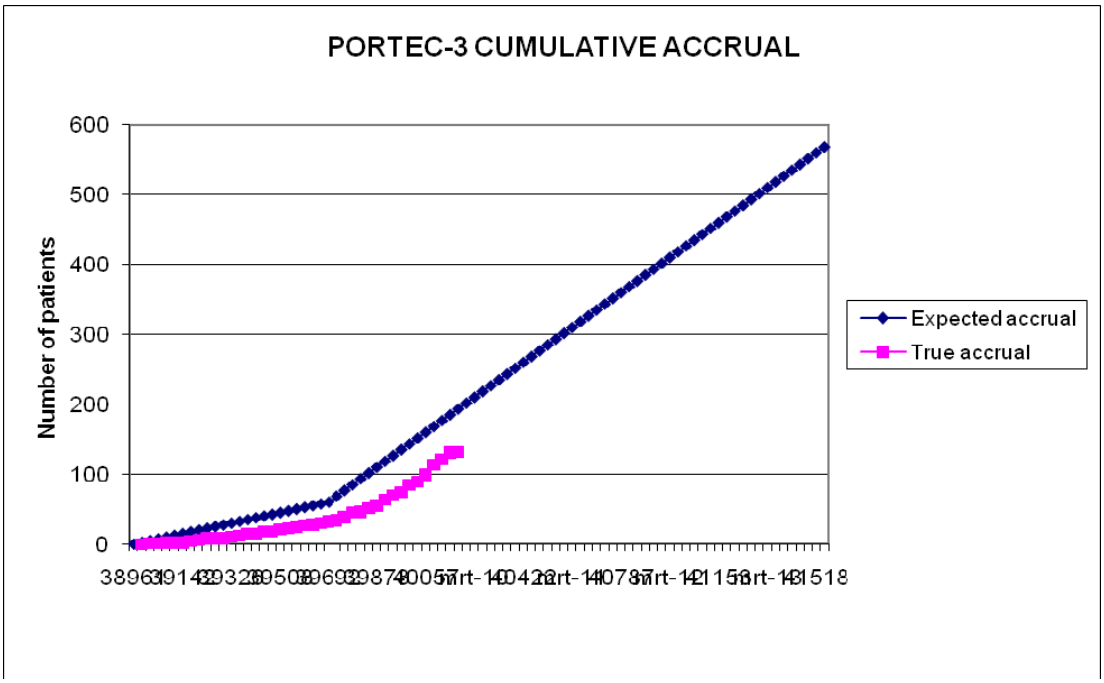
PORTEC-3 Newsletter no 6 22 January 2010

Accrual to PORTEC3

Since January 2009, accrual to PORTEC3 has sharply increased thanks to the active international participation to the study. Total accrual on January 1, 2010 was 133 patients. See the Table and graph. Current accrual (Jan 22): 141.

Hospital	2009-1-1-2009-12-31	Total on 1-1-2010
ANZ-Auckland-Auckland City Hospital	1	1
ANZ-Christchurch-Christchurch Hospital	1	1
ANZ-East Bentleigh-Monash Medical Centre	6	6
ANZ-Herston-Royal Brisbane &Women's Hospital	1	1
ANZ-Melbourne-Peter MacCallum Cancer Centre	10	12
ANZ-South Brisbane-Mater Adult Hospital	1	1
ANZ-South Coast Mail Centre-Wollongong Hospital	1	2
ANZ-Wellington-Wellington Blood & Cancer Centre	4	6
ANZ-Wentworthville, Sydney-Westmead Hospital	3	3
Total for Australia & New Zealand	**28**	**33**
CA-Calgary-Tom Baker Cancer Centre	3	3
CA-Halifax-Queen Elizabeth II Health Sciences Centr	1	1
CA-Quebec-Hotel-Dieu de Quebec	1	1
CA-Sherbrooke-Centre Hosp. Universitaire de Sherbrooke	4	4
Total for Canada	**9**	**9**
I-Genova-Istituto Nazionale Ricerca sul Cancro	0	1
I-Lecco-AO Ospedale di Lecco	7	9
I-Monza-S. Gerardo Hospital	1	1
I-Palermo-A.O. Vincenzo Cervello	1	1
I-Torino-S.Anna Hospital	7	8
I-Varese-H. del Ponte University of Varese	2	2
Total for Italy	**18**	**22**
NL-Amsterdam-AMC / Afd. Radiotherapie	3	5
NL-Amsterdam-Antoni van Leeuwenhoek ZH	3	4
NL-Amsterdam-AZVU- Radiotherapie	0	1
NL-Arnhem-Arnhems Radiotherapeutisch Instituut	1	4
NL-Den Haag-HagaZiekenhuis, loc Leyenburg / RT	0	1
NL-Den Haag-MC Haaglanden, Westeinde / RT	0	2
NL-Deventer-Radiotherapeutisch Inst. Stedendriehoek	0	1
NL-Eindhoven-Catharine Ziekenhuis / RT	1	1
NL-Enschede-Medisch Spectrum Twente	3	3
NL-Groningen-UMC Groningen, RT	1	8
NL-Leeuwarden-Radiotherapeutisch Inst. Friesland	1	4
NL-Leiden-Leids Universitair Medisch Centrum	0	3
NL-Maastricht-Maastro Clinic	3	7
NL-Nijmegen-UMC St. Radboud / RT	3	5
NL-Rotterdam-AZR DDHK	1	1
NL-Tilburg-Dr. B. Verbeeten Instituut	0	2
NL-Utrecht-UMCU / RT	6	10
Total for Nederland	**26**	**62**
UK-Guildford-Royal Surrey County Hospital	1	1
UK-Northwood-Mount Vernon Cancer Centre	3	4
UK-Norwich-Norfolk and Norwich University Hospital	2	2
Total for United Kingdom	**6**	**7**
Total	87	133



PORTEC-3 international collaboration: first randomization from France

In addition to the active participation from MaNGO group (Italy), ANZGOG (Australia and New Zealand), NRCI (UK), NCIC-CTG (Canada), we have recently welcomed the new group Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) from France, which has been activating the first few of the 18 participating sites, and has randomized the first patient this month.
University Hospital Vienna also expects to start accrual soon.

DSMB

The Data and Safety Monitoring Board has received the annual confidential Safety Report in October 2009, and has held a teleconference on October 20. The DSMB has subsequently sent a memo expressing concern with respect to higher than expected rates of significant (grade 2 or 3) sensorimotor neuropathy in the trial, and requested a response to these concerns in terms of the protocol amendment and plans for reassessment of the neurotoxicity rates. As a result, the protocol amendments dated 25 November 2009 have been implemented, which involve stricter rules for dose reduction, delay or discontinuation in case of neuropathy. The neurotoxicity rates will be reassessed after 6 months, and a specific overview of sensory and motor neurotoxicity rates will be sent to the DSMB in April 2010.
The Data and Safety Monitoring Board has welcomed a new member to replace Prof Malcolm Mason: Prof Nicholas James (NCRI, UK).

SAE

17 SAE have been reported to date. 9 have been discussed during the Investigator's meeting and a overview has been sent. Updated overviews will be sent at 6-month intervals. Please do not forget to report any SAE according to the guidelines provided in paragraph 9.3 of the protocol.

New protocol version: 25 November 2009

After discussion during the Investigator's meeting and approval by all participating groups, new protocol and CRF versions dated 26 October 2009 had been finalized. However, the DSMB Report necessitated some further rules for dose reductions or discontinuation in case of neuropathy, and these have been added in protocol version 25 November 2009. This version has been approved by central Ethics. Thus, the current protocol version is 25 November 2009, and the current CRF version 26 October 2009. These are available from the trial website.

Overview of amendments: 26 October 2009 items 1-8; 25 November 2009 items 9-10.

1. **Addition of the newly participating French Group FNCLCC** (FEDEGYN Group) with approval status, contact information (pages 1, 2, 5, 6, 12, 32) and the FNCLCC group-specific Appendix (Appendix K, page 72).
2. **FIGO 2008 staging system**: incorporated into summary, inclusion and exclusion criteria, references, Appendix A, B (pages 6, 7, 12, 13, 34, 35, 36). Need to report both FIGO 1988 and 2008 staging as there are essential differences with risk of errors (e.g. FIGO 1988 stage IC is in FIGO 2008 stage IB) and many centres have not switched to 2008 yet. CRFs adapted to include both FIGO 1988 and 2008.
3. **Proportion of serous or clear cell component** in mixed endometroid and serous or clear cell tumors (pages 19, 20, 38). Protocol defined if serous component >25%, tumor should classified as serous cancer; same for clear cell. However, lower percentages of serous or clear cell component are of prognostic significance and have been reported on CRF as 'other'. For the evaluation of prognostic significance it is relevant to report % components. This has been defined in the procotol and new items have been added to CRF Form 2 and the Path Review Form.
4. **Eligibility** criteria:
    a. *non-melanomatous skin cancer* in past 10 years eligible (instead of only basal cell carcinoma; pages 6, 13)
    b. Exclude if significant hearing impairment of grade 3 or greater (hearing aid) or if born deaf (pages 6, 14).
    c. Radical hysterectomy allowed if stage IIB grade 3 or stage III at pathology (pages 6, 13)
    d. Clarification that with exclusion of uterine sarcoma, this also involves carcinosarcoma (pages 6, 13)
5. **Laparoscopic surgery** allowed (if centre has this as routine procedure after learning curve and clinical evaluation have been completed), as this is the practice in many participating countries (pages 13, 15)
6. **Chemotherapy schedule and dose modifications:**
    a. Hydration for cisplatin: volumes of pre- and post hydration was too variable. Specified use of minimum of 1500 ml total hydration fluids (page 17)
    b. Dose reductions or delay: for patients with established grade 2 neuropathy (with imminent progression to grade 3) dose reduction of paclitaxel to 135 mg/m2 should be allowed. For fever with grade 3 neutropenia consider use of G-CSF, or prophylactic antibiotics at subsequent cycles (page 18).
7. **Specification of Timing**
    a. Brachytherapy: specification that brachytherapy should be completed during last weeks of EBRT or in first week after, overall time not > 50 days (page 16). Specification that same schedule of RT (including brachytherapy in case of cervical involvement) is used in both arms (pages 14, 35)
    b. Pre-randomization and pre-treatment investigations: specification of timing (pages 55-56)
    c. Specification for Follow up forms at 6-month intervals etc. from date of randomization (page 21)
8. **Some minor administrative changes** (pages 1, 2, 24, 29, 30, 32)

9. **Stricter rules for dose reduction or discontinuation of chemotherapy in case of neuropathy grade 2** (paragraph 7.4, pages 17-18)
10. **Administrative changes:**
    a. Addition of new Data and Safety Monitoring Board member, page 3
    b. Addition of 2 new ANZGOG sites and local coordinators (paragraph 16.4, page 31).

Pathology review

Although not always convenient for the clinical situation, upfront pathology review has already 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.
In case of absence of a center's review pathologist, the slides can either be sent to one of the other national review pathologists, or be evaluated by a local colleague gynecological pathologist who routinely covers, with the center's review pathologist confirming upon return and completing Path Review Form 2A.

PORTEC-3 Investigator's Meetings

The 2009 PORTEC3 Investigator's Meeting has been held during ESGO, Belgrade, on October 11, after the GCIG meetings. Minutes have been sent to all groups.
The 2010 PORTEC3 Investigator's Meeting will be organized during IGCS in Prague after GCIG meetings, presumably on October 22. Specific information and invitation will follow.

TRIAS database program

A new web-based data management program TRIAS has been implemented by the IKW Trial Centre. TRIAS is a dedicated, user-friendly data base program using electronic CRF. TRIAS has now been introduced to Dutch participating centres. Over the next 1-2 years it is planned to introduce this web-based program with e-CRF to the coordinating centres of the international groups.

PORTEC3 trial website: www.clinicalresearch.nl/portec3

All updated documents, relevant information and links are available on the trial website. Please check the website regularly for most recent versions the protocol and CRF. The SAE report form (CRF 9) has been put on the website separately to facilitate rapid reporting.

Data management news

Due to many other responsibilities, Bep Maltha has left the position of central datamanager for PORTEC-3 as of January 2010. She will however continue a number of related tasks such as TRIAS development and implementation, and other organizational issues. We are greatly indebted to Bep for the past years of excellent work and great commitment to PORTEC-3.
Karen Adema will continue to be central datamanager and first responsible person, please email her at k.w.adema@lumc.nl and always copy the message to trialbureau_hemato-oncologie@lumc.nl

Data management issues

- Please use the most recent **CRF version Oct 26, 2009**
- The TOP web randomization program has been adjusted to incorporate the protocol amendments dated Oct 26 and Nov 25, 2009. If these have not yet been formally implemented by a participating group, the unavailable items can be filled out by entering "99". Both FIGO stage 1988 and 2008 have to be completed in TOP and on the CRF to avoid confusion.
- **Toxicity Form**: this covers the period of each treatment **including** 3 wks follow-up thereafter, so RT toxicity is scored 3 weeks after completion of RT; toxicity for each chemotherapy cycle is scored 3 weeks after the cycle (often on the date of the next cycle), etc. Only toxicities **grade 2 or greater** have to be reported: please score both the toxicity type(s) and their CTC grade(s).
- **Date off treatment** (Form 5) is 3 weeks after the date of last treatment, to include the 3-week follow-up period to assess toxicity.
- Please do **complete ALL boxes**, do not leave any box blank or crossed. Appropriate answers are "0"(e.g. for zero nights in hospital), "uk"(unknown), "nd"(not done, e.g. for an investigation), "na"(not applicable)
- Please check the **appropriate units** for lab investigations, please report in the units stated on the CRF.
- In the Chemotherapy Registration form and CRF 2 (On Study form, boxes 17-18), CRF 4 (Chemotherapy form, box 22) and CRF 7 (Follow-up form, box 13) the unit for **Ca-125** had erroneously been written U/l instead of the SI unit **kU/l.** This has been corrected in the current versions of Chemotherapy Registration form and CRF on the website.