Gynaecologic Cancer Intergroup

Cervix Cancer Research Network

INTERLACE

A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer

Chief Investigator - Dr Mary McCormack

University College London Hospital

LACC and Survival 2018

- 1999- NCI announcement---incorporation of CHEMO—30-50% reduction in risk of dying
- Meta-analysis 2008-----CRT improved outcome 5yr OS 66% (RT 60%)
- Advances in Radiotherapy—esp Brachytherapy -RetroEMBRACE

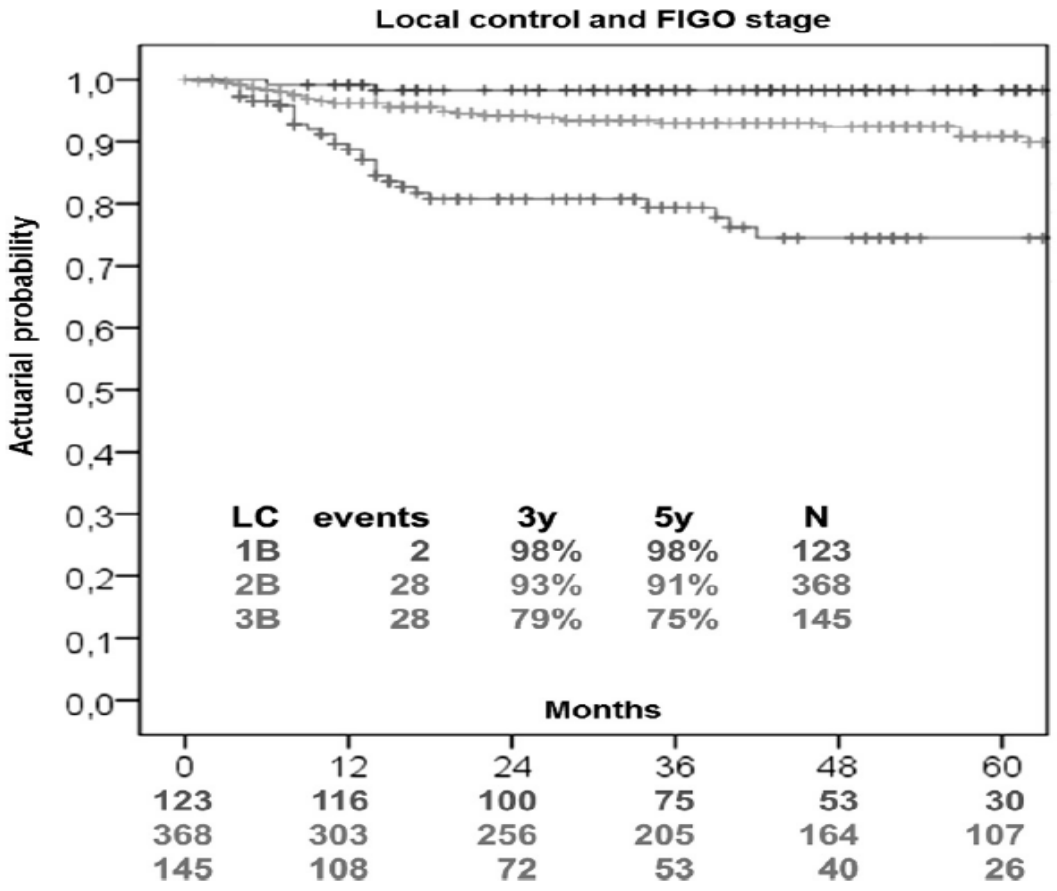
RetroEMBRACE

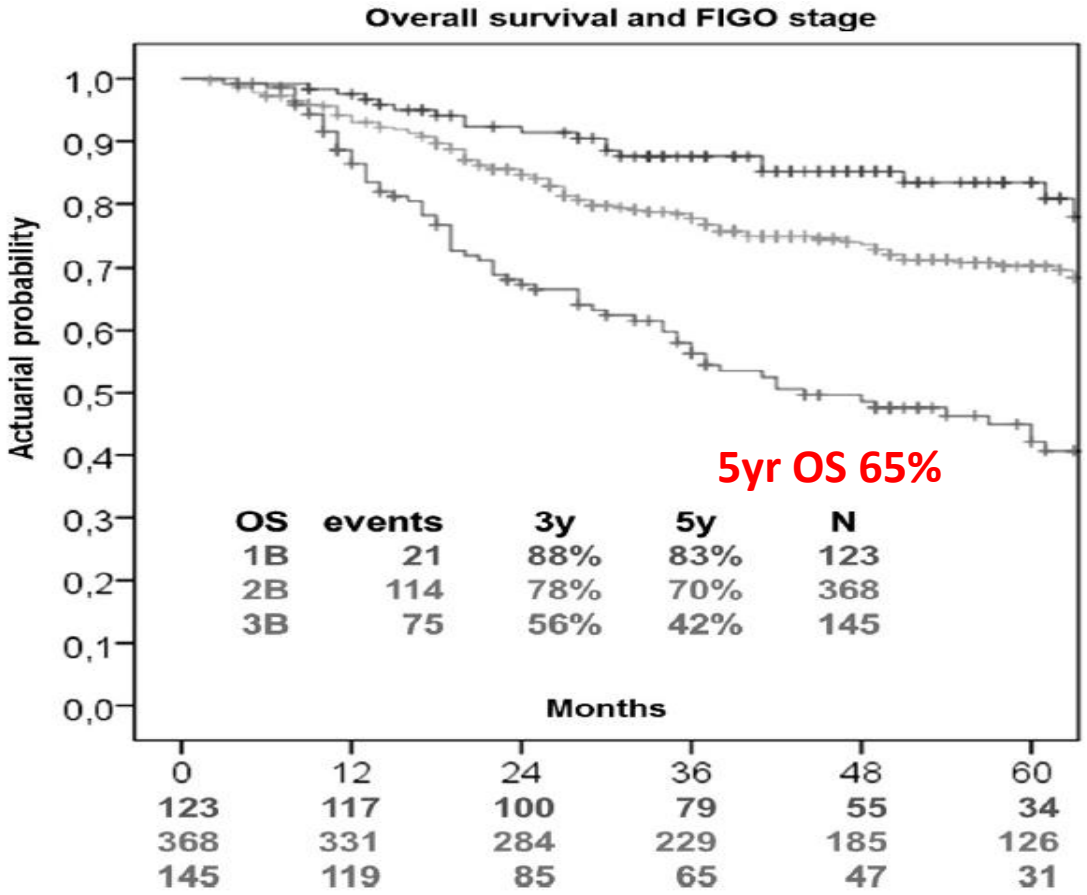
Table 1
Patient and tumour characteristics.

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%)

- Retrospective study 12 institutions
- 91% treated 3D conformal EXBRT & IGABT

RetroEMBRACE- outcome





Additional Chemotherapy in front line setting

- Intensification CRT [1] (Gem/Cispl) & adjuvant chemo (GC x 2)
  - 9% improvement PFS at 3 years (65% → 74%)
  - significant toxicity & no OS data

- OUTBACK [2] –CRT v CRT + 4 cycles adjuvant Carbo/Paclitaxel
  - recently completed accrual
  - 915 patients/ 325 sites

Role of additional chemotherapy remains to be defined

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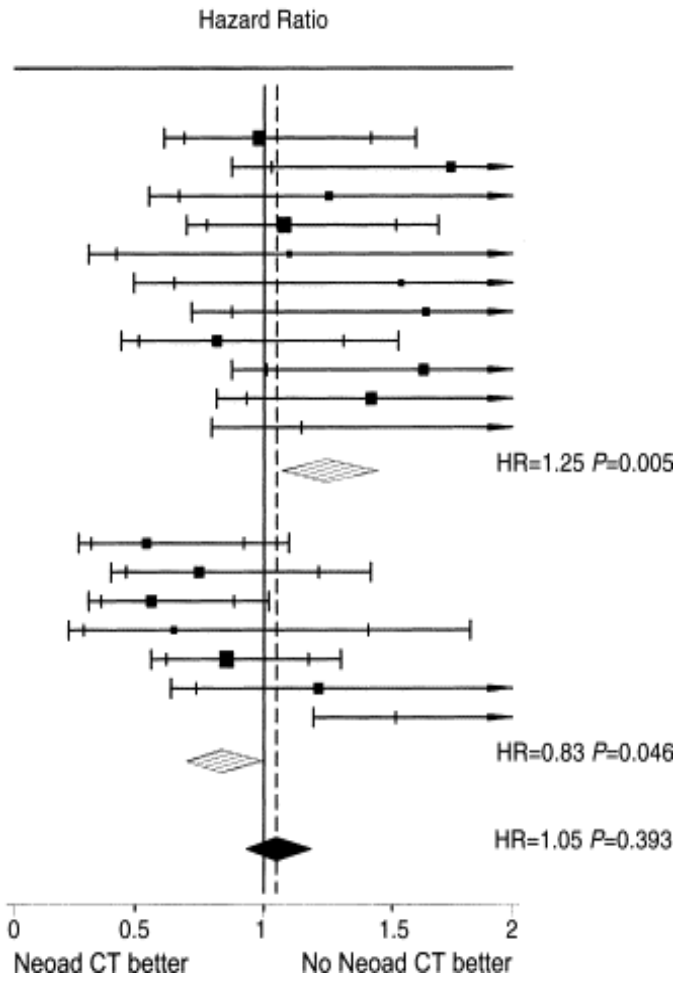
Neoadjuvant (induction) chemotherapy & RT

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



- >1000 Pts in 18 published studies
- Small numbers/ plethora regimens /most failed to show a benefit
- Suggestion of benefit with short cycle schedules….

Sentinel lymph node status in patients with locally advanced cervical cancers and impact of neoadjuvant chemotherapy

J. Slama [a,*], P. Dundr [b], L. Dusek [c], D. Fischerova [a], I. Pinkavova [a], M. Zikan [a], P. Vrzackova [a], M. Kojanova [d], D. Cibula [a]

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

- 82 pts-FIGO IB-IIB retrospective evaluation of 2 cohorts
- 31 NACT then SLNB + Rad surgery
- 51 SLNB then NACT
- 3 cycles short cycle (10-12d) platinum based chemo
- Nodal status & NACT

- Macroscopic nodal mets less freq seen in pts given NACT
- NACT appears to be even more effective at eliminating low volume nodal mets (micro/ITC)

SN status (result of pathologic ultrastaging).

SN status	Total	Group SN-NAC	Group NAC-SN	*p*-value
Negative (*n*; %)	44 (53.7)	21 (41.2)	23 (74.2)	0.013
Macrometastasis (*n*; %)	29 (35.4)	22 (43.1)	7 (22.6)	
Micrometastasis (*n*; %)	5 (6.1)	4 (7.8)	1 (3.2)	
ITC (*n*; %)	4 (4.9)	4 (7.8)	0	
Separate comparison based on the prevalence of macrometastasis or LVD[a]				
Macrometastasis (*n*; %)	29 (35.4)	22 (43.1)	7 (22.6)	0.033
LVD (*n*; %)	9 (11.0%)	8 (15.7%)	1 (3.2%)	0.049

ITC = isolated tumor cells; LVD = low volume disease (micrometastases and ITC).

[a] Prevalence rate calculated in subgroup with positive SN ($n = 38$): macrometastases–76.3%; micrometastases–13.2%; ITC–10.5%; LVD–23.7%.

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Induction chemo- new 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

CX II - phase 2 single arm feasibility study

Weekly Paclitaxel (80mg/m^2)

&

Carboplatin (AUC2)

Weeks 1-6

Radical ChemoRT weeks 7-13

(cisplatin 40 mg/m^2)

CX2 – Demographics

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)

- 46 pts from 3 centres
- Most IIB/IIIB
- 72% SCC
- 5 pts with positive PA nodes on imaging

CX2- Compliance & Toxicity

Compliance

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

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)

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.

- 69% PR/CR to NACT at end week 6
- 85% RR at 12/52 post CRT

Progression free and Overall survival

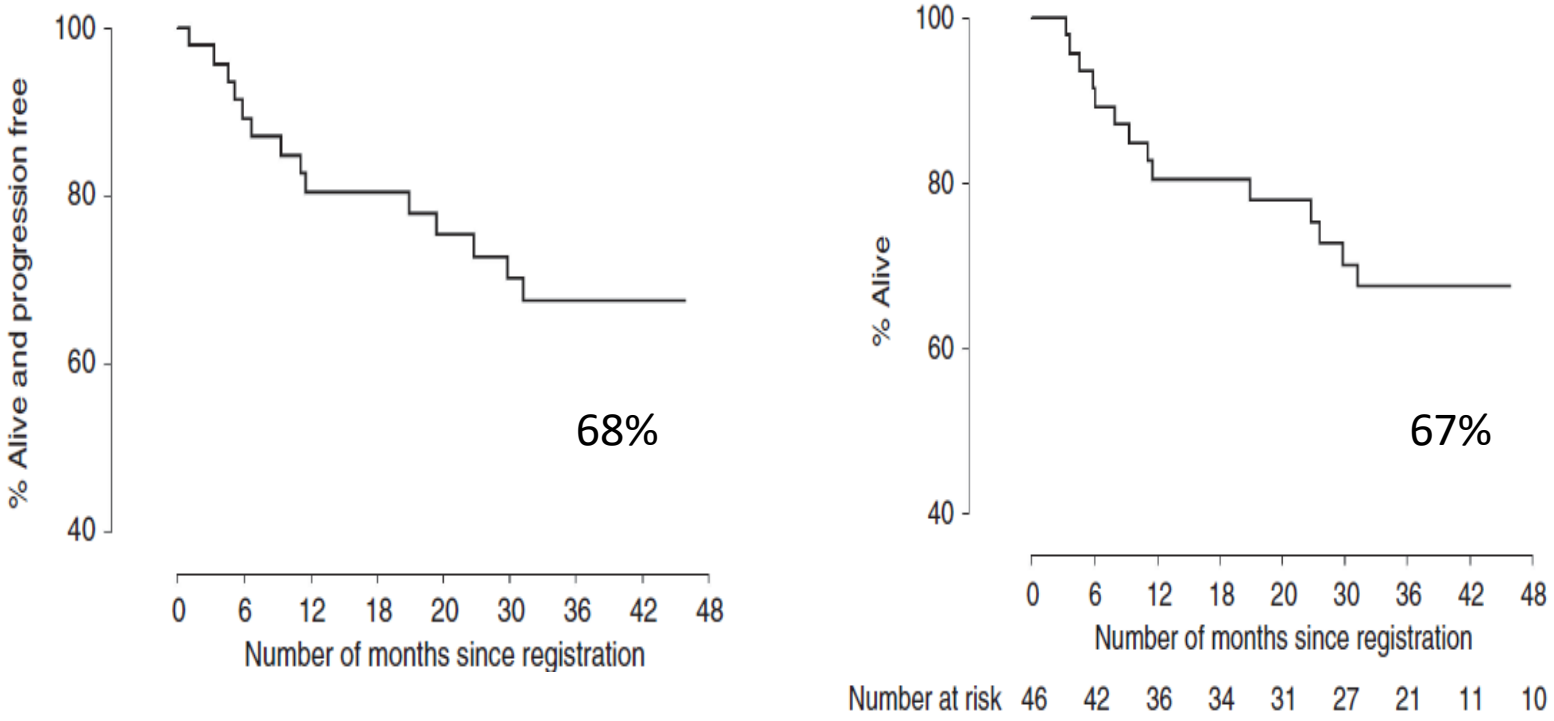

Figure 1. Kaplan–Meier plots for progression-free survival (PFS; upper) and overall survival (OS; lower) for the 46 patients in the study. The PFS and OS rates are the same for 3 and 5 years (68% and 67%) as there were no PFS or OS events between 3 and 5 years.

- 69% PR/CR to NACT at end wk6
- 85% RR at 12/52 post CRT

Br J Cancer 2013 ,108

BJC
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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]

- Dose –dense chemo delivered before CRT is feasible
- Toxicity is manageable
- Patients completed RT on time
- No evidence of detrimental effect on outcome

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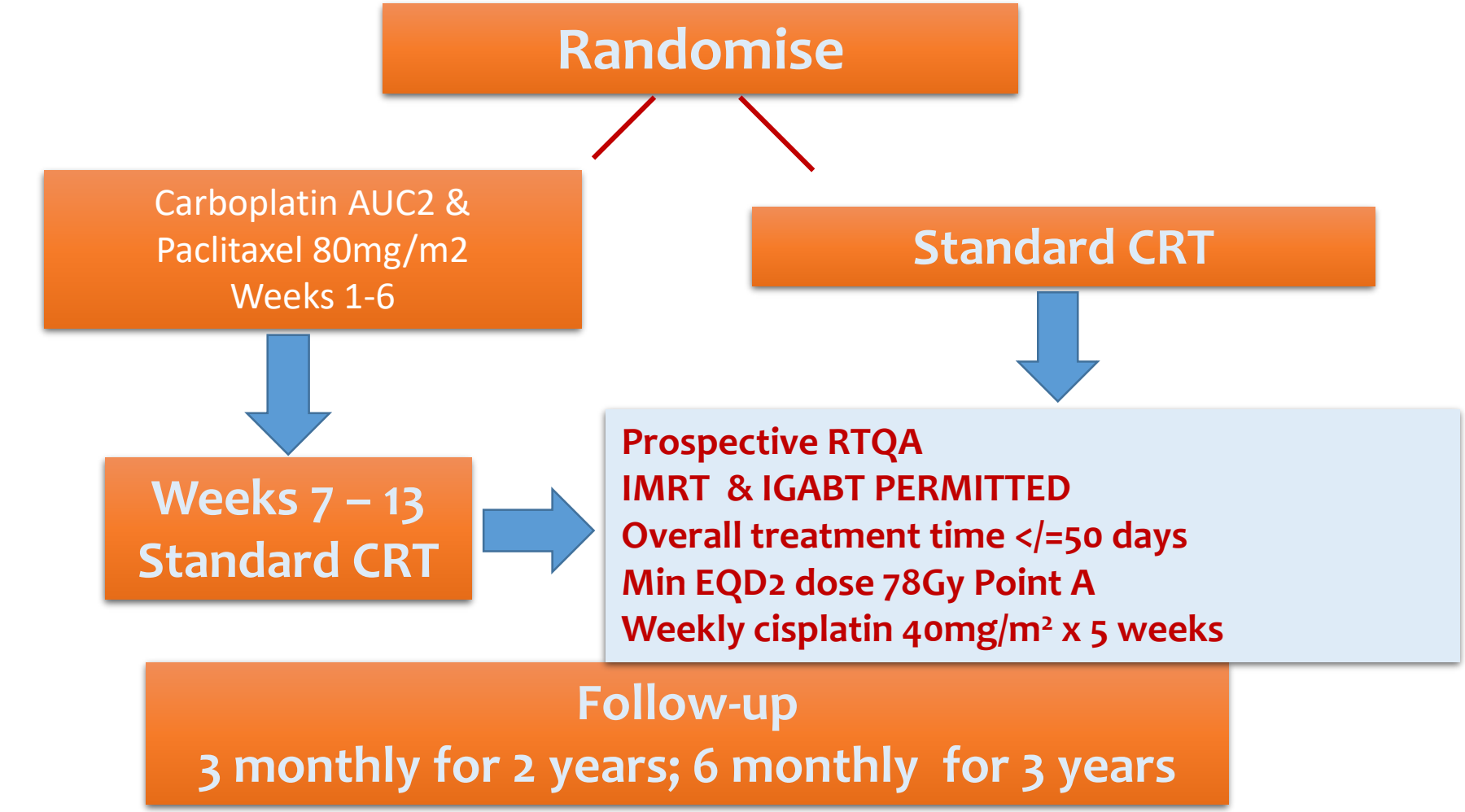

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Inclusion criteria

- FIGO 1b1 node positive
- 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
- Prior history Crohn's/ UC
- Hydronephrosis-unless relieved by stenting/ nephrostomy except if non functioning kidney
- Enlarged (>15mm CT/MRI) lymph nodes above aortic bifurcation

Stratification

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

Statistics

- 80% power to detect a 10% difference (HR 0.70) in OS (60% to 70%)

- Recruitment target 630

Recruitment update

- 29 centres UK & Mexico City / Italy
- 290/630 recruited
- 56 (20 %) from INCAN Mexico
- Funding for another 2 years (end of 2019)

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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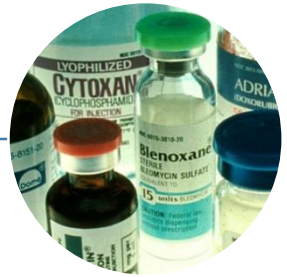
Obstacles abroad

RT facilities

Personnel



Drugs

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Thank You

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