possible to estimate the radiosensit ivity using functional imaging, thus predicting the required radiation dose. Work package 4 (three di mensional in-vivo dosimetry) was already completed and implemented on time. This allows early on-line detection of errors in treatment delivery of sophisticated radiotherapy in each participating cen ter, see 3rd period report.
Work package 5 (Biological markers to predict the response of head & neck tumors to Cetuximab or Cisplatinum + Radiotherapy) provided important prognostic and predictive information. A meta-analysis revealed prognostic impact of the immune infiltrate: novel organ-specific features of the im mune infiltrate in distinct cancer types, as well as a strategy for defining new prognostic biomarkers. The calreticulin expression constitutes a new powerful prognostic biomarker that reflects enhanced local antitumor immune responses in the lung. While the importance of formyl peptide receptor 1 mutation (FPR1) was highlighted in chemotherapy-induced anticancer immune responses. It was shown that overexpression and hyperactivation of poly(ADP-ribose) polymerase 1 (PARP1) and the downregulation of pyridoxal kinase (PDXK), correlated with elevated apoptosis resistance. Further exploration showed that PAR and PDXK were predictive biomarkers in non-small cell lung cancer:
For head & neck cancer radiomics features provided an added value to HPV status as prognostic and predictive biomarker treated with the combined modality radiotherapy with Cisplatinum or Cetuxim ab.
The combination of microvascular density and CA-IX expression might give additional prognostic information in these patients with known HPV status. High CD8+ TIL level was an independent pro gnostic factor independent of HPV/p16status. CD8+ TILs and PD-L1 expression could provide com plementary information to HPV status in selecting sub population for treatment de-intensification. In

traepithelial macrophage expression may play different roles in patients with p16+ vs. p16- disease. CD163+ cells density in stroma may provide information for selecting suitable patients for concur rent Cetuximab or Cisplatinum with radiotherapy. Established molecular signatures were assessed for their response prediction value in HNSCC patients treated with Cisplatinum and radiotherapy. Drug response and DNA repair defect linked expression markers were therefore developed and further im prove the detection of poor prognosis patients. The validation of these biomarkers for predicting the Cisplatinum and radiation sensitivity will be performed after closing the ARTFORCE head & neck phase III clinical trial in 2019.

In work package 6

In work package 7 the clinical trial: Dose-escalation by boosting radiation dose within the primary tu mor on the basis of a pre-treatment FDG-PET-CT scan in stage IB, II and III NSCLC: A randomized phase II trial. The interim analysis on toxicity has led to temporary closure of the trial. The trial data were submitted to the Independent Data Monitoring Committee (IDMC) and to the Medical Ethical Committee (MEC). After modification of the protocol, approval was obtained for continuing the trial by the MEC. For this lung trial 4 centers have contributed patients, without formerly entering the consortium; four Third parties therefor assisted in accruing patients for this trial. The trial is now closed with 107 randomized and 150 registered patients. The final analysis for the end results will be performed at the end of 2018, when all patients have at least one year follow up.
In work package 8: the phase III head & neck clinical trial: A randomized study with Cisplatinum or Cetuximab and standard or adaptive high dose radiotherapy for advanced head & neck cancer is, after initial delays, now well underway; it accrued already 181 patients and will finish in the beginning of 2019.There were 3 important, external reasons for this delay. In addition to a number of minor reas ons. The first major reason was the termination of the free delivery of Cetuximab due to the expira tion of the patent and due to budget limitations of the pharmaceutical company. This was unforeseen and unexpected and had a major impact on the project. The second major reason for delay is the long time it took to obtain Medical Ethical Approval and Regulatory Affairs Approval for the trials in all participating centres in the different countries. The third major reason for delay was slow accrual caused by severe restrictions due to radiation safety imposed on the daily life of the patients treated with radiolabelled Cetuximab. The protocol for this head & neck trial has been adapted by removing the imaging studies with the radiolabelled Cetuximab. The adapted protocol does not impose the sig nificant life-style restrictions on the patients (they can now freely interact with their close relatives) and this has improving accrual. To further improve accrual, we have invited more hospitals to join ARTFORCE as a partner (UMC Utrecht, EMC Rotterdam and UMC Groningen). These centers were selected because of their large head & neck cancer population. In Work package 1 a no-cost exten sion has been requested and obtained. Despite the initial unforeseen and unexpected delays caused by external factors, we now expect with the actions taken (reduction of the complexity of the head & neck trial protocol, addition of partners/third parties, and monthly teleconferences with all trial part ners) that the head & neck trial will be finalized in the beginning of 2019. At that time, we can start with analyzing the data from the clinical trial protocols and with validation of the predictive assays in work package 5
In work package 9 the dissemination of knowledge and expertise is being developed in close coopera tion with the European Society for Therapeutic Radiology and Oncology (ESTRO). Presentations of the project are given at the annual society meetings and published in the ESTRO Newsletter. In volved personnel from consortium institutes are eligible for travel/exchange grants supported by the project and 4 grants for courses and 1 grant for an exchange visit have been awarded during this peri od.

Expected final results and potential impacts

This ARTFORCE project is aimed at improving the treatment outcome in patients with head & neck or lung cancer, treated with a combined modality of radiotherapy and systemic treatment. The im provement in better tumour control will be reached by delivering higher radiation doses to the tumour while minimizing the radiation dose to normal tissues and by reducing toxic side effects of the sys temic treatment. This will be obtained by:
1. Novel irradiation methods using information from innovative imaging approaches for the individu al treatment design.
2. Adapting the radiation treatment plans to individual patients' anatomical and biological changes during treatment.
3. Designing and validating new QA methods for sophisticated high tech radiation procedures.
4. Validating methods of patient selection for treatment with a combination of radiation and cisplatin.
Expected clinical benefit: Novel irradiation methods by using information from innovative imaging approaches for the individual treatment design, resulting in better treatment outcome.
In over 150 publications the EU has been acknowledged so far as the funding body for the ART FORCE project, of which 35 publications in the period -September 2015- November 2017.

Project public website address:	www.cancerartforce.eu

2. Core of the report

Project objectives, Work progress and achievements, and project management during the peri od

The Project Summary Pdf document contains the core of the report.

3. Deliverables and milestones tables

Deliverables (excluding the periodic and final reports)

Del. no.	Deliverable name	Version	WP no.	Lead beneficiary	Nature	Dissemination level	Delivery date from Annex I (proj month)	Actual / Forecast delivery date	Status	Comments
1	Formulation of management office	1.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	3	14/02/2012	Submitted	
2	Consortium agreement	1.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	6	01/06/2011	Submitted	
3	Formation of the executive committee	1.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Other	PP	3	14/02/2012	Submitted	
4	Formation of the external advisory board	1.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Other	PP	6	14/02/2012	Submitted	
5	Formation of the ethical review committee	1.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Other	PP	6	14/02/2012	Submitted	

6	Periodic report	2.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	18	19/02/2013	Submitted	
7	periodic report 2	0.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	36	31/03/2014	Not submitted	
8	final report	0.0	1	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	78	30/09/2017	Not submitted	
1	Quantified accuracy of deformed registration algorithms	1.0	2	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	18	06/11/2012	Submitted	
2	Platform for dose accumulation	1.0	2	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Other	PP	18	06/11/2012	Submitted	
3	Cross validation of accumulated dose and in-vivo dosimetry	0.0	2	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	60	31/03/2016	Not submitted	
4	Database of delivered dose of patients participating	0.0	2	STICHTING HET NEDERL	Other	PP	78	30/09/2017	Not submitted	

	in clinical trails			ANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS						
1	A systematic method for the evaluation of tumour response.	1.0	3	KAROLINSKA INSTITUTET	Report	PU	28	25/09/2013	Submitted	
2	A systematic method for the evaluation of tumour response.	1.0	3	RAYSEARCH LABORATORIES AB	Other	PP	36	20/04/2015	Submitted	
3	An adaptive algorithm for response'based corrections	0.0	3	KAROLINSKA INSTITUTET	Other	PP	55	31/10/2015	Not submitted	
1	Portal dosimetry QA platform suitable for 3-D dosimetry	1.0	4	MAASTRO INNOVATIONS BV	Other	PU	18	10/10/2012	Submitted	
2	3D in-vivo portal dosimetry system	1.0	4	MAASTRO INNOVATIONS BV	Other	PU	24	16/04/2014	Submitted	
3	Calibrated CBCT suitable for dose calculation	1.0	4	MAASTRO INNOVATIONS BV	Other	PU	24	16/04/2014	Submitted	
4	Online 3D in-vivo dosimetry	1.0	4	MAASTRO INNOVATIONS BV	Report	PU	36	16/04/2014	Submitted	
1	Optimization of candidate biomarkers	1.0	5	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)	Report	PU	24	01/05/2013	Submitted	
2	Immunohistochemical evaluation training set	1.0	5	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)	Report	PU	36	26/02/2014	Submitted	
3	Immunohistochemical evaluation calibration set	0.0	5	INSTITUT NATIONAL DE LA SANTE ET	Report	PU	78	30/09/2017	Not submitted	

				DE LA RECHERCHE MEDICALE (INSERM)						
4	Assessment of prognostic value of HPV	0.0	5	KAROLINSKA INSTITUTET	Report	PU	78	30/09/2017	Not submitted	
1	SOP for calibration of the PET and approval of ZR89 Cetuximab	2.0	6	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PP	18	23/10/2012	Submitted	
2	Analysis of the matching “pattern of relapse three months after treatment” and “Cetuximab uptake bef	0.0	6	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PP	60	31/03/2016	Not submitted	
3	Analysis predictive value of uptake Zr89-Cetuximab for outcome completed	0.0	6	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PP	73	30/04/2017	Not submitted	
4	Analysis of the intra-tumour pattern of relapse three and twelve months after treatment on FDG-PET-C	0.0	6	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PP	72	31/03/2017	Not submitted	
5	Analysis predictive value of uptake [18F]HX4 for outcome completed	0.0	6	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PP	72	31/03/2017	Not submitted	
1	Protocol written and distributed to all participating centres	3.0	7	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CLINIC	Report	PU	18	02/04/2014	Submitted	
2	Development of SOPs	2.0	7	STICHTING	Report	PP	36	02/04/2014	Submitted	

				MAASTRICHT RADIATION ONCOLOGY MAASTRO CL INIC						
3	First toxicity results avail able	2.0	7	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CL INIC	Report	PU	36	02/04/2014	Submitted	
4	Analysis of matching	0.0	7	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CL INIC	Report	PU	60	31/03/2016	Not submitted	
5	Analysis of local tumour progression, survival and toxicity of phase II trial completed	0.0	7	STICHTING HET NEDERL ANDS KANKER INSTITUUT - A NTONI VAN LEEUWENHOE K ZIEKENHUIS	Report	PU	72	31/03/2017	Not submitted	
6	Analysis of predictive va lue of uptake hypoxia PET tracer and tumour p erfusion for outcome completed	0.0	7	STICHTING HET NEDERL ANDS KANKER INSTITUUT - A NTONI VAN LEEUWENHOE K ZIEKENHUIS	Report	PU	72	31/03/2017	Not submitted	
7	Supply of the Ethical app roval to the EU	2.0	7	STICHTING MAASTRICHT RADIATION ONCOLOGY MAASTRO CL INIC	Report	PU	36	02/04/2014	Submitted	
8	Final version of the prot ocol	1.0	7	STICHTING HET NEDERL ANDS KANKER INSTITUUT - A NTONI VAN LEEUWENHOE K ZIEKENHUIS	Report	PU	18	27/03/2014	Submitted	

9	Status of posting of trial results	0.0	7	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	78	30/09/2017	Not submitted	
1	Protocol phase II written and distributed to all participating centres	3.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	18	02/04/2014	Submitted	
2	Standard Operational Procedures (SOP) of the quality control of the study written	1.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	18	13/11/2012	Submitted	
3	First toxicity results available	1.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	36	02/04/2014	Submitted	
4	Toxicity interim analysis after 100 patients	0.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PP	60	31/03/2016	Not submitted	
5	Analysis of initial response and toxicity of phase II-III trial completed	0.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	72	31/03/2017	Not submitted	
6	Supply of the Ethical approval to the EU	2.0	8	STICHTING HET NEDERL	Report	PU	36	02/04/2014	Submitted	

				ANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS						
7	Final version of the protocol and registration	1.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	18	12/02/2014	Submitted	
8	Status posting of trial results	0.0	8	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Report	PU	78	30/09/2017	Not submitted	
1	Establish working party	1.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Other	PP	6	14/02/2012	Submitted	
2	Symposium / workshop at ESTRO meeting	2.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Other	PU	36	29/09/2014	Submitted	
3	Symposium / workshop at ESTRO meeting	2.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Other	PU	54	19/10/2015	Submitted	
4	Issuing of exchange and ESTRO course grants	2.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Other	PU	18	29/10/2012	Submitted	
5	Issuing of exchange and ESTRO course grants	1.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ON	Other	PU	36	21/05/2014	Submitted	

				COLOGY						
6	Issuing of exchange and ESTRO course grants	1.0	9	STICHTING HET NEDERLANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS	Other	PU	54	19/10/2015	Submitted	
7	Publication on ESTRO newsletter, ESTRO web site, www.cancerartforce.eu	3.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Report	PU	18	19/12/2012	Submitted	
8	Publication on ESTRO newsletter, ESTRO web site, www.cancerartforce.eu	1.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Report	PU	36	21/05/2014	Submitted	
9	Publication on ESTRO newsletter, ESTRO web site, www.cancerartforce.eu	0.0	9	EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY	Report	PU	72	31/03/2017	Not submitted	

Milestones

Milestone no.	Milestone name	Work package no	Lead beneficiary	Delivery date from Annex I	Achieved Yes/No	Actual / Forecast achievement date	Comments

4. Explanation of the use of the resources

The **explanation on the use of resources** was removed from the scientific periodic reports in SESAM. These deta ils now have to be entered in the cost statement forms in FORCE instea d.

Attachments	
Grant Agreement number:	257144
Project acronym:	ARTFORCE
Project title:	Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment out comE
Funding Scheme:	FP7-CP-FP
Project starting date:	01/04/2011
Project end date:	30/09/2017
Name of the scientific representative of the project's coordinator and organisation:	Prof. Harry Bartelink STICHTING HET NEDER LANDS KANKER INSTITUUT - ANTONI VAN LEEUWENHOEK ZIEKENHUIS
Period covered - start date:	01/10/2015
Period covered - end date:	30/09/2017
Name	
Date	

This declaration was visaed electronically by H.G.A.M. VAN LUENEN (ECAS user name nlueneva) on