David K. Gaffney, M.D., Ph.D., FACR, FASTRO
Senior Director for Clinical Research, HCI
Professor, Dept of Radiation Oncology, University of Utah
J Robert and Ann K Stewart Endowed Professorship

Cervix Cancer GCIG TRIALS

Cervix Cancer Rresearch Network

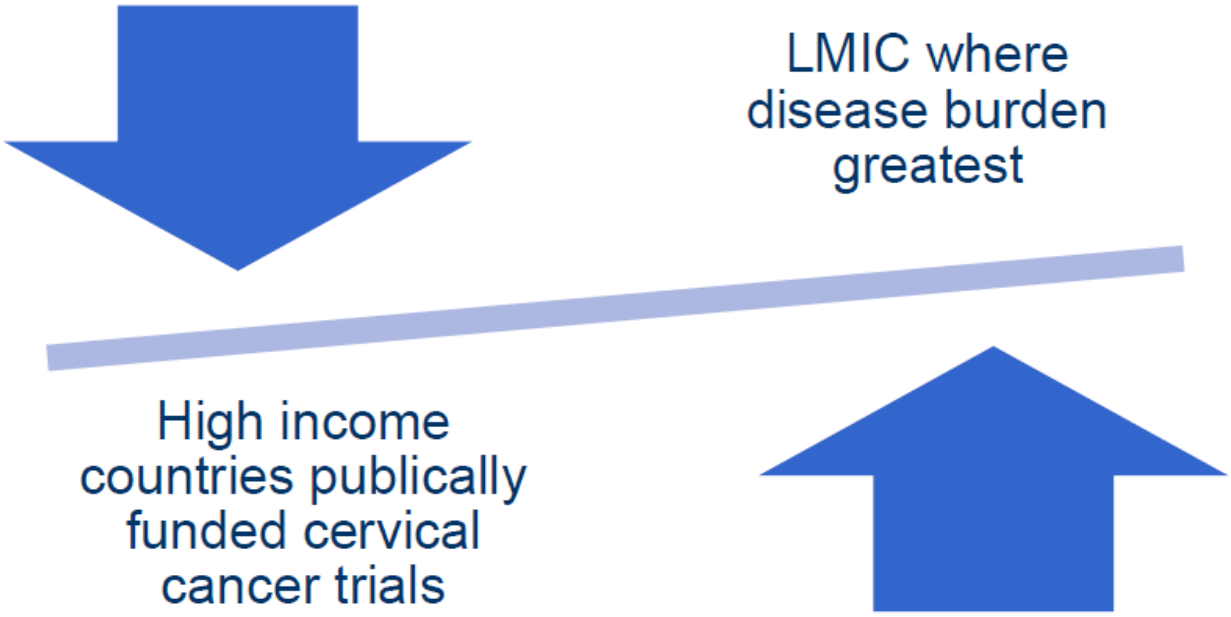
Surgery Trials

Radiation Trials

Chemotherapy Trials

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

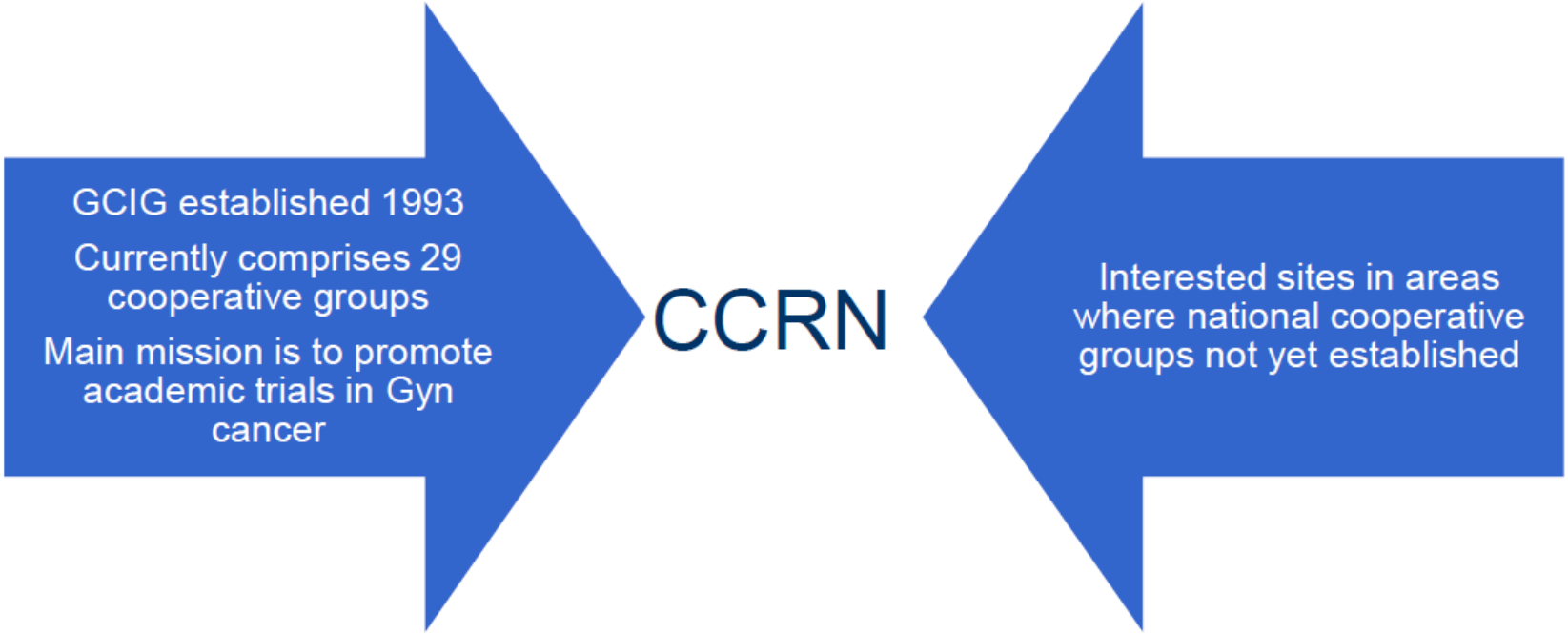
Cervical Cancer



Slide courtesy of Mary McCormack, MD, Chair CCRN

Gynecologic Cancer InterGroup
Cervix Cancer Research Network

CCRN background



Gynecologic Cancer InterGroup
Cervix Cancer Research Network

What is CCRN ?

- A Network of sites with expertise in the management of cervical cancer
- Established in 2011 by Prof Henry Kitchener & managed by GCIG
- These sites are generally in LMIC
- Common goal to promote research and good clinical practice in the treatment of women with cervical cancer
- Recognised that participation in research raises the standards for all patients.
- Inclusion of patients from diverse ethical and cultural backgrounds in clinical trials is essential to validate potentially practice changing approaches.

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Current CCRN studies

EARLY STAGE DISEASE

- SHAPE (NCIC)
- SENTICOL III(GINECO)

LOCALLY ADVANCED

- INTERLACE (NCRI)
- TACO (KGOG)
- Hypofrac (G-GOC)

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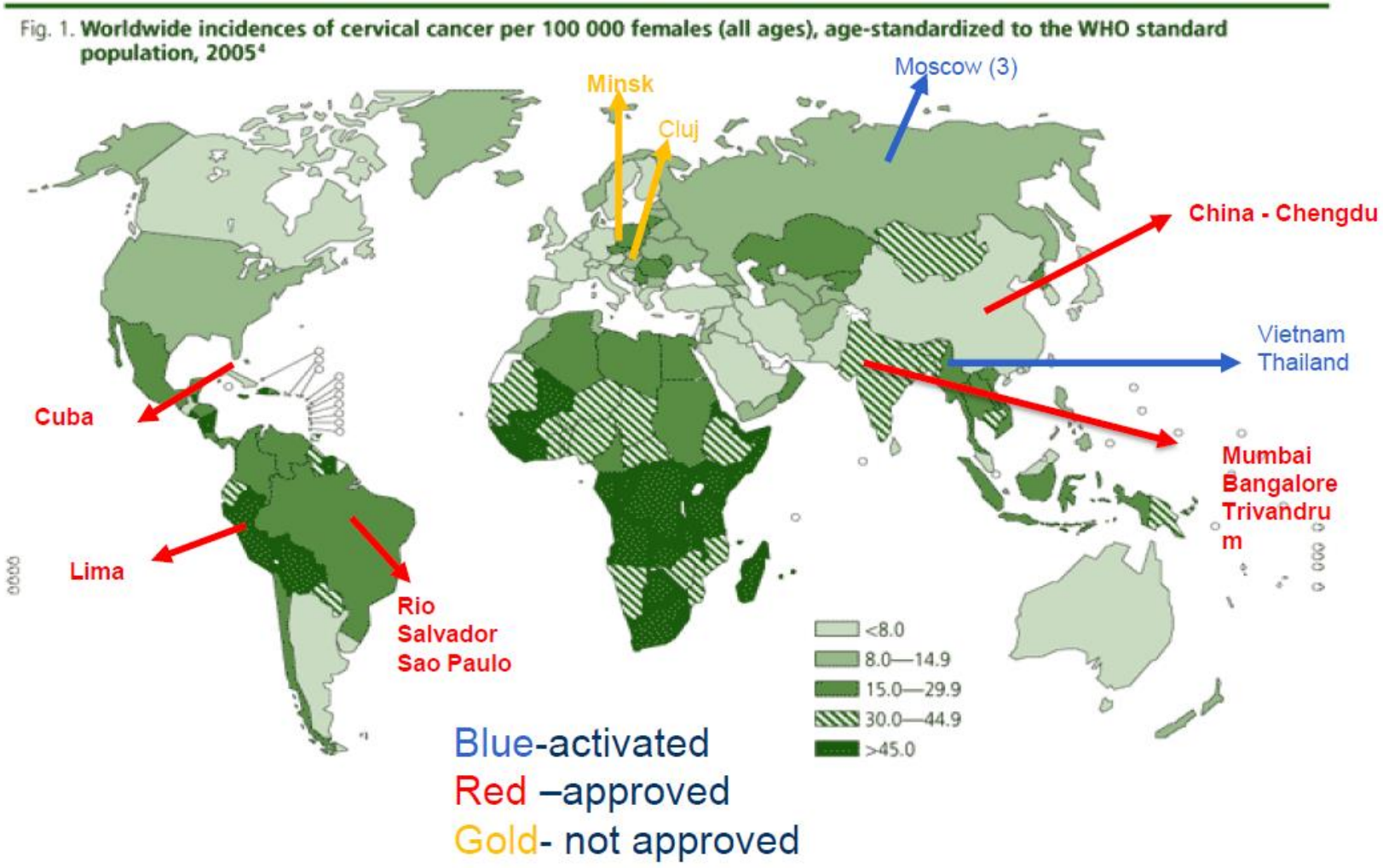
Current CCRN sites



Slide courtesy of Mary McCormack, MD, Chair CCRN

Cervix Cancer Research Network

Cervix Cancer Education Symposium
January 2017, Mexico City

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Annual meetings: Bangkok, Mexico City, Bucharest, South Africa

Surgery Trials

Trial Schema

Low-risk cervical cancer as defined by:

- squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and modified IB1
- < 10mm SI on LEEP/cone
- < 50% stromal invasion on MRI
- max dimension of ≤ 20 mm on MRI
- Grade 1-3 or not assessable

RANDOMIZE

↗ ARM 1 (Control)
Radical Hysterectomy*

↘ Arm 2 (Experimental)
Simple Hysterectomy*

→→Pelvic relapse

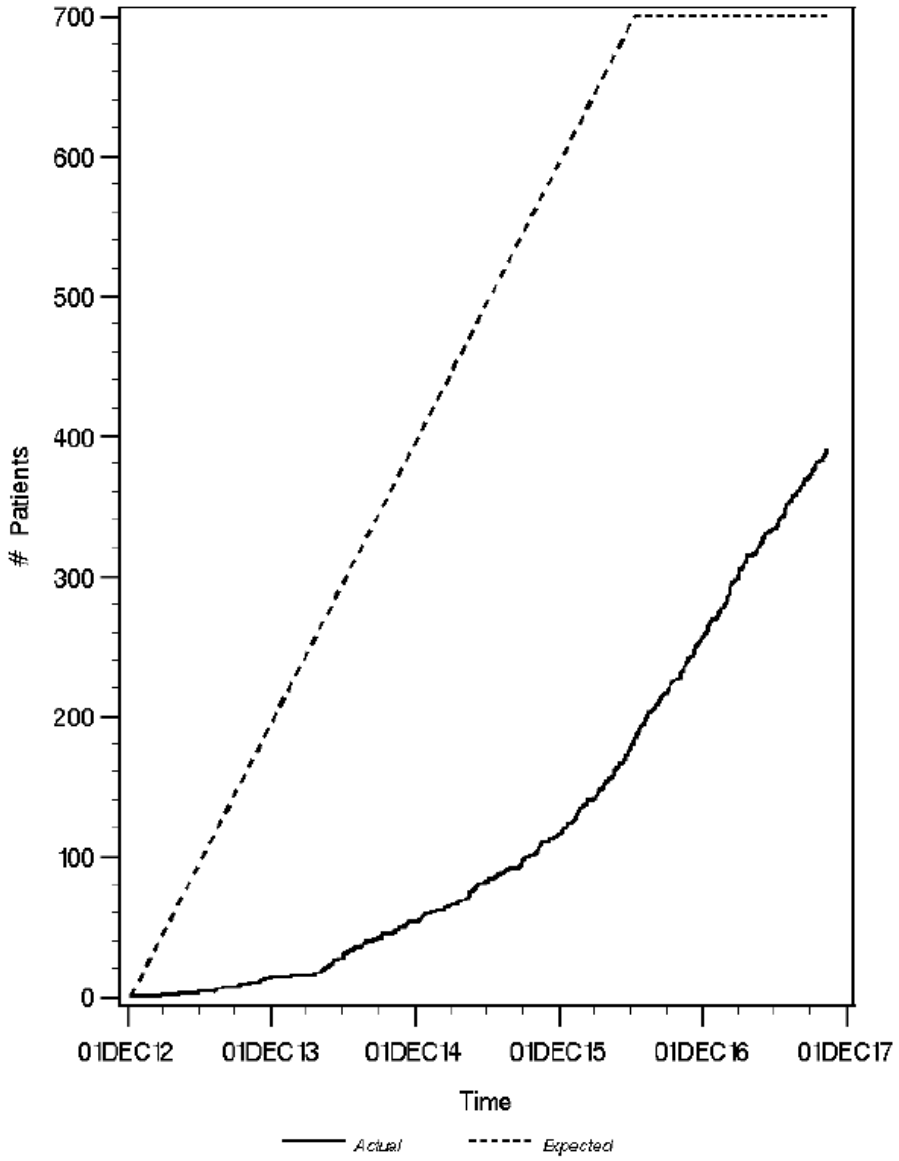
* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)

Target completion: Late 2019
63% of 700 accrued as of Feb 2018
1/3 are getting SLN dissection
9.2 % get RT

Canadian Cancer Trials Group / Groupe canadien des essais sur le cancer

Current Status



- We have reached 56% of total accrual
- Accrual Rate for past 12 months = 13 pts/month
- The first AGO Germany site was activated on Sept. 17!
- We hope to be able to activate two CCRN sites in Brazil in Q1 of 2018.

Current Status

Country	# Sites Activated
Canada	17
France	33
United Kingdom	23
Belgium	8
The Netherlands	7
Austria	7
South Korea	3
Ireland	1
China	1
Russia	1
Germany	1
Total	**101**

Country	# Patients Accrued
Canada	133
France	74
United Kingdom	56
The Netherlands	53
Belgium	29
Austria	21
Ireland	10
South Korea	10
China	2
Russia	2
Germany	0
Total	**390**

SENTICOL III Study
International prospective validation trial of sentinel node biopsy in cervical cancer

Trial setting: **Cervical cancer; early stages (Ia1 LVSI+ - IIa1)**

Study Design: **Prospective randomized, single blind phase III trial**

Sponsor(s): **Hospital Besançon for GINECO**

Planned No. of patients: **950** randomized

Current accrual: *Not started, openning soon*

Other important information: Funding OK for France and international coordination - Approval in France from CA, pending EC

Interested groups :AGO, NOGGO,MITO, MaNGO,EORTC,CTI, SAKK,DGOG,ANZGOG,KGOG,NSGO...

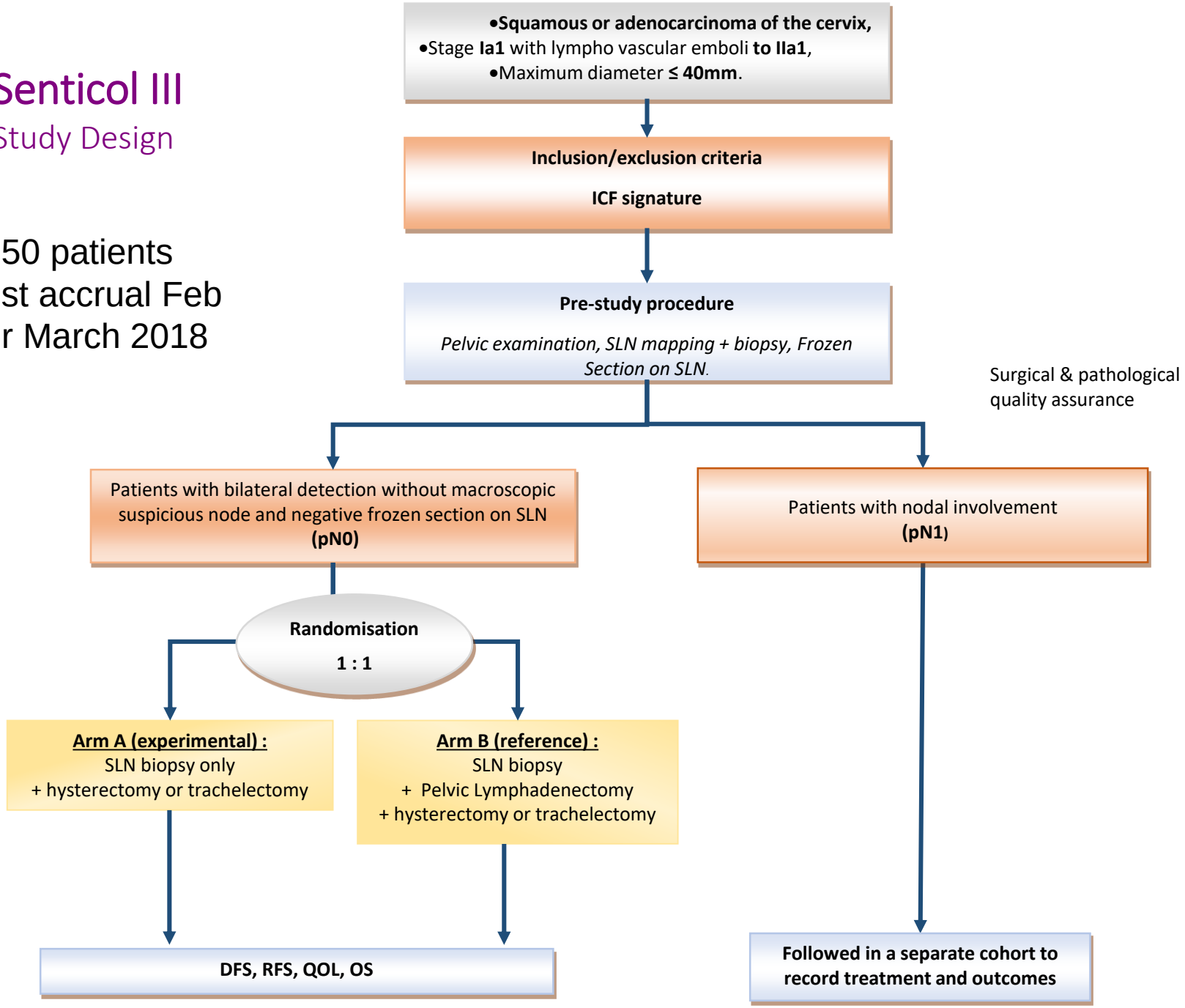
State of the art

- Despite several studies and some prospective (randomized) trials, SLN biopsy is not a standard of care.
- SLN improves sensitivity, has a low FN rate (when quality criteria met: ~0.1%, 1/1259), detects nodes outside of classical basins and detects micrometastases (and ITC)
- ~15% more positive nodes detected with ultrastaging
- Results of SENTICOL II
  - 105 SLN vs 101 SLN + PLN (in N0 patients)
  - Lymphatic complications 31.4 vs 51.5% (<0.001)
  - Neurological symptoms 7.8 vs 20.6% (p<001)

Senticol III

Study Design

950 patients
1st accrual Feb
or March 2018



GOG 278

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PROTOCOL GOG-0278

EVALUATION OF PHYSICAL FUNCTION AND QUALITY OF LIFE (QOL) BEFORE AND AFTER NON-RADICAL SURGICAL THERAPY (EXTRA FASCIAL HYSTERECTOMY OR CONE BIOPSY WITH PELVIC LYMPHADENECTOMY) FOR STAGE IA1 (LVSI+) and IA2-IB1 (≤ 2CM) CERVICAL CANCER

NCI Version Date 09/20/2012

POINTS:
PER CAPITA - 20
MEMBERSHIP - 6

Enrollment: 152/200 as of 2/16/18

NCT01649089

ConCerv-G-GOC

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Cervical Cancer-Conservative Management

Cone/Simple Hysterectomy + SLN Only

Stage IA2-IB1 (<2cm) LVSI (-)

Study Design: Prospective Phase II

Sponsor(s): None

Planned No. of patients: 100

Current accrual: 81

Other important information:

8 Countries

14 Sites Overall

Primary: MD Anderson

LACC-G-GOC

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Cervical Cancer-Open vs. MIS Radical Hysterectomy

Stage IA2-IB1

Study Design: Prospective Randomized (50/50)

Sponsor(s): None

Planned No. of patients: 740

Current accrual: 636

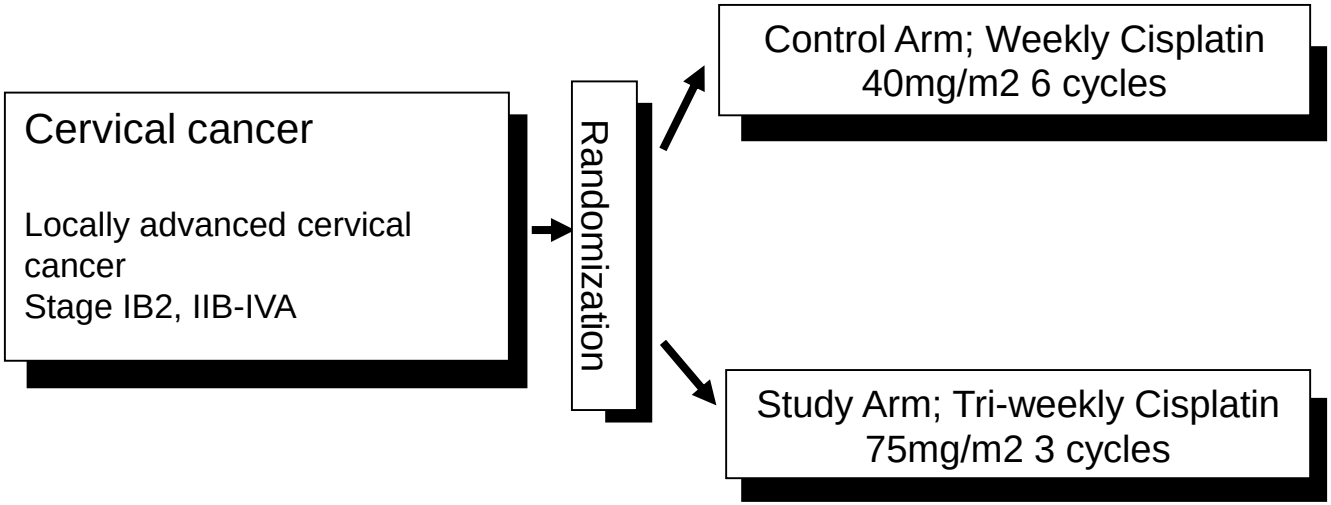
Other important information: **29 Sites Overall**

Primary: MD Anderson

Radiation or Chemo-Radiation Trials

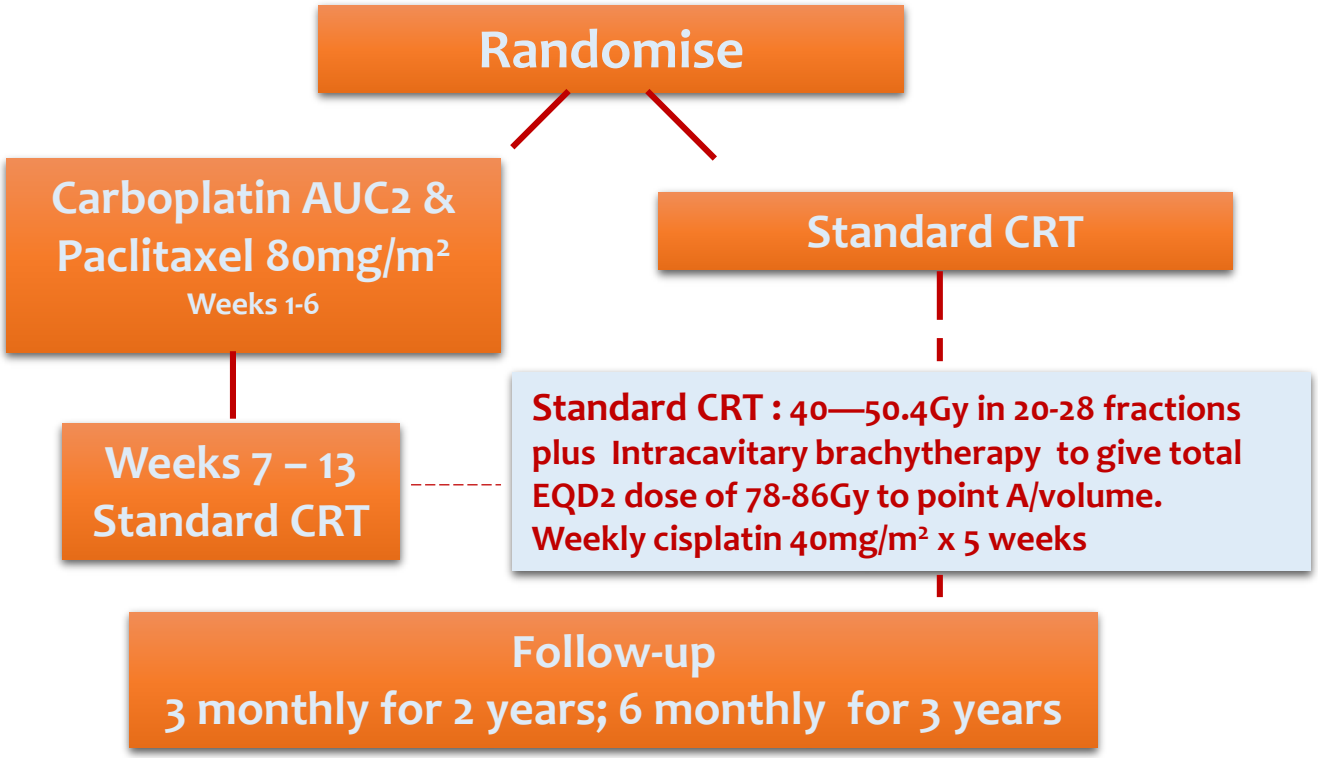
TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)



230 patients accrued

INTERLACE



30 sites open as of November 2017,
253/630 accruals

GY006

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NTO-1151-Triapine:

- Small molecule chelator – Inhibits ribonuclease reductase /ribonucleotide reductase inhibitor

- PI = TREY LEATH MD
- N = 188
- Enrollment to June 2017 = 50
- Primary Endpoint = RFS

Newly diagnosed uterine cervix cancer
- Squamous
- Adenosquamous
- Adenocarcinoma

Clinical stage bulky (> 5 cm) IB2, or
Clinical stage II, IIIB, or IVA followed by
Negative para-aortic nodal staging by PET/CT

Stratify para-aortic node-negative patients by:
a. Age (≤ 45 years or > 45 years)
b. Performance status (0, 1, or 2)
c. Intensity Modulated Radiation Therapy (yes or no)
d. Stage (≤ clinical stage II, or ≥ clinical stage III)

RANDOMIZE

Arm 1:
- Radiation
- Cisplatin

Arm 2:
- Radiation
- Cisplatin
- Triapine

Radiation: 45 Gy / 25 fractions of 1.8 Gy + 5.4 Gy / 3 fraction parametrium boost + 40 Gy LDR or 30 Gy HDR brachytherapy

Cisplatin: X1 weekly cisplatin 40 mg/m² (maximum 70 mg) days 2, 9, 16, 23, 30 of radiation (5 total infusions; a sixth administration on day 36 is permissible at the treating physician's discretion.)

Triapine: X3 weekly 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) 25 mg/m² (maximum 50 mg) days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 of radiation (15 total infusions)

NCT02466971

AIM2CERV/GOG 3009

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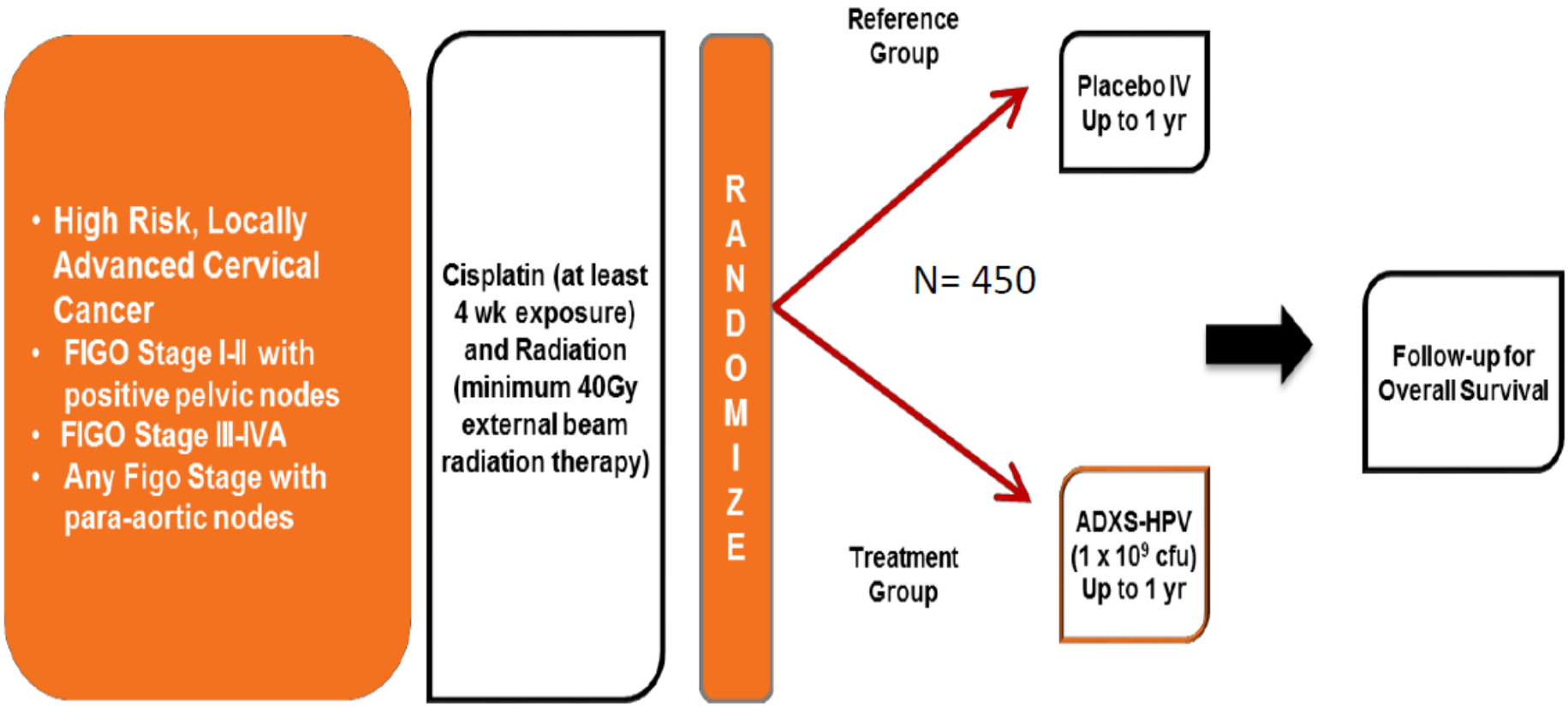


Baseline tumor imaging must be performed within 28 days prior to the first study treatment infusion

Randomization 1:2 Reference and Treatment Groups

Primary Objective is Progression Free Survival

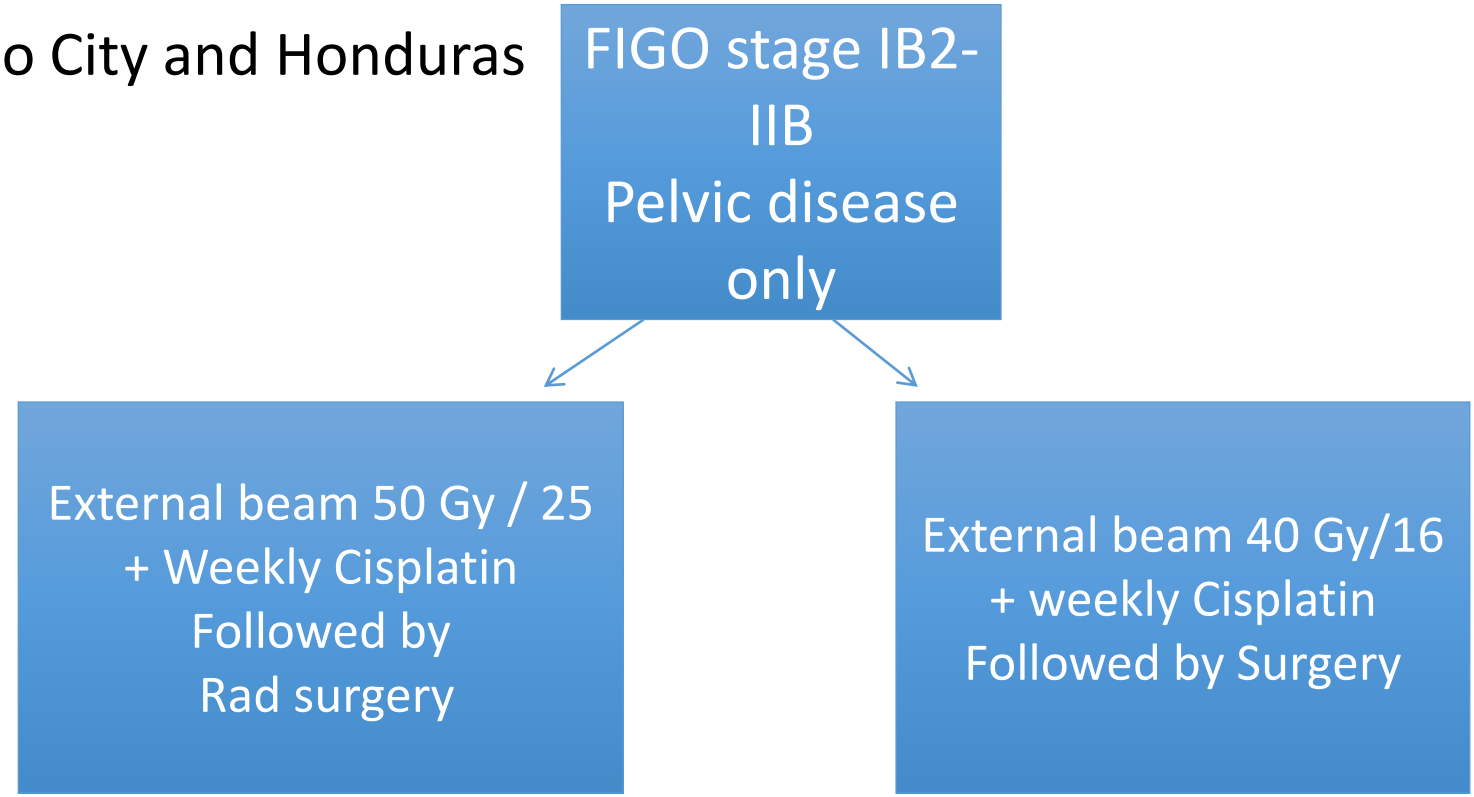
NCT02853604

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Phase II - No brachytherapy

G-GOC

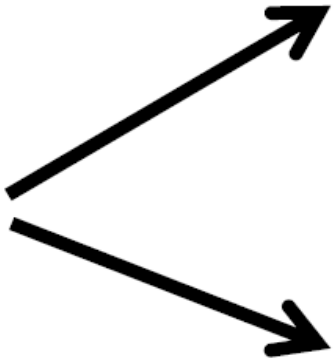
Mexico City and Honduras



10 patients accrued as of Feb 3, 2018

RTOG/GOG/KGOG 0724 – for high-risk Cervical Carcinoma

Radical hysterectomy – positive nodes, positive parametrium



Weekly cis + RT

Weekly cis +RT + 4 courses of Carbo/Taxol

- PI = Anuja Jhingran
- N = 285
- Primary Endpoint = DFS

Enrollment – 163/285

NCT00980954

Chemotherapy Trials

A phase II study of weekly paclitaxel and cisplatin followed by radical hysterectomy in stages IB2 and IIA2 cervical cancer

AGOG14-001/TGOG1008

NCT02432365

Chyong-Huey Lai, MD

On behalf of

Principal investigator Huei-Jean Huang, MD

GOG 316 (R2810-ONC-1676)

NCT03257267

- Recurrent, persistent, and/or metastatic cervical cancer
- Progressed within 6 months of the last dose of platinum

RANDOMIZE

REGN2810 350 mg Q3W, for up to 96 weeks

Physicians choice chemotherapy

Pemetrexed 500 mg/m2 Q3W
Topotecan 1 mg/m2 daily for 5 days, Q21 days
Irinotecan 100 mg/m2 days 1, 8, 15, & 22, followed by 2 weeks rest (6-week cycle)
Vinorelbine 30 mg/m2 days 1 & 8, Q21 days
Gemcitabine 1000 mg/m2 on days 1 & 8, Q21 days

PI = Krishnansu S. Tewari, MD
N = 436
Primary Endpoint = OS

REGN2810, a fully human monoclonal antibody against programmed death-1 (PD-1)

A randomized double-blind placebo-controlled phase II trial of Rucaparib maintenance therapy for patients with locally advanced cervical cancer

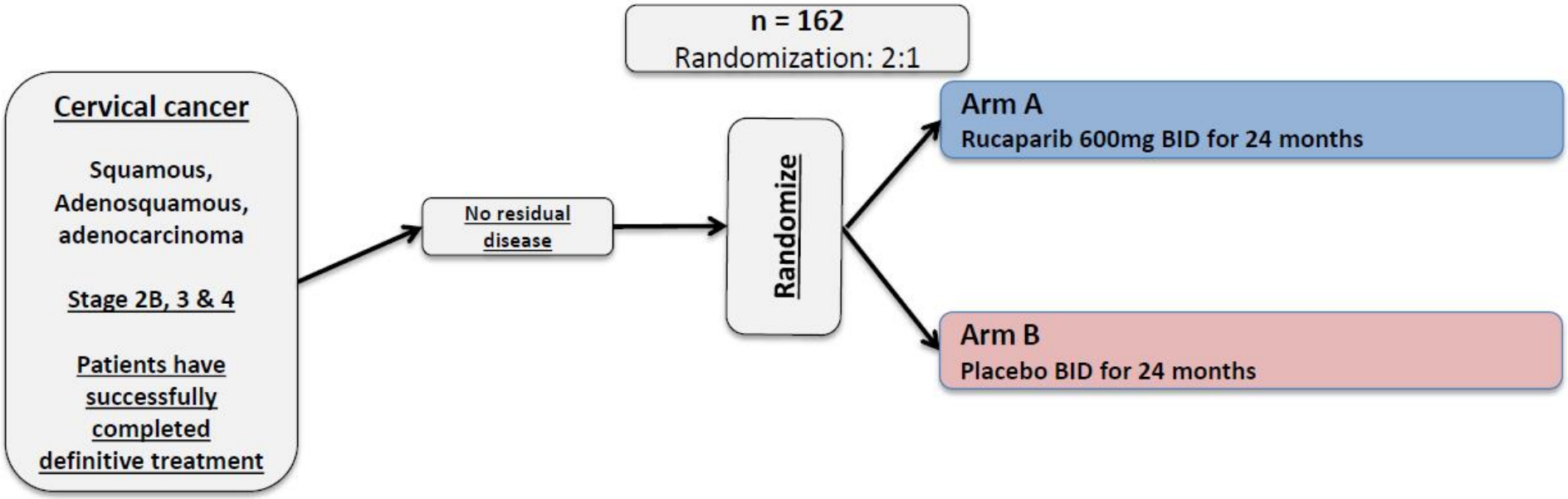
ENGOT-CX7 / NSGO / MaRuC

Rationale

- DNA repair in cervical cancer is less established
- HPV infection and oncoviral proteins E6 & E7 causes inactivation of p53 & pRB tumour-suppressor genes leading to cell cycle dysfunction and impaired DNA repair
- Cells are therefore increasingly dependent on residual repair pathways
- A correlation between response to DNA repair pathways has been noted in the clinic:
  - Patients treated with chemoradiation have high expression of the nucleotide excision repair protein ERCC1 associated with decreased PFS & OS & activation of the BRCA pathway correlated with treatment failure
  - Impaired NHEJ repair was related to increased OS
- Early phase trials incorporating modulators of DNA repair such as PARP inhibitors are underway

Duensing S et al. Cancer Res. 2002; 62:7075–7082
Balacescu O et al. BMC Cancer 2014; 14:246
NCT01281852: Olaparib & radiotherapy in H&N cancer
NCT02686008: Olaparib in patients with HPV positive & HPV negative HNSCC

ENGOT-CX7 / NSGO / MaRuC



Stratification factors

- Histology (squamous vs adenosquamous, adenocarcinoma)
- FIGO stage (2b-pos. nodes vs. 3 vs 4)

Enrolment of patients with squamous cell histology will be capped once 60% patients with this histo-type are enrolled

Ongoing Trials – status update

ENGOT-cx1 Randomized Phase II of paclitaxel-carboplatin +/- Nintedanib

- Advanced stage IVB, or recurrent cx ca
- **Up to one prior line of chemotherapy for metastatic cervical cancer now allowed***
- **Prior treatment with angiogenesis inhibitors now allowed***

n = 70/120

Randomization 1:1

Stratification

1. Primary advanced Stage IVB versus recurrent disease.
2. Previous line of chemotherapy for metastatic disease

Carboplatin AUC5 + paclitaxel 175 mg/m2 (tri)weekly + Nintedanib 200mg

followed by Nintedanib maintenance

Carboplatin AUC5 + paclitaxel 175 mg/m2 (tri)weekly + Placebo

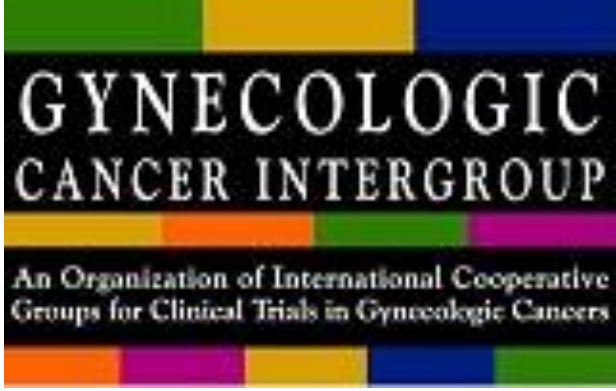
followed by Placebo maintenance

* Protocol v5.0 or above

Trial setting: Cervix/ primary stage IVB, recurrent
Sponsor(s): BGOG
Planned No. of patients: 120
Current accrual: 70
FPI: Mar 2014 ; LPI: expected Aug 2018
Primary endpoint: PFS Secondary endpoint: OS, toxicity, safety, QOL and RR

Nintedanib is a TKI of VEGFR and PDGFR

Conclusions



- **Cervix cancer is challenging and rewarding to treat**
- **Trials improve care for women and cancer centers**
- **GCIG and CCRN can aide in trials**

Thanks for your attention!