Cervix Cancer Committee
Tuesday, Nov.10, 2015,  1:30p.m. – 3:30 p.m.
3F Room, Jikei University, Tokyo

Satoru Sagae (JGOG)
Bradley Monk (GOG)

Harmonization Liaisons: Hiltz (Ops), Reuss (Stats)
AGENDA

Published/ In preparation
Advances & Concepts in Cervical Cancer Trials (GCIG report) – IJGC

CURRENT ACTIVE RANDOMIZED TRIALS WITH GCIG PARTICIPATION:
Surgery plus Radiation +/- CT
   Post-Op RT
   2) KGOG 0801/GOG 263 (RTOG): RT vs CCRT (intermed.risk post op) Ryu 185 -> 200/480
   3) RTOG0724 (GOG): ChemoRT +/- CT (high risk post op) Small 100 -> 150?/250

Chemoradiation
   5) TACO KGOG–Thai (CCRN) (RTOG, GICOM, VietNam, +?) Ryu 168 -> 200/500
   6) OUTBACK ANZGOG (CCRN) (GOG, RTOG, +?) Mileshkin 558 -> 656/780
   7) INTERLACE MRC–NCRI (CCRN) (GICOM, MaNGO, + ??) McCormack 60 -> 89 /770

8) TIME–C RTOG IMRT study closed

Small
Minimal Invasive Surgery

9) SHAPE NCIC CTG (CCRN) (DGOG, + ?) Plante 81 -> 113/700
10) ConCerv G–GOC Anuja Jhingran, 55/102 enrolled
11) LACC G–GOC Anuja Jhingran, 380 -> 405/740

12) GOG 0278 Conservative surgery (cone/nodes or hyst/(nodes) in early stage cervical cancer. (evaluation of physical function and QOL) Miller ?/220

Vulvar Cancer

13) GOG 0279 Phase II Trial Evaluating Cisplatin and Gemcitabine Concurrent with IMRT in Treatment of Locally Adv. SCC of the Vulva Miller ?/52

Immunotherapy

14) GOG high risk maintainance (ADXS–HPV) Miller
Advaxis Sponsored Ph 3: ADXS11-001 Administered Following Chemoradiation as Adjuvant Treatment for High Risk Locally Advanced Cervical Cancer: AIM2CERV

Cervix Cancer

- FIGO IB2, IIA2 and IIB with + pelvic nodes
- FIGO IIIA, IIIB and IVA
- All FIGO stages with + para-aortic nodes

R 2:1

*EBRT with Cisplatin

ARM A
Placebo
wks 3, 6, 9 and every 8 wks for 1 year (ie. 8 doses)

ARM B
ADXS-HPV
wks 3, 6, 9 and every 8 wks for 1 year (ie. 8 doses)

N=450

1º endpoint: Progression Free Survival
2º endpoint: Overall Survival

*Concurrent chemo radiation therapy administered with curative intent according to national/institutional guidelines
NEW/PROPOSED OR DEVELOPING CONCEPTS:

1) RTOG Hypofractionation  
   Small/Gaffney

2) NCIC–CTG Neo–adj. CT & fertility sparing surgery (stage IBI)  
   Plante

3) GINECO Sentinel lymph node biopsy  
   Lecuru/Plante
   Survey status  
   Keller/Sehouli

4) EORTC–GCG 1411 CCRT (Phase II/III VGX–3100 and INO–9012)  
   Ottevanger

5) EORTC ROG–GCG–QLG  
   CURative Radiotherapy to the primary tumor vs. bEST supportive care in patients with initially metastatic Cervical carcinoma (CURE–C trial)  
   Ottevanger
Hypofractionated RT in Cervix Cancer: Clinicaltrials.gov

- 919 cervix trials
- 134 hypofractionated RT trials
  - Prostate, breast, NSCLC, GBM
- 0 cervix trials with hypofractionation
Palliative RT: Trial Example

10 Gy x 2 q month

5 Gy x 5

- endpoints (short term):
  - PRO’s
  - Pain relief, bleeding, narcotic usage
Definitive CRT: Trial Example

45 Gy/25 fractions

37.5 Gy/15 fractions

7 Gy x 4 Brachy

9 Gy x 2 Brachy

EBRT + SURGERY

ENDPOINT: RFS
Hypofractionation: Where do we go from here?

- Goal: Improve care delivery, not improving OS
  - May need public funding
- Culturally sensitivity and practical
- Integration with chemo: watch out for acute toxicity (q weekly vs q 3 week)
- Remember: Our standard need not be the standard elsewhere
  - Some countries have no cervical cancer care
Outcomes: Non-inferiority to External Beam & Brachy for 2-year survival; Equivalence for Toxicity/QoL
Analysis: Stratify on Stage and Node Involvement
Data: Standardized; Tissues (Genetics; HPV type); Blood (Nutritional Status)
Sites: Brazil and Mexico; Minimum requirement---CT image of Abdomen and Pelvis and Chest x-ray
Stage IB1 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CoNteSSa)

Marie Plante (NCIC)

Jeffrey Goh & Vivek Arora (ANZGOG)

GCIG Meeting Tokyo – November 2015
Primary Objective

To estimate the rate of fertility preserving surgery in women with node negative, stage IB1 cervical cancer measuring 2-4 cm who receive neoadjuvant chemotherapy (NACT)
Cervical cancer size **2-4 cm**
MRI - corpus negative, node negative
Laparoscopy - pelvic lymph node dissection / **SLN mapping (optional)**, node negative
Pathology - squamous and adenocarcinoma
LVSI - negative or positive
Patient age ≤ 40 years
Desireous of preserving fertility

Baseline AMH, FSH, E2 levels (baseline and 6 / 12 months post Rx)

3 cycles of NACT
Carboplatin / Cisplatin + Paclitaxel

After 3 cycles
Clinical assessment and pelvic MRI
Radical hysterectomy

No response / progression
- Chemoradiation
  - Radical hysterectomy

Complete response after 3 cycles
- Trachelectomy
  - Simple / modified radical vaginal / abdominal / laparoscopic

Partial response >50% after 3 cycles
- Trachelectomy
  - Modified radical vaginal / abdominal / laparoscopic

Suboptimal response < 50% after 3 cycles or residual tumor > 2 cm
- Consider chemoradiation or radical hysterectomy

Adjuvant chemoradiation (or radical hysterectomy)
- Positive margins
- Stromal involvement in outer 1/2
- ≥5 mm stromal invasion
  - < 10 mm margin

< 5 mm ??
Points of discussions

- LEEP after trachelectomy?
- Free endocx margins: 5 or 10 mm ??
- PET-CT Mandatory or as per local practice ??

- Chemo regimen TIP, TC, ddTC, IP, AP 9wks=63days

- Type of FPS Cone/Trachelectomy and lymph node
  - Simple trachelectomy/cone in complete or optimal (< 3mm residual) chemo-responders
  - Modified radical trachelectomy in sub-optimal chemo-responders (> 3mm residual)
Cervix Cancer Committee

International prospective validation trial of sentinel node biopsy in cervical cancer

N Abu-Rustum, F Lécuru, P Mathevet, M Plante.

F Bonnetain (Statistics)
G Chatellier (Clinical Research Unit)

For GINECO Group

GCIG Tokyo, nov 2015
Sentinel Node Biopsy – early cervical cancer

- Feasibility ✓
- Reproducibility ✓
- Diagnostic accuracy ✓ *
- Anatomical information ✓
- Histological information (micromets) ✓
- Reduced morbidity ✓
- Similar prognosis ?

*: high NPV in case of bilateral detection and respect of the Cormier algorithm

Need for a validation study

Altgassen G & al 2008
Lécuru F & al 2011
Plante M, Roy M & al 2011
Cormier B & al 2011
Mathevet P & al 2015
Schema

SCC/Adk
Stage ≤ IIa1
<40mm
No pregnancy

Cormier algorithm
SLN biopsy
Frozen section

Quality of life
Disease free survival

pN0
SLN only
SLN + PLN Dissection

pN0
Prognosis of Limited Nodal Metastases

- Patients with ≥1 metastatic SLN / nSLN (ITC, micromet, macromet).

- disease free survival and overall survival

- according to
  - size of metastasis
  - Treatment (local policy, defined before the beginning of the study).
Number of subjects

- 1-DFS
  - With a 3 years-disease free survival of 85% to demonstrate a non-inferiority of SLN biopsy vs SLN biopsy + lymphadenectomy with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373). With a unilateral alpha error of 5%, and a power of 80%, 900 patients in 3 years, with 4 years of follow-up should be included to observe the required 219 events. An interim analysis is planned when at least 110 events will be observed to reject H0 or H1 using O Brien Fleming and alpha spending function.

- 2-HRQoL
  - We target 3 HRQoL dimensions global health, pain and physical functioning of EORTC QLQC 30.
  - To demonstrate a superiority of at least one of the 3 targeted dimensions without significant deterioration in at least one with a minimal important difference in mean score of at least 5 points (SD: 20), and a bilateral alpha type one error of 0.015 (Bonferroni adjustment) it would be required to have 815 patients with available HRQoL scores to reach 85% statistical power.

- 200 patients will be recruited in France (39 centers).
- 780 000€
- International collaboration requested
International survey about the sentinel lymph node biopsy in cervical cancer
Survey within the GCIG

Jalid Sehouli (AGO)
Thank you very much for your support and participation on the survey!

- Start: October 2015
- Duration: 6 Month
- 63 replies from 9 groups (6th of November)
- Analysis at the next meeting in Chicago 2016

Please answer (if you have not already done so)
- https://de.surveymonkey.com/s/SLN_cervicalcancer
Q20: If you perform FS what are the consequences for the treatment in case of pN+ in the SLNB?

<table>
<thead>
<tr>
<th>Antwortoptionen</th>
<th>Beantwortungen</th>
</tr>
</thead>
<tbody>
<tr>
<td>You stop the operation and opt for chemo radiation (RCT)</td>
<td>34,15% 14</td>
</tr>
<tr>
<td>You stop the operation and opt for exclusive chemotherapy</td>
<td>0,00% 0</td>
</tr>
<tr>
<td>You go on operating and you perform systematic pelvic and aortic LNE</td>
<td>39,02% 16</td>
</tr>
<tr>
<td>You go on operating and you perform systemativ lymphoectomy and radical hysterectomy</td>
<td>26,83% 11</td>
</tr>
<tr>
<td>Other</td>
<td>19,51% 8</td>
</tr>
</tbody>
</table>

Befragte gesamt: 41
Q21: If you perform FS what are the consequences in case of pN0 of SLNB?

<table>
<thead>
<tr>
<th>Antwortoptionen</th>
<th>Beantwortungen</th>
</tr>
</thead>
<tbody>
<tr>
<td>You still perform systematic pelvic and aortic LNE</td>
<td>40,54%</td>
</tr>
<tr>
<td>It allows you to avoid systematic lymphadenectomy</td>
<td>45,95%</td>
</tr>
<tr>
<td>It allows you to perform fertility sparing surgery</td>
<td>13,51%</td>
</tr>
<tr>
<td>Gesamt</td>
<td>37</td>
</tr>
</tbody>
</table>
Q24: What do you use for SLNB?
EORTC - 1411 – GCG – ROG

A Phase II Clinical Trial of Chemo-radiotherapy in combination with INO-3112 in Patients with Locally Advanced Cervical Cancer

EORTC SC: F. Herrera
G. Coukos
INO-3112:HPV immunotherapy (1)

- INO-3112 is the combination of VGX-3100 and INO-9012 vaccines
- VGX-3100 is formulated at 6 mg/mL and is a combination of equal amounts of two DNA plasmids (pGX3001 and pGX3002). These plasmids are also referred to as pCon16E6E7 and pCon18E6E7 respectively.
INO-3112:HPV immunotherapy (2)

• INO-9012 = IL-12 DNA plasmid $\rightarrow$ IL-12 is a key cytokine for induction of cellular immune responses
Main Objectives

The aim is to test the potential benefit of the addition of immunotherapy with INO-3112 to concomitant CRT in patients with locally advanced cervical cancer.

- **Safety run-in**
  To test the safety and immunogenicity of CRT combined with immunotherapy with INO-3112.

- **Phase II**
  To select the optimal combination treatment regimen for an ensuing randomized phase III evaluation, based on PFS at 18 months.
Design

- Phase II with safety run-in

Randomization 1:1:1

- FIGO stage
- Nodal status
- Histological subtype

- Chemo+RTX
- Chemo+RTX + VGX-3100 / INO-9012
- Chemo+RTX + VGX-3100 / INO-9012

Routine FU
N = 30
Routine FU
N = 30
VGX-3100 INO-9012
N = 30

Safety run-in: Aim is to ensure adequate safety of the 2 experimental treatment arms.

End Phase II: Aim is to select optimal experimental treatment arm for phase III.
Curative Radiotherapy to the primary tumor vs. bEst supportive care in patients with initially metastatic Cervical carcinoma (CURE-C trial)

EORTC ROG-GCG-QLG

Study coordinator
Igor Sirák, M.D., Ph.D
Department of Oncology and Radiotherapy
University Hospital
Hradec Králové
Czech Republic

Joint study coordinator
Fernanda G. Herrera, M.D.
Lausanne University Hospital
Department of Oncology – Radiotherapy Service
University of Lausanne
Switzerland
Purpose

To prove the superiority of primary tumor radiotherapy to “curative” doses over palliative treatment (best supportive care) in the setting of initially metastatic stage IVB cervical carcinoma in patients with response after standard platinum-based systemic chemotherapy.
Phase II randomized trial

100% PLATINUM-BASED CHT 4x (+/- BEV) → CT scan → CR, PR, SD → RANDOMIZATION

66% STANDARD ARM

EXPERIMENTAL ARM

RT → BSC

BSC: including palliative RT up to 40Gy BED2 in case of symptomatic progression, 2nd line CHT, etc.
Endpoints

**Primary:**

*Time to symptomatic deterioration*
- deterioration of PS with discontinuation of further treatment
- symptoms requiring surgical procedure (including nephrostomy, urine derivation, colostomy, abdominal surgery)
- death

**Secondary:**

Quality of life *(A Translational part of the research)*
OS, PFS
Treatment toxicity
Evaluation of treatment feasibility in a multi-institutional setting

**Stratification factors**
Response to initial chemotherapy: CR, PR vs. SD
Squamous cell carcinomas vs. adenocarcinomas
Bevacizumab yes/no

*EORTC*

The future of cancer therapy
Sample size estimate

Due to the variability of the BSC, a comparative phase II design is proposed

As proposed by Korn et al (JCO 2001), a phase II comparative screening design can be implemented as a superiority phase III trial design with an increased type I error and optimistic treatment effect.

For this trial, using a one-sided log-rank test at a level of significance of 10% (alpha), to test for an HR=0.63 (increase from 50% to 65% event-free survival at 12 months) at 80% power would need about:

- 80 events ~100 patients in 1:1 randomization.
- 90 events ~110 patients in 2:1 randomization.

The event-free curves between the two arms will be compared with a non-parametric test stratified for the stratification factors.

With the above assumptions, a hazard ratio of minimum would need to be observed 0.75 to reach significance.