PORTEC-4a Newsletter No 4 9 April 2020

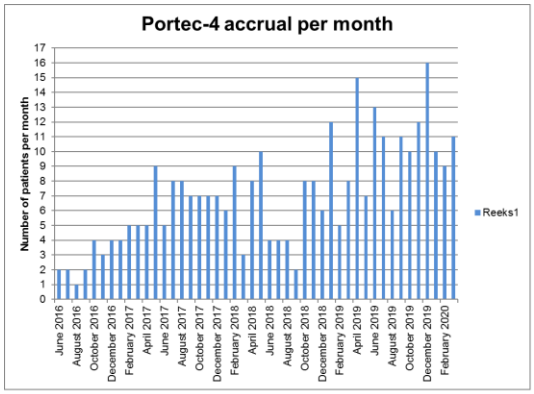
Accrual to the PORTEC-4a trial has reached 323 on March 30th 2020!

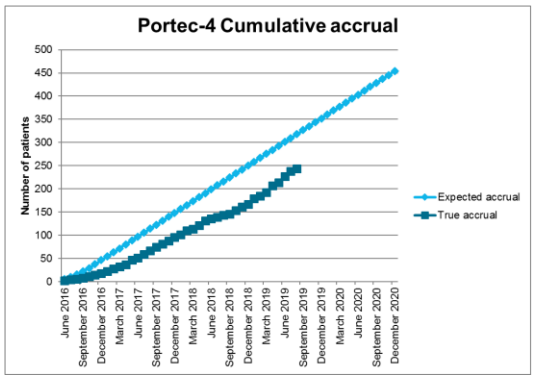
Accrual to PORTEC-4a trial has continued to increase over the past year. Even in March 2020, when the corona crisis hit all of Europe, eleven patients were included, thanks to your continued efforts.

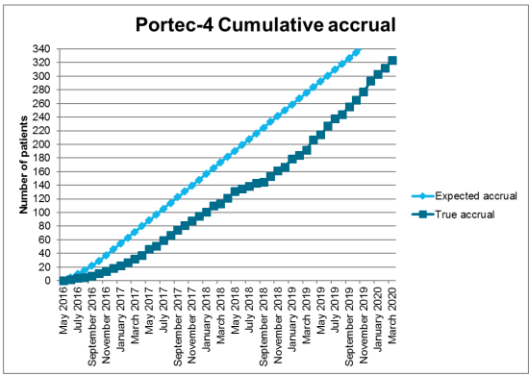
Since the last newsletter sent 27th May 2019, a total of 109 patients were included in the trial – this shows the significantly increased accrual rate over the past year. In 2019, **125** patients have been recruited, compared to 76 and 72 in the years before. The top month was December 2019, with 16 included patients.

See the graphs below and the table showing the accrual by month and by site, respectively.

Center	control arm	molecular profile	Total
Amsterdam UMC	7	14	21
Catharina Hospital	5	15	18
Erasmus Medical Center	6	9	15
Haaglanden Medical Center	3	4	7
Isala Hospital	3	1	4
Leiden UMC	14	37	50
Maastro Clinic	19	40	59
NKI/AvL	4	9	15
Radboud UMC	2	3	5
Radiotherapy Group Arnhem/Deventer	12	34	46
Radiotherapy Institute Friesland	6	13	19
Rotkreuzklinikum München (D)	-	4	4
St Luke's Hospital (Irl)	1	-	1
Tuebingen University Hospital (D)	6	9	15
UMC Groningen	3	6	9
UMC Utrecht	1	4	5
University Hospital Gent (B)	1	1	2
University Hospital Prague (Cz)	2	3	5
Verbeeten Institute	13	6	19
Zeeuws Radiotherapy Institute	1	3	4
Total	109	214	323







New international sites

We are very pleased to report that new international sites were activated for participation in the PORTEC-4a trial.
Cancer Trials Ireland / St Luke's Hospital and Radiation Oncology Network, Dublin (PI Charles Gilham) was activated on 25 June 2019, and has included a first patient.
Two new German sites, the Rotkreuzklinikum in München (PI Moritz Hamann) and Kliniken Essen-Mitte in Essen (PI Beyhan Ataseven) were activated on 24 september 2019 and 23 January 2020, respectively, and München has included their first patients. The molecular profile for all German sites is being determined at the path lab in Tübingen (Dr Annette Staebler). Tübingen University Hospital (PI Stefan Kommoss) has included 15 patients up to now. Universitätsklinikum Schleswig-Holstein, Campus Lübeck is a new German site which will be activated soon.
The Czech CEEGOG group / University Hospital of Prague (PI David Cibula) was activated on 6 Sept 2019, and already included 5 patients in the PORTEC-4a trial.
Currently, the French GINECO group with multiple sites (for which the pathology lab and trial coordination will be done at Institut Gustave Roussy, Paris, PI Cyrus Chargari) and the Medical University of Vienna (Austria, PI Stephan Polterauer) are in the final stages of preparing for participation.

We thank the local PIs and their teams for all the work they have done for activation of the trial in their centers.

PORTEC-4a during the COVID-19 pandemic

Sadly, all participating sites, teams and patients have been suffering from the COVID-19 crisis since early 2020. Different recommendations on the management of gynecological cancers and of clinical trials during the COVID-19 pandemic have been issued in the various countries and regions.
As PORTEC-4a is a trial of de-escalation and more individualised assignment of adjuvant treatment, and does not involve extra hospital visits or procedures, it has been decided to keep the PORTEC-4a trial open as usual.
Some minor adaptations may be needed on the individual patient or hospital level. For example, if a follow-up visit has been done by telephone instead of by out-patient visit this can be specified on the follow-up CRF by filling in items on physical examination as 'not done due to COVID crisis' in TRIAS. It is recommended to do a maximum of 1 in 2 FU visits by telephone. Also, the annual chest X-ray and lab tests can be postponed to a next visit.
The validation of pathology labs has been delayed due to the COVID crisis but will be resumed as soon as possible.

Protocol amendments – protocol version 2.5

On 6th March 2020, a number of protocol amendments have been submitted to the Ethics Committee for their evaluation and approval. The updated protocol version 2.5 will be sent immediately after Ethics approval. The amendments are mainly administrative updates and clarifications (specification of international participation, specification about the total study duration, information to resolve inconsistencies and provide more specific information), but also we had to delete the patient's date of birth from the patient information sheet and to update the ABR (Dutch regulatory document) due to some local PI changes (retirement) and the inclusion of more participating European countries. After approval of the amended protocol version 2.5, all documents will be sent 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.

Validation of pathology labs

The international pathology laboratories which have been validated for determination of the profile are those in Tübingen, Dublin, and Prague. The lab at Paris has almost completed the validation procedure, and the lab in Vienna has started the procedure.

Over the coming year, several regional labs in the Netherlands will start the validation process as well, in order to facilitate regional determination of the molecular profile and future implementation of the profile provided the trial is successful. Currently these validation procedures are on hold due to the corona crisis.

New junior investigator in the PORTEC-team
Anne-Sophie van den Heerik is our new PORTEC-4a junior investigator and PhD candidate; she has started working on the PORTEC-4a trial and related studies as of 1st February 2020. After 2 years she will combine her projects with clinical training in radiation oncology. She is currently working on a review paper, on the validation of the regional pathology labs and on the design of the health economics analysis. Over the coming years, she will be working on the analyses of toxicity and QoL, the final results, molecular aspects and health economics of the trial.

Data management and monitoring
Karen Verhoeven-Adema is the PORTEC-4a central data manager and coordinator at the Trial Office, please email her at portec@iknl.nl
All trial documents can be found on the PORTEC-4a website: www.msbi.nl/portec4

Central monitoring and data checks of CRF entered via the TRIAS 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 in the Netherlands is ongoing and most sites have been visited. In 2020 the sites with only a few patients included will be visited as well by our monitor Dorien Berends-vd Meer. Monitoring has turned out to be useful; although most sites are doing very well there have been suggested improvements based on the monitor findings which have led to enhanced study quality. It should be emphasized that it is essential that a subject screening log be kept up to date, and that all study personnel should have a valid GCP or BROK certificate.

SAE – Three SAE have been reported to date, of which two in 2017 and one in 2019. Of these SAEs one was possibly related to study treatment, the other two were unrelated.

DSMB
The Data and Safety Monitoring Board have had their annual teleconference on 28 November 2019, and were pleased with the increased accrual and overall conduct of the trial. Their report has been sent to the Ethics committee and to the local PIs. The next DSMB teleconference will be held in November 2020.

PORTEC-4a update meetings at GCIG

At each GCIG meeting, a PORTEC-4a investigator's update meeting is being held, the most recent at GCIG in Athens in November 2019. The trial continue to attract international interest. Sadly, the GCIG meeting in Chicago in May 2020 has been canceled due to the corona crisis.

Presentations and publications

- A Dutch clinical trial article has been published in NTVO in 2017
- A paper reporting on the results of the pilot phase has been published in Gynecologic Oncology in 2018 - Wortman et al, Gynecol Oncol 2018 151(1): 69-75.
- A presentation on the dummy run has been held by Remi Nout at ESTRO 2017, and a presentation on the QA results has been held by Bastiaan Wortman at ESTRO 2019.
- Two review papers in which the PORTEC-4a trial is being discussed have been published: Wortman et al, Selecting Adjuvant Treatment for Endometrial Carcinoma Using Molecular Pathways. Curr Oncol Rep 2019;21(9):83; and Creutzberg et al, Uterine Cancer: Adjuvant Therapy and Management of Metastatic Disease. J Clin Oncol 2019;37(27):2490-2500.
- A publication on the dummy run and QA (Bastiaan Wortman) is in final stages of preparation and will be sent soon.
- The background and design of the PORTEC-4a trial have been presented at many international meetings, such as IGCS 2018, ESMO 2018 and 2019, and ESGO 2019