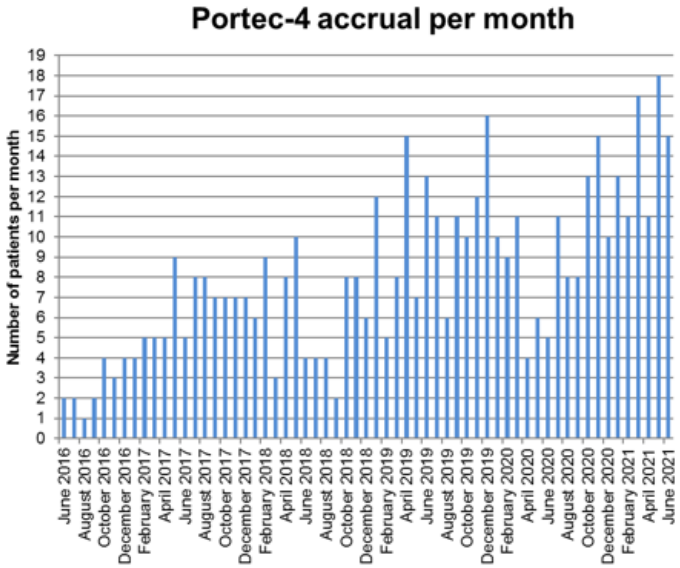
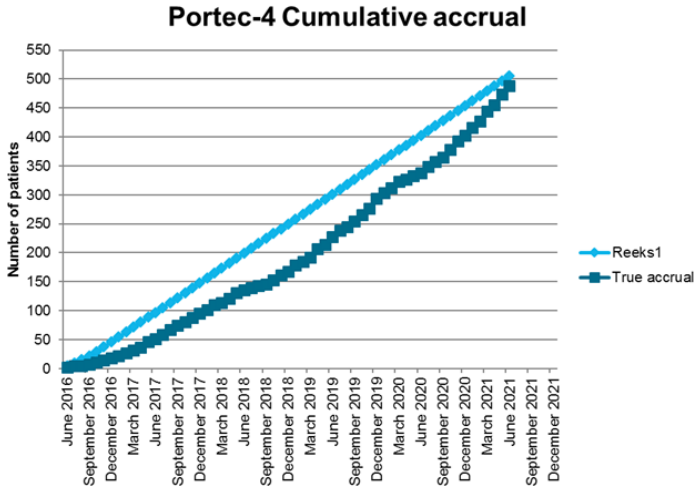
PORTEC-4a Newsletter No 6 23 July 2021

Current accrual number of 499 patients in PORTEC-4a !

The PORTEC-4a inclusion number is nearing the 500 eligible and evaluable patients, thanks to the high accrual rate over the past few months. Since the last newsletter, which was sent in February 2021, a total of 83 patients were included in the trial. The top month was May 2021, with a total of 18 included patients.

Please see the graphs and the table below showing the accrual by month and by site, respectively (based on the available data up to the 1st of July, with n=488).





Center	control arm	molecular profile	Total
Amsterdam UMC	8	18	26
Catharina Hospital	5	16	21
Erasmus Medical Center	7	11	18
Evang. Klinik Essen-Mitte (D)	1	3	4
Haaglanden Medical Center	5	7	12
Institut Gustave Roussy (Fr)		2	2
Isala Hospital	5	3	8
Kaiserswerther Diakonie Dusseldorf (D)	1	2	3
Leiden UMC	24	47	71
Luzerner Kantonsspital Frauenklinik (CH)	1		1
Maastro Clinic	22	48	70
NKI/AvL	8	17	25
Radboud UMC	4	3	7
Radiotherapy Group Arnhem/Deventer	20	49	69
Radiotherapy Institute Friesland	6	14	20
Rotkreuzklinikum München (D)	2	7	9
Sankt Gertrauden Krankenhaus Berlin (D)		2	2
St Luke's Hospital (Irl)	3	5	8
Tuebingen University Hospital (D)	7	15	22
UMC Groningen	5	7	12
UMC Utrecht	1	5	6
Universitatsfrauenklinik Wien (CH)		1	1
Universitätsklinikum Heidelberg (D)	1	2	3
Universitätsklinikum Luebeck (D)	2	5	7
University Hospital Gent (B)	3	3	6
University Hospital Prague (Cz)	8	14	22
Verbeeten Institute	13	13	26
Zeeuws Radiotherapy Institute	2	5	7
Total	164	324	488

PORTEC-4a total recruitment target increased to 550 evaluable patients

During the last evaluation of trial data for the DSMB it has been observed that the true distribution of favourable, intermediate and unfavourable profiles is slightly different than expected at the design of the PORTEC-4a trial, with a somewhat lower percentage of favourable profiles. This has the consequence that the power for the **primary** analysis will slightly increase, with some reduction of the power for the second analysis comparing the outcomes of the patients with favourable profiles, who have received observation (experimental arm) or brachytherapy (standard arm), respectively. At design of the trial it was already stated in

the protocol that the target number would be extended if feasible, to increase the power of the secondary analyses.

It has therefore been decided to increase the target number to 550 eligible patients, especially since this is feasible with respect to the current high accrual rates, and within the budget. Both IKNL and Dutch Cancer Society have approved and an amendment will be sent to the Ethics Committee. We expect that the trial will remain open to accrual until late December 2021. All sites will be informed well in advance about the final date of closure.

Transition from Trias to Castor for electronic data capture (EDC)
In week 35 (August 30th – September 5th) the PORTEC-4a trial is scheduled to have a transition of the electronic data entry system from the currently used TRIAS to CASTOR. This is a general IKNL transition.

Our central data manager, Karen Verhoeven-Adema, will provide all data managers and trial coordinators with the essential information regarding the e-learning for Castor, and when and how to get access to the data when the transition will be completed. She will also send the date of opening of the Castor data entry for PORTEC-4a eCRF, likely late September.

To make sure all data in TRIAS is as up-to-date as possible before the temporary closure and transition, we kindly ask all data managers to make sure that all (over)due eCRF are completed and all queries have been resolved before 27 August.

New international sites
We are pleased to report that new international sites were activated for participation in the PORTEC-4a trial in the beginning of the year 2021.

On the 23rd of February the 8th German site, Sankt Gertrauden Krankenhaus in Berlin, has been activated (PI Jana Barinoff). On the 24th of March we welcomed the Kantonsspital Frauenklinik in Lucerne, Switzerland (PI Christine Brambs), to the PORTEC-4a study.

After the activation of the French GINECO group with the leading site IGR on 19th January, the group has recently activated the Hôpital Européen Georges-Pompidou (PI Durdux), and is now in the final stages of activating Hôpital Tenon (PI Rivin del Campo). If feasible, 1-2 other French sites will be activated before 1st September.

We would like to thank all local PIs and their teams for all the work they have done for activation of the trial in their centres. No new centres will

be permitted from 1st September onwards, as the trial is nearing completion of accrual.

Protocol amendments – protocol version 2.6
In the upcoming weeks, a protocol amendment will be submitted to the Ethics Committee. The amendment includes some administrative updates and clarifications, the extension of the target accrual, and the statistical analysis plan. After approval of the amended protocol version 2.6, all documents will be sent to all investigators and trial coordinators, and updated on the PORTEC-4a website, and all PIs will be requested to complete and return the Protocol Signature Sheet for the new version and use the new version from the date of receipt.

Validation of pathology labs for the integrated molecular profile
For the international sites and groups, central pathology labs have been validated for determination of the molecular profile before their initiation.

Over the past year, the majority of the large regional Dutch pathology laboratories have been validated for the molecular profile as well (Amsterdam University Medical Center, Maastricht University Medical Center, Erasmus University Medical Center). Some pathology labs are still in the process of validation (NKI/AvL Amsterdam, University Medical Center Utrecht, University Medical Center Groningen).

It is one of the purposes of the trial to facilitate future implementation of the results by ensuring that the determination profile is available in all large pathology labs.

Data management and monitoring
Karen Verhoeven-Adema is the PORTEC-4a central data manager and coordinator at the Trial Office, portec@iknl.nl
All up-to-date trial documents (including the latest versions of the protocol, quality of life questionnaires, CRF) can be found on the PORTEC-4a website: http://www.msbi.nl/portec4

Central monitoring and data checks of CRFs entered via the TRIAS (from September onwards: CASTOR) electronic database system are done on a 3-monthly basis and queries sent accordingly; please make sure all queries are dealt with in a timely fashion.

On-site monitoring
Due to the Covid situation, on-site monitoring has been on hold and has been replaced by virtual monitoring by our monitor Dorien Berends-vd Meer, and our junior PI Anne-Sophie van den Heerik.
Virtual on-site monitoring of international sites has been initiated as from March 2021, and some international sites have already been virtually monitored, and others will be monitored in the upcoming months.

Please note that it is essential that a subject screening log is kept up to date, and that all study personnel has a valid GCP or BROK certificate.

SAE – One new SAE has been reported in June 2021. Currently a total of 4 SAE have been reported, two in 2017, one in 2019 and one in 2021. Of these SAEs only one was possibly related to study treatment, the other three were unrelated.

DSMB

The DSMB will have their annual teleconference on 23rd of November 2021. Afterwards a report of this meeting will be send to the Ethics committee and to the local PIs.