PORTEC-3 Newsletter no 5 26 March 2009

PORTEC-3 international collaboration

PORTEC-3 has truly become an international Intergroup trial, with participation from MaNGO group (Italy), ANZGOG (Australia and New Zealand), NRCI (UK), NCIC-CTG (Canada), and 2 centres in Vienna (Austria). A Northern French collaborative Group has recently decided to participate and is currently in the process of trial organization and activation.
In 2008 the first international patients have been included in PORTEC-3. The first patient from Italy (Lecco, MaNGO Group) was randomized in April 2008, and the first ANZGOG patient in November 2008.
The first UK centre has been activated last week (Mount Vernon). As UK has 36 centres in the process of local approval we expect many more centres to follow soon! NCIC-CTG expects to activate their first centres over the next months as well.

Accrual

Until November 2008, accrual to PORTEC-3 was slow with 2 patients per month. With ANZGOG trial activation accrual has increased: current total of 55 patients, 21 randomized since November 2008. ANZGOG has accrued 10 patients (all since November!), MaNGO 6, the Netherlands 39. See the Table on page 2.
As local activations often take a long time, it is expected that accrual will continue to increase steadily over the next months with UK and NCIC-CTG activations and first randomizations.

DSMB

The Data and Safety Monitoring Board has welcomed two new members representing the participating groups: Prof Danny Rischin (ANZGOG) and Dr Wendy Parulekar (NCIC CTG). A DSMB Charter is currently being prepared and the 2009 full annual safety report will be sent to the DSMB in October 2009.

PORTEC3 website

All trial documents, relevant information and links are available on the trial website: http://www.clinicalresearch.nl/portec3
Please check the website regularly for most recent versions the protocol and CRF.

SAE

3 SAE have been reported to date. Please do not forget to report any SAE (also including important medical events requiring or prolonging hospitalization) according to the guidelines provided in paragraph 9.3 of the protocol.

Radiotherapy and chemotherapy for high-risk endometrial carcinoma – PORTEC-3 Randomization.

Arm data 1 = Radiotherapy alone
Arm data 2 = Radiotherapy + concurrent and adjuvant chemotherapy

Hospital	Arm data 1	Arm data 2	Total	Since 2008-11-1
ANZ-East Bentleigh-Monash-	.	1	1	1
ANZ-Herston-Royal B & W-	1	.	1	1
ANZ-Melbourne-Peter MacCallum-	2	1	3	3
ANZ-South Brisbane-Mater-	.	1	1	1
ANZ-South Coast Mail Centre-Wollongong-	.	1	1	1
ANZ-Wellington-Wellington-	1	2	3	3
I-Genova-Genova-	.	1	1	.
I-Lecco-Lecco-	.	3	3	1
I-Torino-S.Anna Torino-	1	1	2	2
NL-Amsterdam-AMC / RT-	1	1	2	.
NL-Amsterdam-AVL-RT	2	1	3	2
NL-Amsterdam-AZVU-RT-	.	1	1	1
NL-Arnhem-Arnhems RI-	3	.	3	3
NL-Den Haag-Ley RT-	.	1	1	.
NL-Den Haag-WEZ RT-	1	1	2	.
NL-Deventer-RI Stedendriehoek-	.	1	1	.
NL-Groningen-UMCG RT-	4	3	7	1
NL-Leeuwarden-RI Friesland-	3	1	4	1
NL-Leiden-LUMC-RT	3	.	3	.
NL-Maastricht-Maastro-	2	2	4	.
NL-Nijmegen-Radboud RT-	1	1	2	.
NL-Tilburg-Verbeeten-RT	1	1	2	.
NL-Utrecht-UMCU / RT-	2	2	4	.
Total	-	-	55	21

New protocol version: 28 January 2009

After discussion and approval by all participating groups the new protocol version dated 28 January 2009 has been finalized. The amendments have been approved by central Ethics.

The main changes involved:

- Inclusion of Group-Specific Appendices and international participating centers
- Specification of laparoscopic surgery with or without lymphadenectomy in stratification for type of surgery (identical to abdominal surgery)
- Update of literature data
- Recalculation of power and required number of events based on literature data. The original expected 5-year survival of 50% in the RT alone arm was based on population data, which included elderly patients and those with major comorbidities precluding use of chemotherapy. These patients would not be eligible for the trial and thus a certain degree of selection is inevitable. The randomized trials using adjuvant chemotherapy had higher 5-year survivals in the RT alone arm (65-85%), but most had more favourable patient selections– the Italian trial trial had a patient mixture comparable to PORTEC3 (66% stage III), and this trial reported 69% 5-year survival in the RT alone arm. For this reason, the required events for an expected 5-year survival of 65% in the RT alone arm have been calculated (para 12.1) – the trial is powered for detection of 11.5 % survival improvement with 500 patients (145 events required), and for detection of 10% survival improvement with 655 patients (198 events)
- Safety reviews - in view of legal and GCP requirements necessitating annual detailed confidential safety reviews to be presented to the DSMB, it was decided to specify these annual safety reviews rather than specific safety interim analyses, and keep the two planned interim analyses which will address all issues, i.e. efficacy, futility and toxicity (paragraph 12.2).
- Some specifications for staging and treatment, specifically for chemotherapy

Pathology review before randomisation

Although not always convenient for the clinical situation, upfront pathology review has already several times confirmed its value. Rapid throughput of pathology review is best ensured by sending an email message to the review pathologist signalling the receipt of slides for revision and request for rapid diagnosis by mail, fax or occasionally by telephone.

Web-based randomisation and new database program

Registration and randomisation for PORTEC3 is a web-based procedure via the secure TOP PORTEC website https://www.admlumc.hovon.nl
Trial coordinators and data managers randomizing patients have received user names and passwords. After randomization an email with confirmation of registration data and allocated treatment is automatically generated and sent to local and central investigators.
Currently, a new web-based data management program TRIAS is being tested by the IKW Trial Centre. TRIAS is a dedicated, user-friendly data base program using electronic CRF. TRIAS will be launched for use by the PORTEC3 data managers at Dutch IKC centres as of mid April, 2009. After full introduction in the Netherlands, this web-based program will be introduced to the coordinating centres of international groups.

PORTEC-3 Investigator's Meetings

Investigator's meetings have been held in October 2007 (during ESGO, Berlin), April 2008 (during ASCO, Chicago) and November 2008 (during BGCS, Liverpool). Minutes have been sent to all groups.
The 2009 PORTEC3 Investigator's Meeting will be organized during ESGO, Belgrade, at the Continental Hotel on Sunday, October 11, 1.30-2.30 pm (after GCIG meetings).

Other relevant trials

GOG #249 is soon to be activated. In this trial, patients with high-intermediate and high risk stage I-II endometrial carcinoma will be randomized to receive pelvic EBRT or vaginal brachytherapy followed by 3 cycles carboplatin/paclitaxel. This trial will provide valuable information to compare to PORTEC3 results.
The **ASTEC trials** have recently been published in the same Lancet issue Lancet 2009 Jan 10; 373(9658):125-36 and 137-46.
The **Italian lymphadenectomy trial** (JNCI 2008;100: 1 – 10) confirms the ASTEC results with a median number of 30 nodes removed in the LA arm.