Gynecologic Cancer InterGroup
Cervix Cancer Research Network

THE OUTBACK TRIAL

A Phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone

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Peter MacCallum Cancer Centre, Melbourne Australia

Cervix Cancer Education Symposium, January 2017, Mexico

Treatment of locally advanced disease

- Concurrent cisplatin and radiation the standard of care for locally advanced disease for FIGO stage 1B or higher: NCI alert in 1999

- Individual patient data meta-analysis of 18 trials confirmed benefit of concurrent chemo:
  - significant improvement in 5 year OS rate: (60 to 66%)
  - significant improvement in 5 year DFS rate (50 to 58%)
  - Also improved loco-regional disease-free survival

Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008

Negative prognostic factors

- Larger tumor volume: particularly >50cc
- Higher FIGO stage: clinical staging
- Uterine corpus invasion: determine on MRI
- Nodal involvement: utility of PET staging
- Smoking
- Adenocarcinoma?

Narayan et al, Int J Gynecol Ca 2009
Monk et al, Int J Gynecol Ca 2007
Waggoner et al, Gynecol Oncol 2006
Mileshkin et al, Int J Gynecol Ca 2014
Fujiwara et al, Curr Oncol Rep 2014

Which chemotherapy?

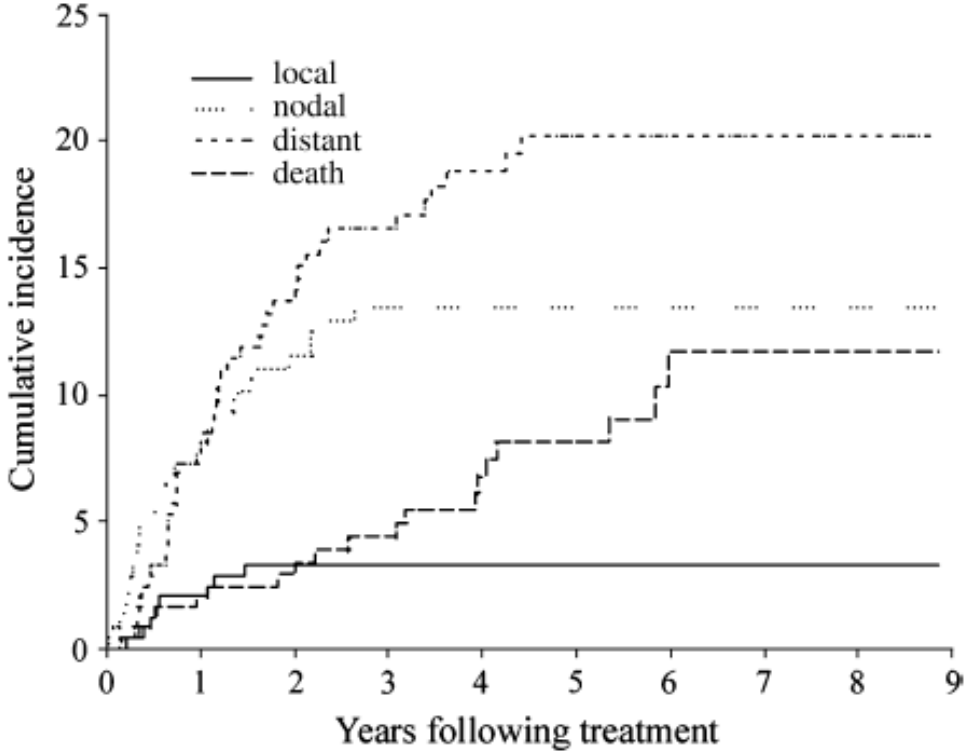
- Cisplatin 40mg/m^2 weekly (5-6 cycles) during chemoRT a recommended standard

- Meta-analysis also suggested similar benefit with non-platinum regimens
  - No effect of cycle length or dose intensity of cisplatin

- Options for those not suitable for cisplatin
  - Carboplatin – tolerable but may be inferior
  - 5FU – tolerable but may be inferior

Au-Yeung et al, JMIRO 2013
Lanciano et al, JCO 2005

Distant failure the most common site of first relapse

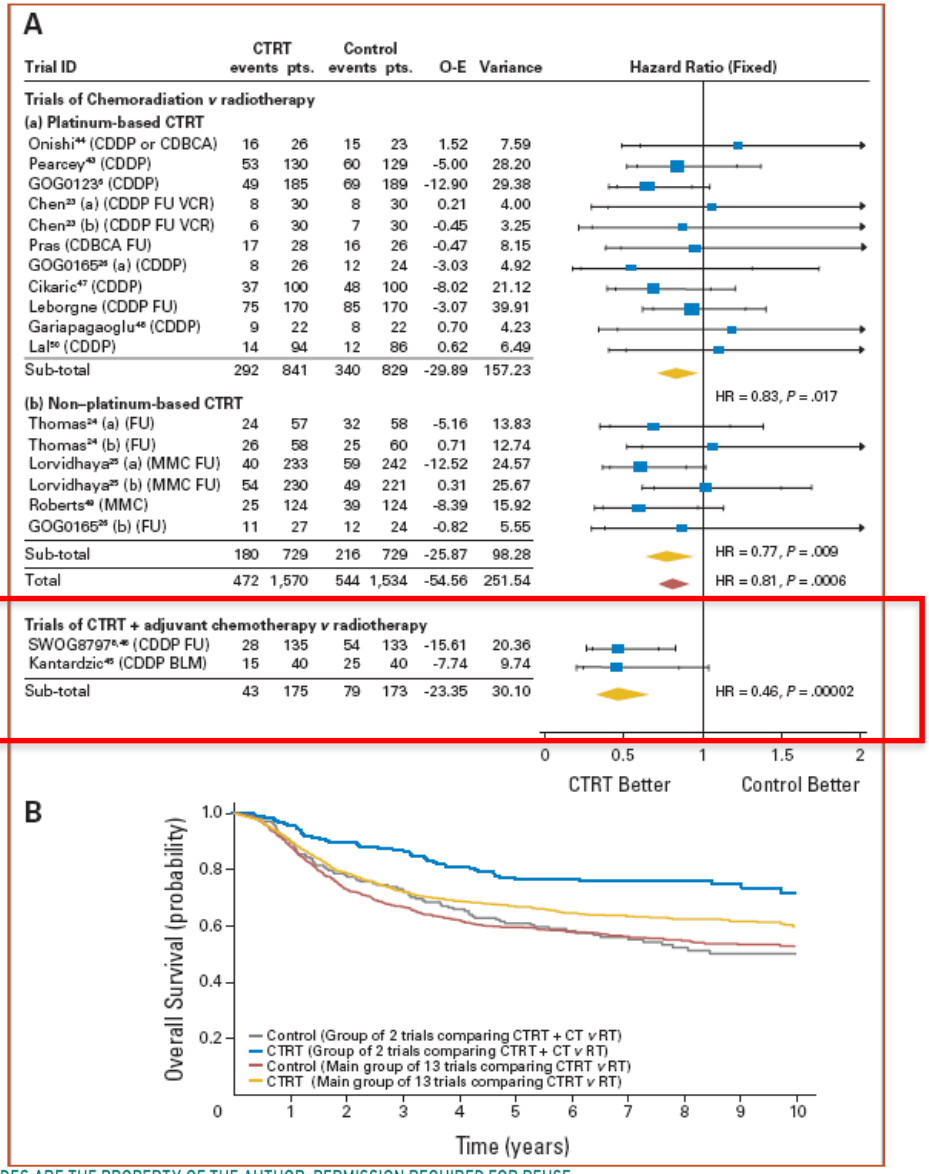


PeterMac
ChemoRT data
n = 436

- Loco-regional failure alone is rare 17/436 (4%)
- Meta-analysis: loco-regional failure in 35%
- Disease often relapses at multiple sites

Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008
Narayan et al, Int J Gynecol Ca 2007

How can we reduce distant failures?



JCO meta-analysis suggested improved survival in the 2 trials that gave 2 cycles of additional chemo ('OUTBACK')

- may treat micromets and improve survival
- Absolute 5 year OS benefit of 19%

Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008

Duenas-Gonzalez et al JCO 2011

Standard cisplatin chemoRT vs

Cisplatin-Gemcitabine chemoRT followed by 2 cycles of cisplatin/gemcitabine

- 9% improvement in PFS (65 to 74%) at 3 years but at a cost of increased toxicity: HR 0.68 (P = 0.022)
- Patients only followed-up for 1 year so unable to evaluate impact on OS
- Local failure 11 vs 16% (P=NS)
- Distant failure 8 vs 16% (P = 0.005)

Duenas-Gonzalez et al, JCO 2011
Puget Sound Oncology, Gynecol Oncology 2006

Subsequent questions

Toxicity	Control arm	Cis/Gem arm	P value
≥ 1 x G3/G4 toxicity	46%	87%	P<0.001
Hospitalized	11 pts	30 pts	P = 0.003
Discontinued Rx	1 pt (< 1%)	18 pts (7%)	P<0.001
Transfusion	28%	49%	P<0.001

- How manageable is the toxicity given others couldn't deliver and what about long-term toxicity? (9 vs 2 pts)
- What is the concurrent gemcitabine adding?
- Would further adjuvant chemo improve the results?
- Would different drugs be better / less toxic

Puget Sound Oncology, Gynecol Oncology 2006
Thomas G, JCO 2011

Recent RCT examining only concurrent treatment

- Cisplatin concurrent chemoRT

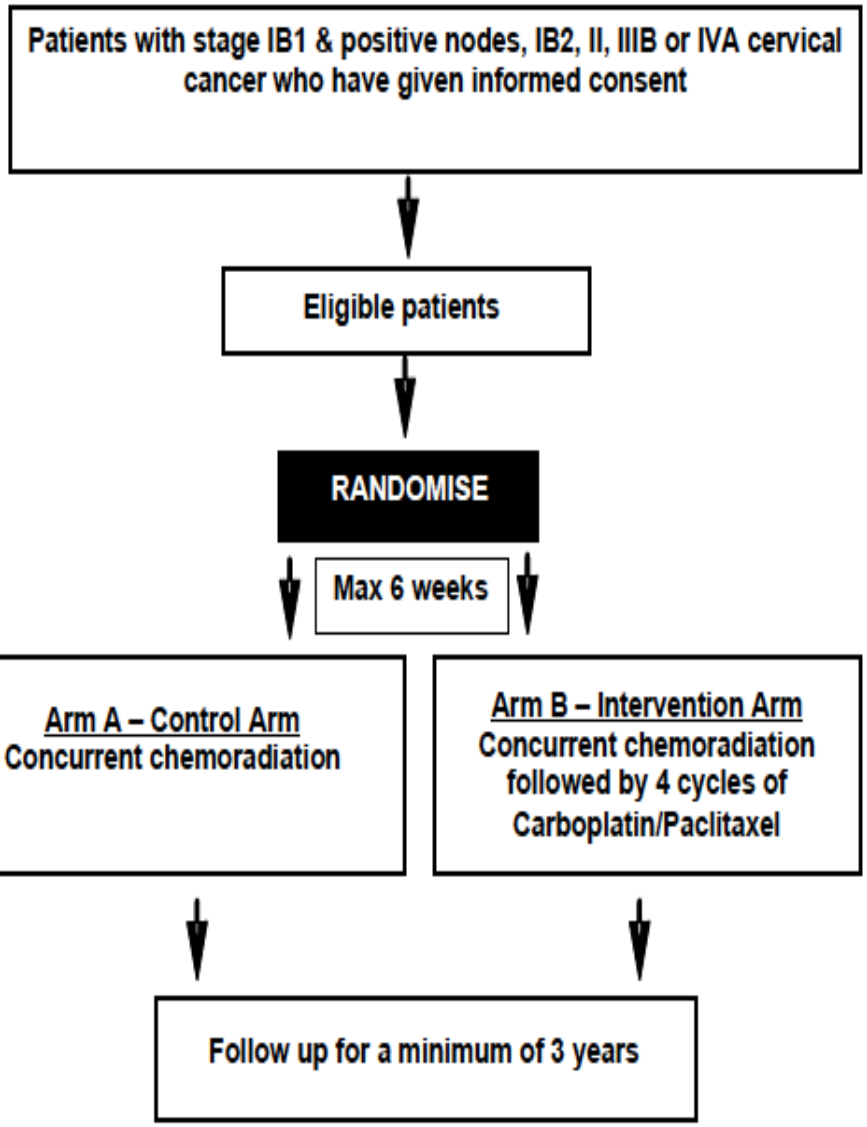
  vs

- Cisplatin/Gemcitabine concurrent chemoRT
- Closed early after interim analysis suggested no potential to improve survival and increased toxicity (n=74)

Wang CC et al,Gynecol Oncol 2015

AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP

OUTBACK trial: randomized phase III study



GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

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OBJECTIVES

Primary objective: To determine if adding adjuvant chemo to standard chemo-XRT improves overall survival

- A sample size of 780 (390 per arm) will have 80% power with 95% confidence for detecting a reduction in the hazard of death of at least 30% (HR 0.68) from the control regimen (approx 10% improvement in OS at 5 years from 63% to 73%)
- Based on 3 year accrual rate and median time to recurrence of 12 months

OBJECTIVES

Secondary objectives: To determine

- Progression-free survival rates
- Acute and long-term toxicities
- Patterns of disease recurrence
- The association between RT compliance and outcomes
- Patient QOL, including psycho-sexual health

Tertiary objectives:

- To collect blood and tissue for translational studies
- To explore the association between complete metabolic response on post-treatment PET and outcomes

Gynecologic Cancer InterGroup
Cervix Cancer Research Network:
The OUTBACK trial

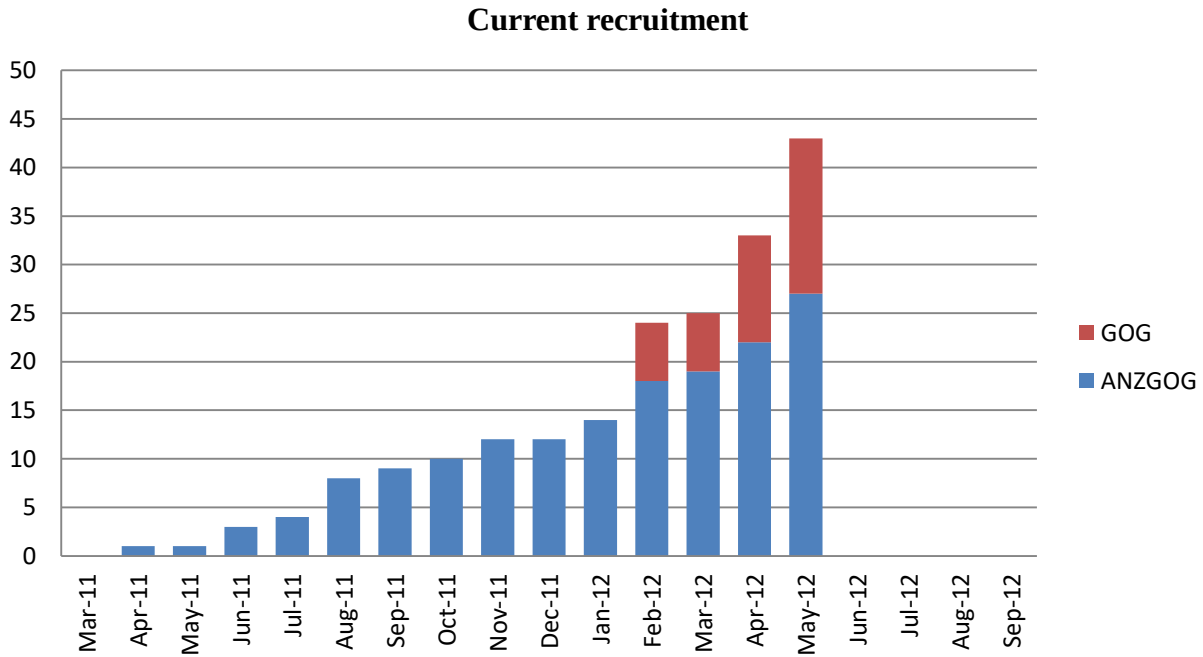
- Multi-centre phase III trial
- International, Cooperative group study
- Led by ANZGOG
- Coordinated at the NHMRC Clinical Trials Centre (CTC), the University of Sydney

How OUTBACK evolved

- Originally presented at the ‘new concepts’ session at the ANZGOG meeting in 2008
- Proposed as a 40 patient phase II to assess feasibility and tolerability
- Protocol taken to ACORD trial development workshop in 2009 by fellow: Dr Carmel Pezaro
- Concurrently presented for discussion at the GCIG Cervix Consensus meeting in Manchester in 2009 and endorsed for further development as a phase III trial

TRIAL OPENED MARCH 2011

- 43 patients: 27 ANZ, 16 GOG (at 24 May 2012)



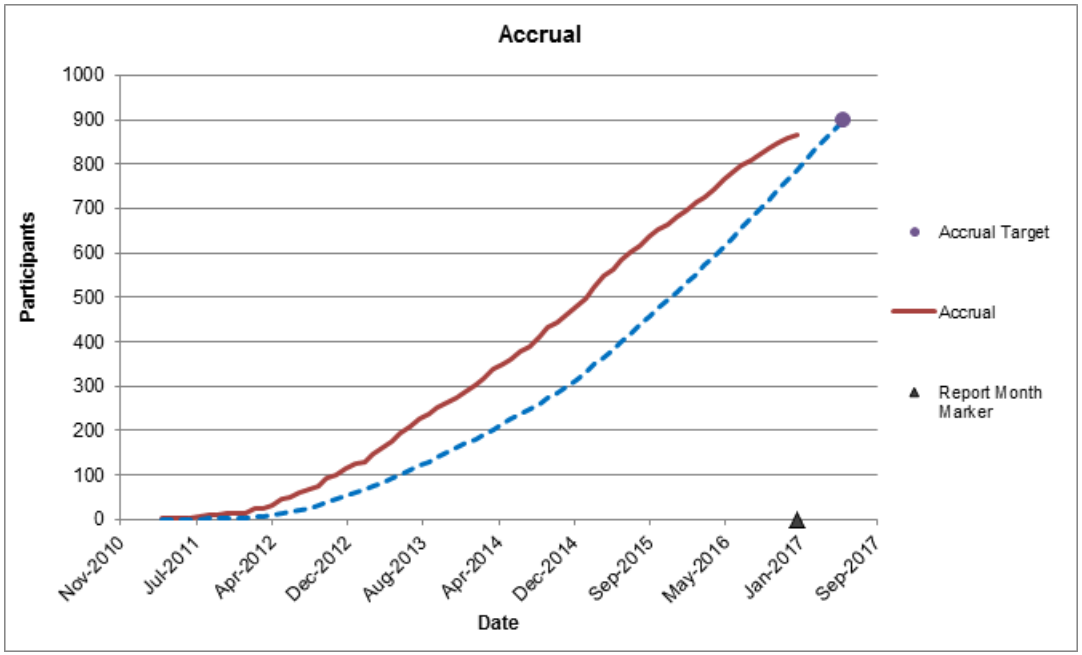
The challenges

- Persuading PHARMA to supply paclitaxel
- Multiple unsuccessful Australian grant apps despite international interest
  - PeterMac, Perpetual, Victorian Cancer Agency
  - NHMRC/Cancer Australia 2009-10, 2011
  - ‘don’t think you can do it’
- Persuading the US GOG to join
- Contracts, insurance, lawyers
- Not being able to open in India or South America
- Need to increase the sample size

The keys to success

- Lots of early morning teleconferences and thousands of emails
- Patience and diplomacy
- Think of it like running a marathon
- A great team of helpers and supporters locally
  - led by Julie Martyn from the CTC
- Mentors – Martin Stockler, Danny Rischin
- Lots of international help and support
  Ted Trimble, Gillian Thomas, Bill Small
  Dave Gaffney, Kathleen Moore, Brad Monk
- Believe in yourself!

Recruitment Jan 2016: 869/900



Country	Accrual
Australia	139
Canada	24
China	9
New Zealand	20
Saudi Arabia	5
Singapore	1
USA	669

Cervix Cancer Education Symposium, January 2017, Mexico

From little things…