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Locally Advanced Cervical Cancer & INTERLACE trial

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REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

MRC Clinical Trials Group London UK

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Meta-analysis

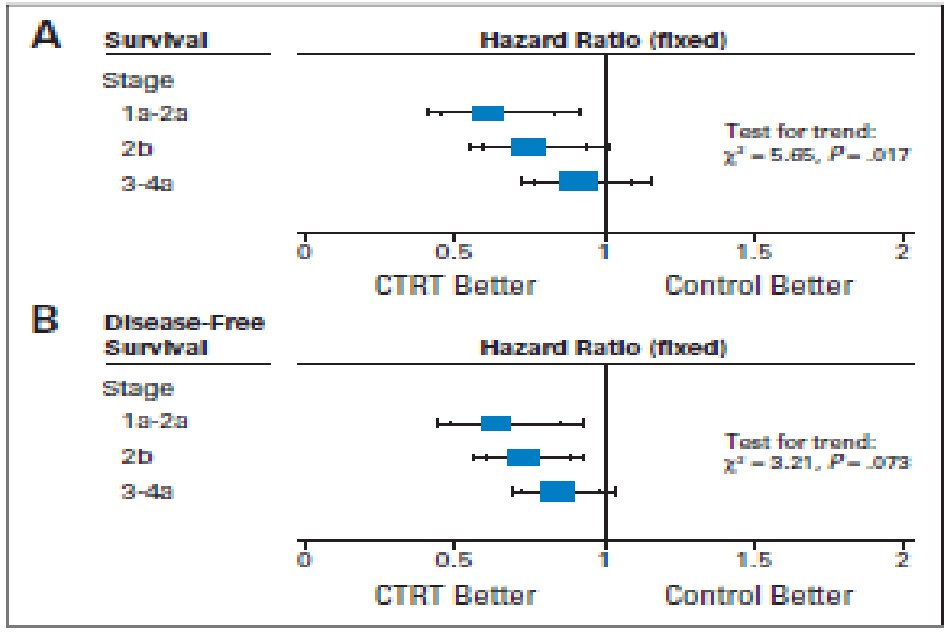

Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only). CTRT, chemoradiotherapy.

- 18 trials from 11 countries/analysis limited to 13 trials
- Confirmed benefit of CRT- smaller effect
- Overall HR survival 0.81 / HR DFS 0.78
- Suggestion that greatest benefit with earlier stage (7-10% I/II vs 3% III/IV)
- Significant benefits with non-platinum agents
- Suggestion that adjuvant chemo may improve outcome further

Beyond ChemoRadiation

- A significant proportion of women with LACC still die from their disease
- Technical advances in imaging and in RT planning facilitated a move towards increased precision in brachytherapy practice
- More accurate definition of target volume & dose escalation
- Dual aim-improve LC & reduce toxicity to OAR
- Colleagues in Vienna, Denmark and France led the way in developing IGABT

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Image guided brachytherapy in cervical cancer

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

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RetroEMBRACE

Table 1
Patient and tumour characteristics.

Variable		No of patients *n*/%
Median age (years)	53 (23–91)	731
FIGO stage	1B	123 (16.8%)
	2A	42 (5.6%)
	2B	368 (50.3%)
	3A	23 (3.1%)
	3B	145 (19.8%)
	4A	23 (3.1%)
Histology	Squamous cell Ca	591 (84.7%)
	Adenocarcinoma	9.3%
	Others	6%
Median tumour width at diagnosis	Clinically: 50 mm	MRT: 46 mm
Nodal status	N+	40%
	N−	60%
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)

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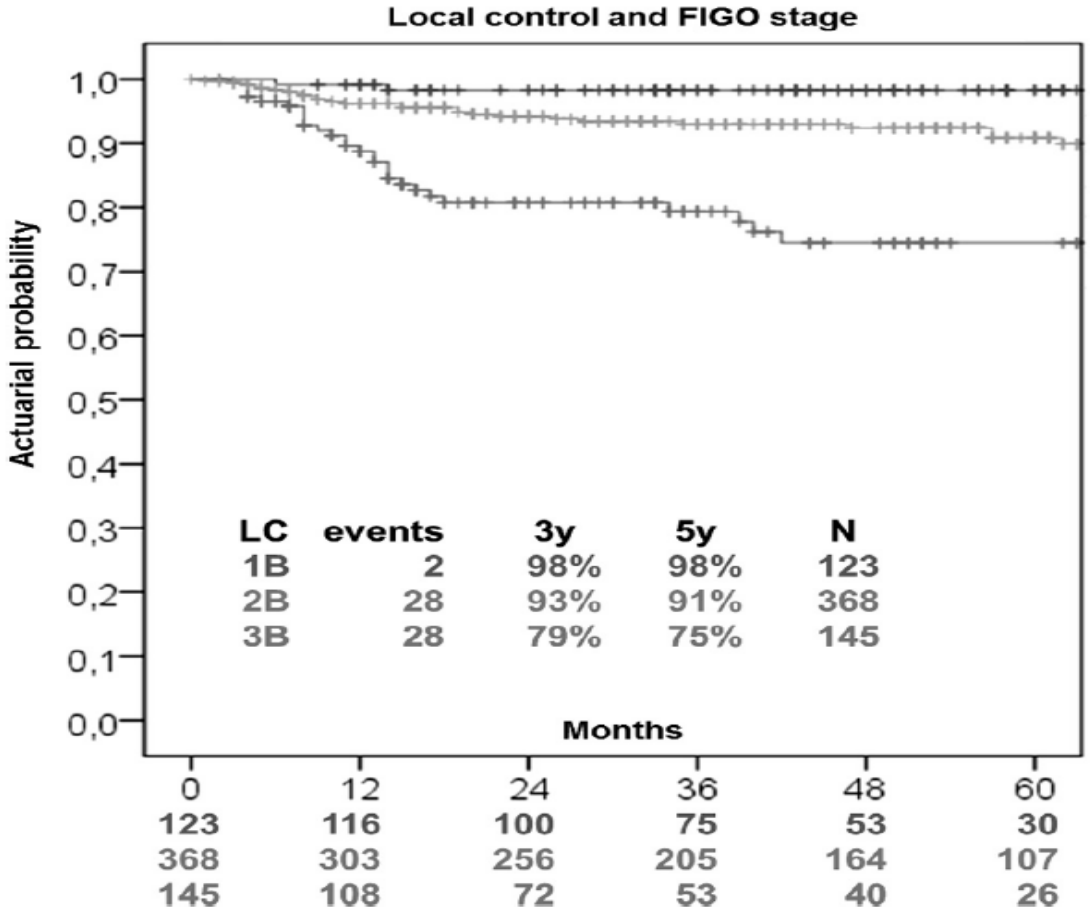
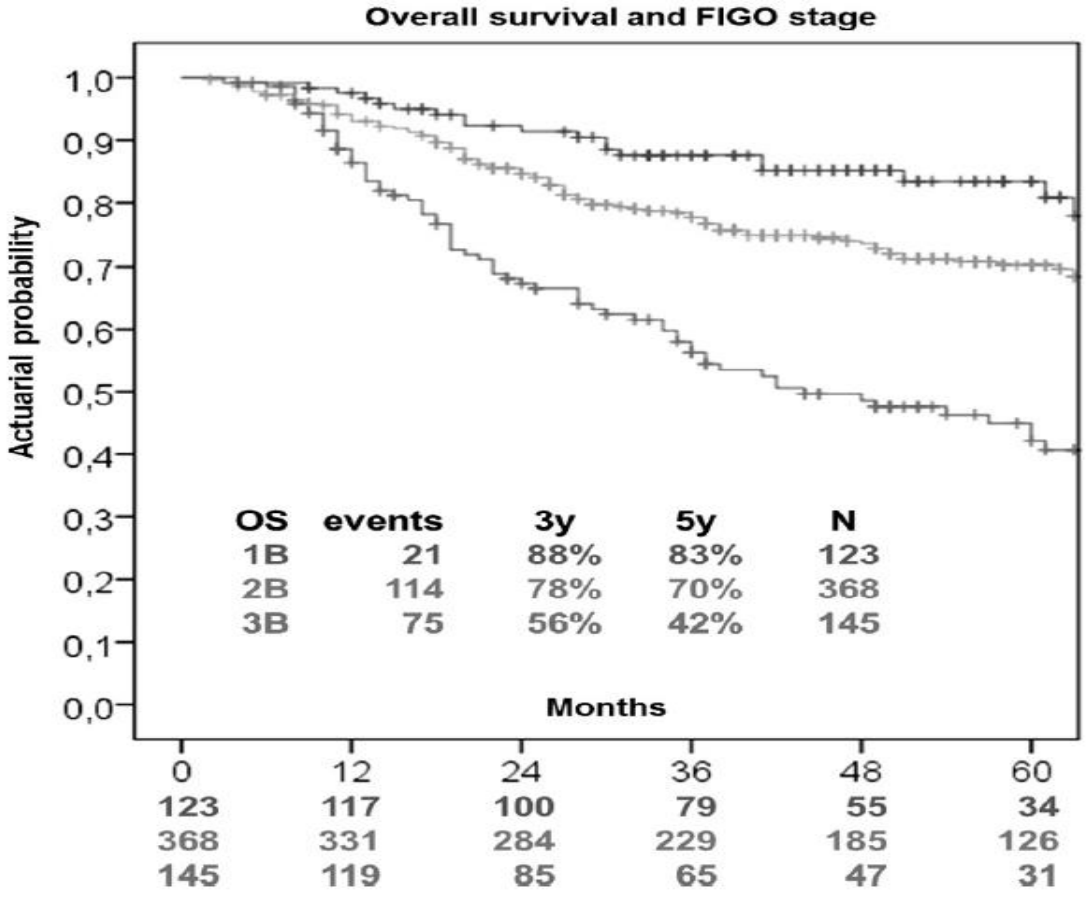
RetroEMBRACE- outcome





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Conclusions from IGABT

- Excellent local & pelvic control even in advanced disease
- Data from single institutions with the most experience confirm reduction in morbidity over historical controls
- BUT ? real impact on survival- better than historical controls treated with much lower RT doses
- However significant number of patients still die from metastatic disease---so need for additional therapy

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Is there a role for additional chemotherapy in LACC ?

Adjuvant or Induction ?

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Intensification of CRT & adjuvant chemo

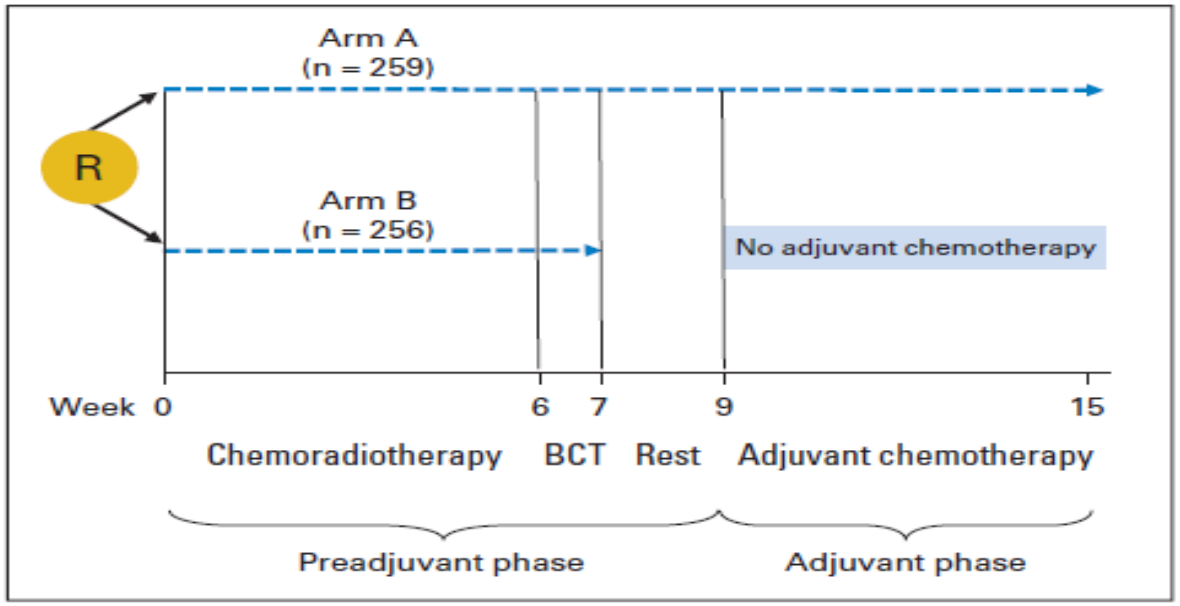

Fig 2. Study treatment schedule. Arm A treatment consisted of gemcitabine plus cisplatin chemoradiotherapy for 6 weeks. Arm B treatment consisted of cisplatin chemoradiotherapy for 6 weeks. All patients received 28 fractions of 1.8 Gy per day, 5 days per week, over the 6 weeks of chemoradiotherapy. After chemoradiotherapy, all patients were scheduled to receive 30 to 35 Gy of brachytherapy (BCT) in week 7. After BCT and a subsequent 2-week rest period, patients randomly assigned to arm A received adjuvant chemotherapy (cisplatin 50 mg/m^2 on day 1 plus gemcitabine 1,000 mg/m^2 on days 1 and 8, every 3 weeks for two cycles). R, random assignment.

- 515 pts
- 61% IIB / 37% IIIB
- 93% non adenoca
- Median age 45 yrs
- Median size 6cm

Duenas-Gonzalez et al JCO 2011

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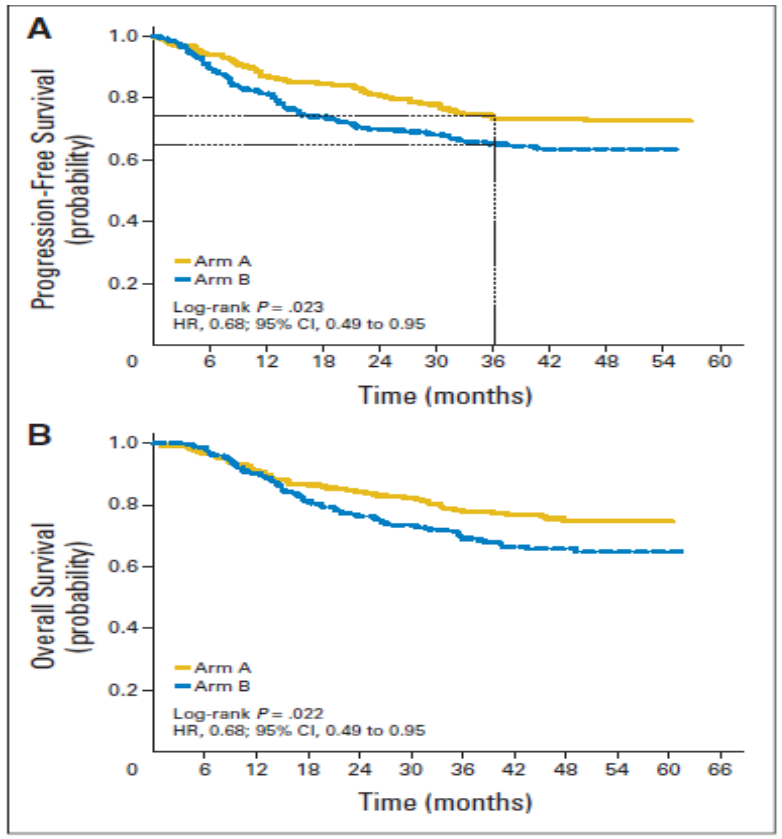

Fig 3. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival for patients who were randomly assigned to arm A or arm B. PFS at 3 years is shown by the dotted black lines and was 74.4% for arm A and 65.0% for arm B (P = .029). HR, hazard ratio.

Dueñas-González et al

- Cisplatin 40mg/m2 , Gem 125mg/m2 wx6
- Adjuvant therapy-C 50mg/2 D1 & G 1g/m2 d1,8 q21
- Significant toxicity- 72%G3/4 haem Arm A vs 24% CRT
- 9% improvement in PFS 3 years 65% (B) to 74% (A)

Duenas- Gonzalez et al JCO ,vol 13 ,2011

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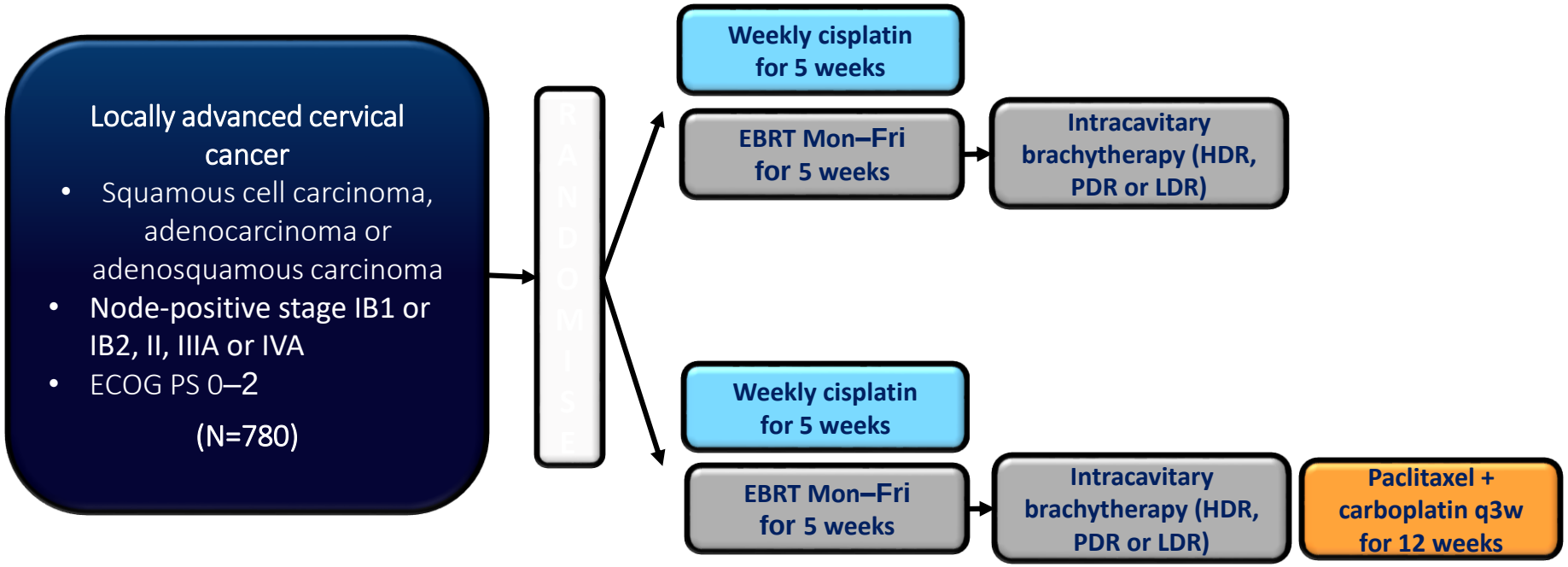
OUTBACK (GOG 0274/RTOG 1174/ANZGOG 0902): Trial design



NCT01414608

NACT Chemotherapy- background

- Several trials NACT followed by radical radiotherapy vs radiotherapy alone
- Conflicting results
- Meta-analysis of individual patient data (Tierney et al EJC 2003) ;
  -18 RCT
  -2074 patients (neoadj chemo/ RT vs RT alone)

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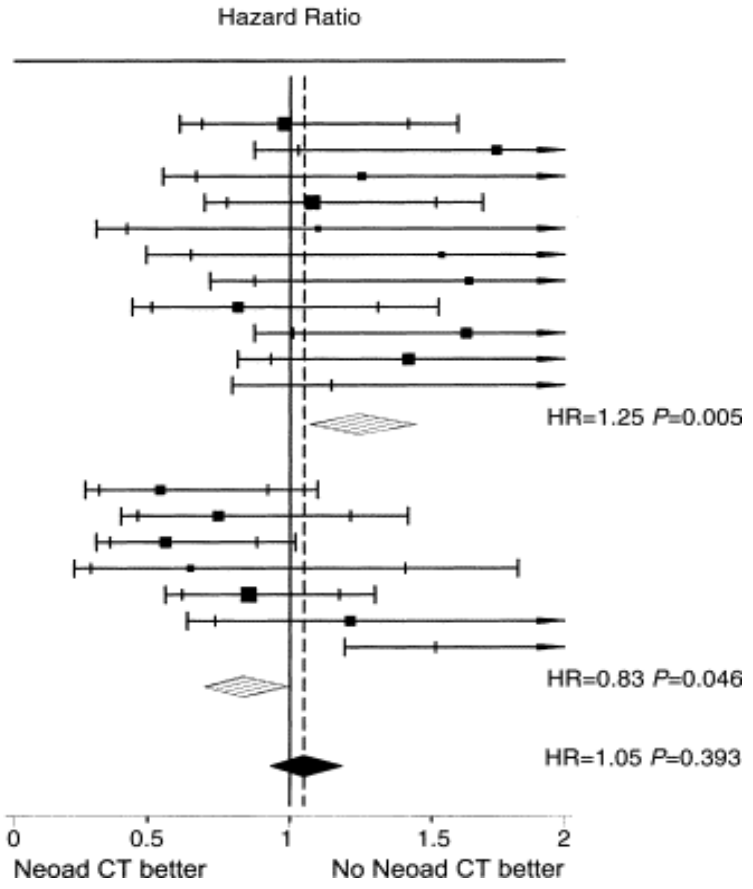
Meta- analysis (Tierney et al, 2003 E J Cancer)

Trial	Neoad CT (no. events/no. entered)	No Neoad CT	O-E	Variance
>14 day cycles				
Chauvergne, 1993	57/92	54/90	−0.47	27.66
Souhami, 1991	29/48	31/55	7.64	13.64
Tattersall, 1992	20/34	18/37	2.17	9.41
Herod, 2001	68/89	62/88	2.60	32.39
Cardenas, 1991	7/13	9/18	0.37	3.84
Cardenas, 1993	12/14	8/16	2.16	4.91
Chiara, 1994	22/32	16/32	4.68	9.33
Sundfor, 1996	31/48	35/48	−3.41	16.40
CCSG AOCOA	38/129	28/131	8.08	16.31
Kumar, 1998	49/88	34/85	7.43	20.73
LGOG	9/15	2/12	3.61	2.73
Sub-total	342/602	297/612	34.85	157.36
≤14 day cycles				
Sardi, 1997	19/104	32/106	−7.97	12.69
Sardi, 1998	30/73	33/74	−4.61	15.56
Sardi, 1996	34/54	41/54	−10.61	17.89
PMB	9/16	15/19	−2.68	5.94
Symonds, 2000	68/105	76/110	−5.86	35.84
Leborgne, 1997	32/48	28/49	2.98	14.94
MRC CeCa	19/24	9/24	7.86	6.64
Sub-total	211/424	234/436	−20.89	109.48
Total	553/1026	531/1048	13.96	266.85



Optimising this approach

- Reduce cycle length --- **weekly** treatment
- Incorporate **taxane** and retain platinum
- **Eliminate delay** between chemotherapy and definitive CRT
- Balance need for systemic treatment with **tolerability** and ease of delivery without significantly delaying definitive treatment.

Why weekly induction treatment ?

- Dose dense schedules- may
  - reduce tumour volume
  - control micrometastatic disease
  - overcome accelerated repopulation
  - impact on survival?
- Greater dose intensity (v q 3-weekly)
- Well tolerated in other patient populations

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BJC
British Journal of Cancer (2013) 108, 2464–2469 | doi: 10.1038/bjc.2013.230

Keywords: neoadjuvant chemotherapy; locally advanced; cervical cancer

A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer

M McCormack*[,1], L Kadalayil[2], A Hackshaw[2], M A Hall-Craggs[1], R P Symonds[3], V Warwick[2], H Simonds[1], I Fernando[4], M Hammond[2], L James[2], A Feeney[2] and J A Ledermann[2]

CX II Study- phase 2 single arm feasibility study

- Weekly Paclitaxel (80mg/m^2)
  &
  Carboplatin (AUC2)

  } Weeks 1-6

- Followed by radical ChemoRT
  (cisplatin 40 mg/m^2)

  } Weeks 7-13

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CX2 – Demographics & Compliance

Table 1. Baseline characteristics	
	N **(%)**
Cell type	
Adenocarcinoma	10 (22)
Adenosquamous	3 (7)
Squamous	33 (72)
Patients with positive para-aortic nodes	5 (11)
FIGO stage	
Ib2	5 (11)
IIb	23 (50)
IIIa	2 (4)
IIIb	13 (28)
IVa	3 (7)

- 80% completed all 6 cycles NACT
- 78% completed 4-6 cycles cisplatin
- 98% (45/46) had radiotherapy
- 4/5 pts with PALN received EFRT

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Toxicity

Toxicity	NACT	CRT
G3/4 Haematol	11%	45%
G3/4 Non-Haem	11%	21%

- CX2 : G3 neutropenia during CRT 35%
- Rose et al 1999 :

  46% (C/5FU/H) ,23% (C)
- Duenas-Gonzalez 2011

  51%(G/C) , 6% (C)

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CX2- Response assessed by MRI

Table 3. Tumour response using RECIST criteria

	Post-neoadjuvant *N* = 46, *N* (%)	12 Weeks after all treatment *N* = 46, *N* (%)
Complete response	2 (4)	29 (63)
Partial response	30 (65)	10 (22)
Stable disease	10 (22)	2 (4)
Progressive disease	2 (4)	2 (4)
Assessment not done	2 (4)[a]	3 (7)[b]

[a]One patient died after cycle 1, and the other had an serious adverse event after starting treatment so stopped early.
[b]The same two patients as above and a third patient due to progressive disease and clinician's choice.

- 70% RR to NACT at end wk6
- 85% RR at 12/52 post CRT

Progression free and Overall survival

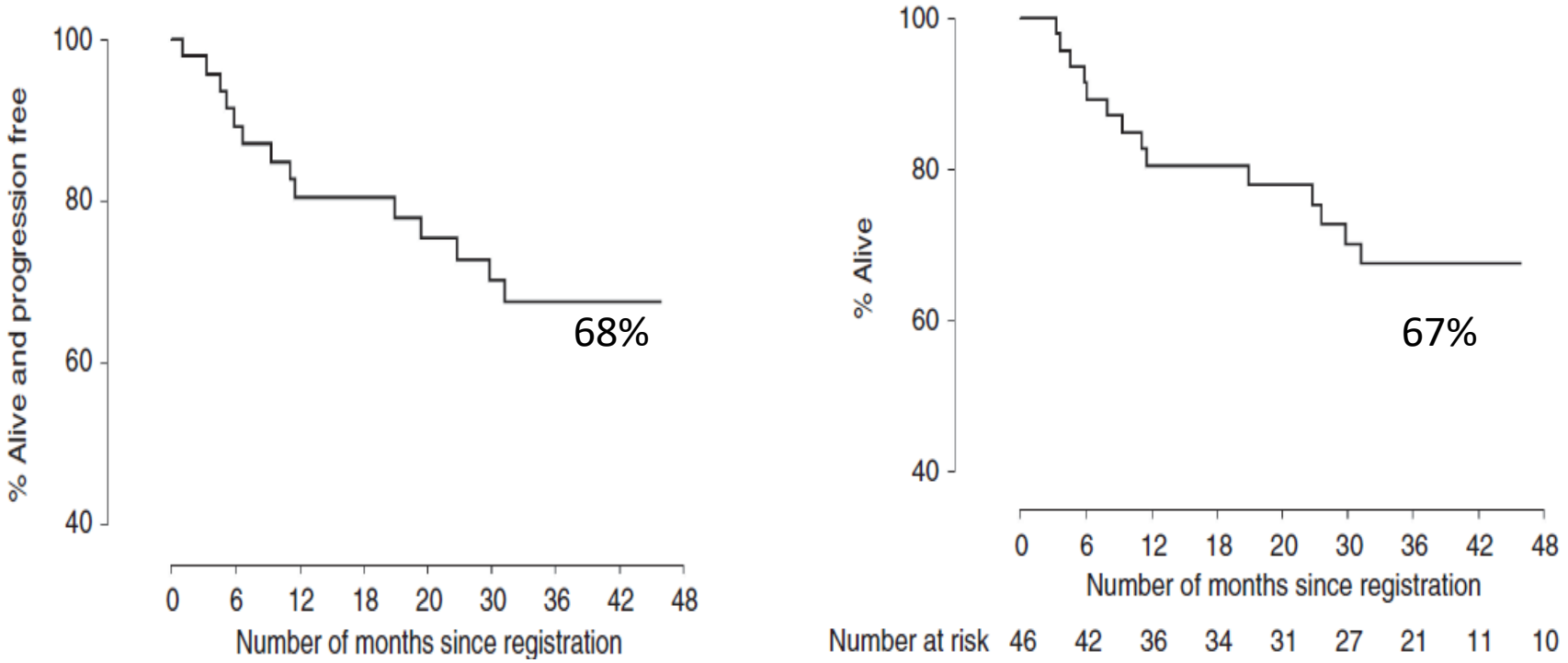

Figure 1. Kaplan–Meier plots for progression-free survival (PFS; upper) and overall survival (OS; lower) for the 46 patients in the study. The PFS and OS rates are the same for 3 and 5 years (68% and 67%) as there were no PFS or OS events between 3 and 5 years.

Br J Cancer 2013 ,108

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Randomise

Carboplatin AUC2 & Paclitaxel 80mg/m²
Weeks 1-6

Weeks 7 – 13
Standard CRT

Standard CRT

Standard CRT : 40—50.4Gy in 20-28 fractions
plus Intracavitary brachytherapy to give total EQD2 dose of 78-86Gy to point A/volume in </=50d
Weekly cisplatin 40mg/m² x 5 weeks

Follow-up
3 monthly for 2 years; 6 monthly for 3 years

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Inclusion criteria

- FIGO Ib2- Iva
- SCC, Adeno, Adenosq
- Adequate renal/ liver/BM
- Documented HIV neg (high risk countries)

Exclusion criteria

- Involvement of lower 1/3 vagina
- Previous pelvic malignancy
- History Crohn's / UC
- Hydronephrosis-unless relieved by stenting/ nephrostomy except if non functioning kidney
- Enlarged lymph nodes above aortic bifurcation

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Stratification

- FIGO stage
- Node status – positive / negative
- Squamous v non squamous histology
- Tumour Volume
- Institution
- IMRT V no IMRT

Statistics

Sample size of 730 (now revised to 630pts) provide 80% power to detect a 10% increase in 5 year OS (60 to 70%) (HR 0.70 , 2 sided test at 5% sig level)

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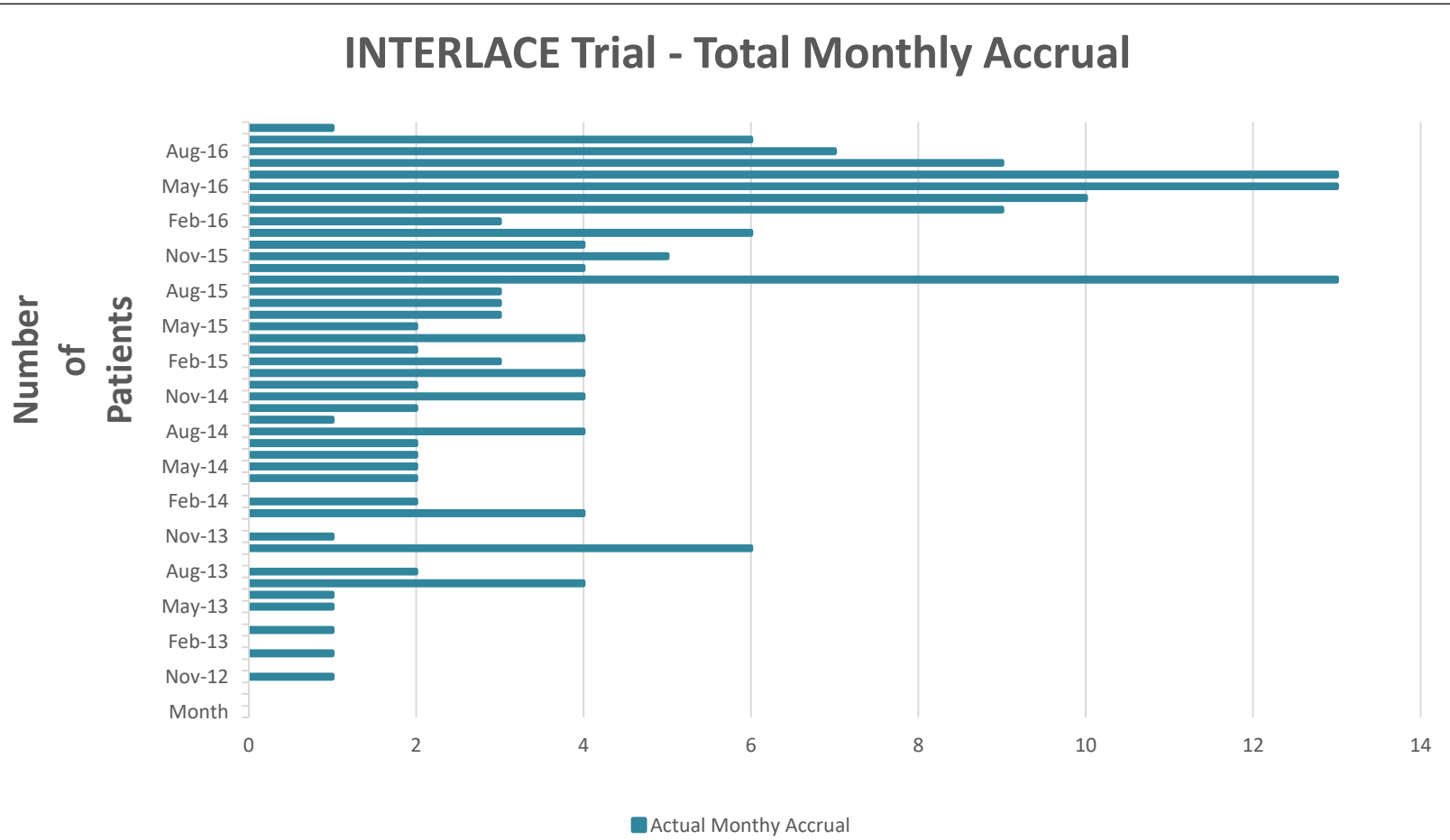

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Current status

Target recruitment –630

Accrual to date (UK and Mexico) –182

Number of sites open - **30**

- GICOM (Mexico) –24 patients recruited since opening in Feb 2016
- MaNGO (Italy) – 5 sites in setup / Milan to open Spring

Challenges at home

- Cervical cancer rare in UK & western Europe
- Expectations of target population are perhaps lower than those of women with say breast cancer
- Extension of overall treatment time – impacts on income/ travel costs
- Implementation of RTQA program
- Balancing competing priorities- *standard of care v clinical trial*

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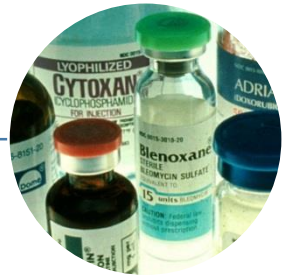
Obstacles abroad

RT facilities

Personnel



Drugs

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How to overcome them----

Greater cooperation between industry & academia

Access to large numbers of patients in real world setting

Annual donation to a charitable trust

Basic infrastructure & training in conduct of clinical trials

Income from commercial studies to fund other personnel

Funding on a competitive basis for locally appropriate trials/projects

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Thank You!