PROJECT DELIVERABLE

REQUITE
Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors

Project acronym: **REQUITE**	GA number: **601826**
Project title: **Validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects and improve quality-of-life in cancer survivors**	
Funding Scheme: **Collaborative Project (FP7-HEALTH-2013-INNOVATION-1)**	
Project start date: **01 October 2013**	Duration: **60 months**
Project's coordinator: **Prof Catharine West (University of Manchester, UK)**	

Deliverable no.: **D2.4**	Title: **Report of patient recruitment on REQUITE website**
Due date: **Month 36 (30 September 2016)**	Actual date: **Month 38 (21 November 2016)**

Aim of the Deliverable:

To carry out an observational study recruiting prospectively a cohort of 5,300 patients undergoing radiotherapy for breast, prostate or lung cancer, and collect longitudinal, standardised radiotherapy toxicity and quality of life data.

Deliverable D2.4 has been achieved in full.

Lead beneficiary for this deliverable: **Jenny Chang-Claude (B2)**

Personnel involved: **Catharine West, Susan Davidson, Rebecca Elliott (B1); Petra Seibold, Anusha Müller, Akke Botma (B2), Hubert Thierens, Liv Veldeman (B3); Adam Webb, Paul Symonds, Chris Talbot (B4); Dirk De Ruysscher (B5, B13); David Azria (B7); Tiziana Rancati, Riccardo Valdagni (B8); Ana Vega, Sara Gutierrez Enriquez (B9); Barry Rosenstein (B12); Sylvie Canisius, Philippe Lambin (B13); Frederik Wenz (B14).**

Dissemination level:		
PU	Public	**X**
PP	Restricted to other programme participants (within the Commission)	
RE	Restricted to a group defined by the consortium (including the Commission)	
CO	Confidential, only for members of the consortium (including the Commission)	

1. Study Set-up

All the main recruiting sites completed the regulatory approvals process and opened for recruitment between April and September 2014. Third party sites to support patient recruitment were also required to complete ethics and R&D approvals, and were opened at various times between 2014 and 2016. Each recruitment site then received a site initiation visit and database training carried out by the observational study staff at DKFZ. This involved training local study personnel in how recruitment should be conducted, and included instruction on how to complete the standardized data collection forms, namely patient factors and treatment data, patient reported outcome (PRO) questionnaires and finally to familiarise staff with the documentation set and SOPs, all of which are critical for best practice when conducting this study. In addition, there was training for local research and laboratory staff on how to handle, store and ship the patient blood samples.

The REQUITE observational study is registered with the International Standard Randomised Controlled Trial Number Register (ref: ISRCTN98496463) http://www.controlled-trials.com/ISRCTN98496463

2. Overall Patient Recruitment

The overall target for this observational study was the recruitment of 5,300 patients undergoing radiotherapy for breast, prostate or lung cancer, and the collection of longitudinal, standardised radiotherapy toxicity and quality of life data. REQUITE set an ambitious two year target from 1st April 2014 to 31st March 2016 to recruit 2,100 breast cancer patients, 2,100 prostate cancer patients and 1,100 lung cancer patients. However, due to delays receiving regulatory approvals at some centres it was necessary to extend recruitment by six months for breast and prostate patients to 30th September 2016, and by 12 months for lung patients to 31st March 2017. Other steps taken to enhance recruitment included the addition of new third party sites to the consortium allowing the recruitment of patients from more radiotherapy centres with close links to the main recruiting sites (as per a hub and spoke model) and also widening the inclusion/ exclusion criteria e.g. no longer excluding small cell lung cancer patients; including patients with a prior malignancy if it was treated more than five years ago.

Across all tumour sites by 30th September 2016, the consortium (including third party sites) recruited 4,314 patients, representing 81.4% of the overall target (Figure 1). This figure shows the initial lag period at the start of recruitment as centres were still moving through the regulatory process and completing study set-up. Monthly accrual shows that on average there were 62 patients recruited per month during this first six month period (April – September 2014). The target accrual line shows that this lag period (common to all clinical trials and observational studies) was not taken into consideration in part due to the tight schedule planned for recruitment.

Once all the 11 main centres had been opened by October 2014, recruitment more than doubled with average accrual of 158 patients per month over the next 12 months (October 2014 – September 2015). This increased further to an average of 170 patients per month from October 2015 until 30th September 2016 when recruitment for breast and prostate closed. It is interesting to note that the rate of actual accrual eventually mirrors the rate of target accrual shown by approximately parallel lines. This figure also highlights the strength of breast and prostate accrual in comparison with the significantly lower lung recruitment (see below).

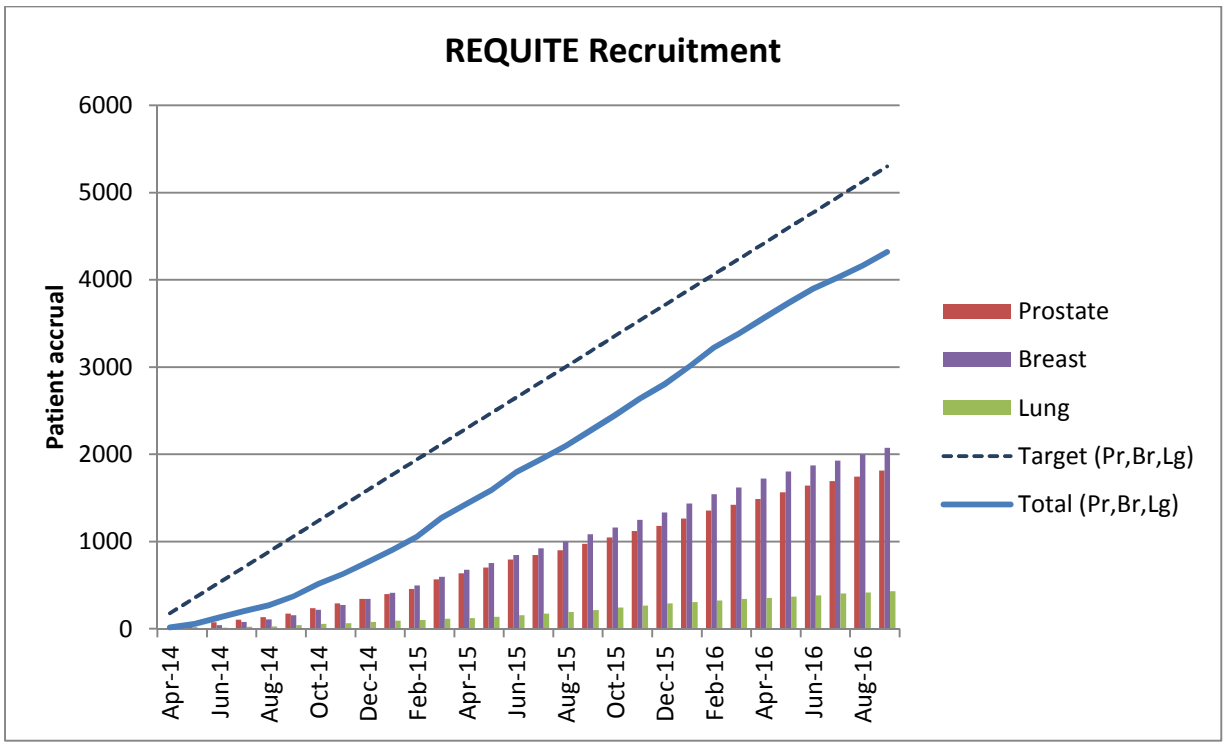

Figure 1: Cumulative patient recruitment (months 7-36)

Recruitment split by tumour site on 30th September 2016 is presented in Table 2. Specifically, the consortium achieved:

- 99% of target for breast (n=2,070)
- 86% of target for prostate (n=1,812)
- 39% of target for lung (n=432)

Table 2: Total number of patients recruited by tumour site

Beneficiary	Breast	Lung	Prostate	Total number of patients	Original target number
B2: DKFZ	174	-	15	189	600
B3: UGENT	298	47	199	544	500
B4: ULEIC	350	42	250	642	600
B5: KU LEUVEN	253	71	127	451	850
B8: INT	103	48	206	357	380
B9: FPGMX	316	92	295	703	570
B10: CNFT	-	40	263	303	400
B12: MSSM	76	5	50	131	200
B13: MAASTRO	-	45	75	120	200
B14: UHEI	42	-	67	109	200
B15: ICM	458	42	265	765	800
TOTAL	**2,070**	**432**	**1,812**	**4,314**	**5,300**

This table highlights that some centres were very successful exceeding their original target, whereas others struggled to identify and recruit patients as per their original expectations. Monthly observational study meetings were held and attended by representatives from each recruitment centre to update on accrual figures, and also share best practice for when to approach patients, take consent and try to provide solutions for any issues that arose.

Table 2 clearly highlights that lung recruitment has been very challenging, although it should be noted that there is still six months remaining and therefore accrual will increase further. Lung patients can be reluctant to enter into research studies, as they often feel more unwell at the time of treatment compared with breast or prostate patients. This has certainly been the experience of the REQUITE study, as demonstrated by the screening logs routinely completed at each recruitment centre, which show that lung patients are more likely to decline their participation. Accordingly, the consortium agreed to identify and include additional lung cohorts collected outside of the REQUITE study for inclusion in the final analyses. Three cohorts were identified and checks made to ensure that the available follow-up data was comparable and could be pooled with the REQUITE data. The following cohorts will be included:

- Gent Lung observational study cohort (n=80) (Universiteit Gent, Belgium)
- RADAR observational study (n=19) (Christie NHS Foundation Trust, Manchester, UK)
- CONVERT phase III national clinical trial (n=169) (led by Christie NHS Foundation Trust, Manchester, UK)

It is expected that with these additional cohorts plus the extended lung recruitment (to March 2017) there will be data and samples from ~800 lung patients available for analysis. This is an estimated 72% of the lung target, and 88% of the overall target.

3. Third Party Recruitment

It was appreciated at an early stage in the study set-up that the 11 main recruitment centres would need the support of ‘third party sites’ i.e. additional patient recruitment centres in order to achieve the overall target. As such, over the course of the observational study 15 third party sites were identified and completed regulatory approval and site initiation in order to participate in this study (additional third party sites were identified but either did not complete the regulatory process or were not successful in recruiting any patients). Table 3 shows the accrual by tumour site for these 15 third party sites. These recruitment figures contributed to the overall accrual of their associated main recruitment centre (Table 2). Some sites were more successful recruiting into the study than others. In total 550 patients were recruited at third party sites accounting for 12.7% of overall accrual. Of particular note is Vall D’Hebron Institute of Oncology (VHIO) in Barcelona with their excellent accrual figures (n=240) representing 44% of all third party recruitment.

Table 3: Recruitment at third party sites in RP1 & RP2					
Beneficiary	**Third Party**	**Breast**	**Lung**	**Prostate**	**Total number of patients**
B2: DKFZ	Baden-Baden	11			11
B2: DKFZ	Darmstadt	12			12
B2: DKFZ	Freiburg	37		2	39
B2: DKFZ	Karlsruhe ST	1		3	4
B2: DKFZ	Karlsruhe VN	66		2	68
B2: DKFZ	Ludwigshafen	22		8	30
B2: DKFZ	Speyer	25			25
B4: ULEIC	Derby		5		5
B4: ULEIC	Nottingham		10		10
B8: INT	Candiolo		12	25	37
B9: FPGMX	Barcelona	215	25		240
B10: CNFT	Birmingham		12		12
B10: CNFT	Salford		1		1
B12: MSSM	Queens	1		1	2
B15: ICM	Nimes	49		5	54
		439	**65**	**46**	**550**

4. Withdrawals

To date, 125 patients have been withdrawn or dropped out. Main reasons were death (34 patients), change of treatment (28 patients) and disease progression (28 patients).

5. Monitoring

The observational study team leads at DKFZ conducted on-site monitoring visits of the main recruitment centres between March and June 2015. These visits are an important part of the quality control required to check various aspects about how the study is operated at each recruitment centre, specifically this includes: protocol compliance, checking the investigator site file, sample storage, correct CRF completion and storage, and staff training. Monitoring reports were compiled after each visit and returned to recruitment centres to respond to any comments and/ or complete the actions identified. Third party sites were monitored by their beneficiary.