IL CARCINOMA AVANZATO DELLA CERVICE

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The Global Burden of Cancer to Women Worldwide

9% of all new cancer cases

8% of total cancer deaths

85% of deaths occur in developing countries
TREATMENT

33.7% Early

**EARLY STAGES**

- STADIO IA1-IA2-IB1

RS or RT

62.4% Locally Advanced

**LOCALLY ADVANCED STAGES**

- STADIO IB2-IIA-III-IVA

- ?

2.7% Metastatic Disease

**ADVANCED/META STATIC DISEASE**

- STADIO IVB

- ?
TREATMENT

EARLY STAGES

- STADIO IA1-IA2-IB1
- RS or RT

LOCALLY ADVANCED STAGES

- STADIO IB2-IIA-III-IVA

ADVANCED/META STATIC DISEASE

- STADIO IVB

33.7% Early

62.4% Locally Advanced

2.7% Metastatic Disease
EARLY STAGES

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2.7% Metastatic Disease

ADVANCED/META STATIC DISEASE

STADIO IVB

33.7% Early

62.4% Locally Advanced

2.7% Metastatic Disease

RS or RT
STANDARD THERAPY FOR STAGE IB2-IVA

CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

Peter G. Rose, M.D., Brian N. Bundy, Ph.D., Edwin B. Watkins, M.D., J. Tate Thigpen, M.D., Gunther Deppe, M.D., Mitchell A. Maiman, M.D., Daniel L. Clarke-Pearson, M.D., and Sam Insalaco, M.D.

I.V. CISPLATIN CHEMOTHERAPY
Cisplatin 40mg/m2 (Max dose 70mg)
IV q wk during RT (6wks)

EXTERNAL BEAM
pelvic radiation (40 to 60 Gy)

BRACHYTHERAPY
(8,000 to 8,500 cGy to Point A)

GOG 120 Rose PG et al. NEJM 1999  Monk et al J Clin Oncol. 2007

CT-RT
CHEMORADIATION IS CONSIDERED THE WORLD STANDARD TREATMENT FOR LACC

Feb-1999: NCI issues clinical announcement on cervical cancer

1. reduction in the risk of death (HR 0.69, 95% CI 0.61-0.77)
2. reduction in the risk of local recurrence OR 0.59, 95% CI 0.50-0.69)
3. Trend in reduction distant metastasis (OR 0.81, 95% CI 0.65-1.01).
To date, no chemotherapy regimen has been found to be superior to 40 mg/m² of cisplatin weekly. However, the meta-analysis does suggest that substituting other agents that have demonstrated efficacy such as carboplatin or 5-flourouracil (5-FU) should be considered for women with a contraindication to cisplatin.
WHICH COMBINATION OF CTRT?

Munetaka Takekuma et al, ASCO 2015

68 PTS

Pts characteristics

- FIGO STAGE III-IVA
- NO PARA-AORTIC LYNPHADENOPATHY

RT (external beam whole pelvic RT and HDR-ICBT) 62-65 Gy

CDDP 30 mg/mq + PTX 50 mg/mq weekly for 5 courses.

<table>
<thead>
<tr>
<th>CR</th>
<th>76.5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 YRS PFS</td>
<td>83.8%</td>
</tr>
<tr>
<td>2 YRS OS</td>
<td>92.7%</td>
</tr>
</tbody>
</table>

CONCURRENT CHEMORADIOThERAPy WITH WEEKLY CDDP/PTX FOR LOCALLY ADVANCED CERVICAL CANCER DEMONSTRATED FAVORABLE ANTITUMOR ACTIVITY, AND IS FEASIBLE AND SAFE.
TACO
(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

Cervical cancer
Locally advanced cervical cancer
Stage IB2, IIB-IVA

Randomization

Control Arm; Weekly Cisplatin
40mg/m2 6 cycles

Study Arm; Tri-weekly Cisplatin
75mg/m2 3 cycles
ACUTE GRADE 3-4 AND LIFE THREATENING

- HAEMATOLOGICAL 19%
- GASTROINTESTINAL 9%

LATE GRADE 3-4

- UP TO 22% URINARY OR INTESTINAL
- UP TO 80% SEXUAL PROBLEMS

RECURRENT OF DISEASE

- 20-30% LOCAL FAILURE
- 18-25% DISTANT FAILURE

DO NOT ALLOW ACCURATE STAGING OF THE DISEASE

FERTILITY REDUCTION

...and more...

Green J, Lancet 2001
Tan L Clin Oncol (R Coll Radiol) 2008
OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation
Chemoradiation With Concomitant Boosts Followed by Radical Surgery in Locally Advanced Cervical Cancer: Long-term Results of the ROMA-2 Prospective Phase 2 Study

Accrual: 103 pts

Eligibility
- Cervix carcinoma stage IB2-IVA
- Age < 80y
- Adequate bone marrow function
- Adequate renal function
- Normal liver function

Clinical Response
- CR 36 pt (34.9%)
- PR 63 pt (61.2%)
- SD 2 pt (1.9%)
- PD 2 pt (1.9%)

DFS 73%
OS 86.1%

RT
39.6 Gy (PELVIC LYMPH NODE DRAINAGE, BULKY TUMOR, PARAMETRIA) + 10.8 Gy (PRIMARY TUMOR, PARAMETRIA)

CT
CISPLATIN 20 MG/M2 P1Q25 + CAPECITABINE 1300 MG/M2 DAILY

TOXICITY
- Leukopenia 19.4% G1
- Gastrointestinal 32% G1, 9.7% G2
- Genitourinary 11.6% G1, 2.9% G2

Relapse 25 pt (24.3%)
Death 10 pt (9.7%)

3 years

• Trial closed for poor accrual
• No difference OS between surgery vs no surgery after CTRT

• This study failed to demonstrate that RH after EBRT-CT is superior to standard BCT
• Chemo/radiation
• Chemo/radiation followed by surgery
• Chemo/radiation-chemotherapy
• Neoadjuvant chemotherapy
  • followed by surgery
  • followed by chemo/radiation
HOW CAN WE REDUCE DISTANT FAILURES?

- Improved survival in the 2 trials that gave 2 cycles of additional CT
- Might treat micrometastasis and improve OS
- Absolute 5 yrs OS benefit of 19%

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008
Accrual: 515 pts

Eligibility
Cervix carcinoma stage IIB-IVA
Para-aortic lymph nodes neg

I línea
Cis 40 mg/mq + Gem 125 mg/mq + RT 50.4 Gy + BCT

Tp adyuvante
Cis 50 mg/mq p1q21 + Gem 1000 mg/mq p1,8,q21

Cis 40 mg/mq + RT 50.4 Gy + BCT

3 y PFS 65% 74.4%

A. More grade 3-4 adverse events:
   • More hematological toxicity, mainly neutropenia (51% vs 5.9%)
   • More vomiting (7.7% vs 2.8%) and diarrhea (17% vs 4.7%)
   • Late Grade 4 GI toxicity (2.4% vs 0%)

B. 3 deaths in the first 30 days, 2 related with CT-RT in Arm A

C. More discontinuations in arm A than in arm B (p 0.001)
   - 14% of pts did not receive 1° adj
   - 24% of pts did not receive 2° adj
OUTBACK trial: randomized phase III study

Patients with stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer who have given informed consent

Eligible patients

RANDOMISE

Max 6 weeks

Arm A – Control Arm
Concurrent chemoradiation

Arm B – Intervention Arm
Concurrent chemoradiation followed by 4 cycles of Carboplatin/Paclitaxel

Follow up for a minimum of 3 years
OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation
NACT: AIMS

- Debunking Effect and Tumor Size Reduction
- Improving Surgical Outcomes
- Better Activity Against Micrometastasis
- Permit Conservative Surgery
- Less Toxicity
- Easier Management of Salvage Therapy
OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation
Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration

- 5 randomized trials
- 872 pts (97% of total)
- Stage:
  - IB 35%
  - II 38%
  - III 26%

### Analysis 2.1. Comparison 2 Treatment comparison 2, Outcome 1 Survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio Exp[(O-E)/V] Fixed 95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Exp[(O-E)/V] Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sardi 1996</td>
<td>25/53</td>
<td>41/54</td>
<td>-</td>
<td>17.4 %</td>
<td>0.41 [0.25, 0.68]</td>
</tr>
<tr>
<td>Sardi 1998</td>
<td>22/80</td>
<td>33/74</td>
<td>-</td>
<td>14.8 %</td>
<td>0.50 [0.29, 0.85]</td>
</tr>
<tr>
<td>Kigawa 1996</td>
<td>10/25</td>
<td>15/25</td>
<td>-</td>
<td>6.9 %</td>
<td>0.62 [0.28, 1.35]</td>
</tr>
<tr>
<td>Benedetti 2002</td>
<td>88/227</td>
<td>101/214</td>
<td>-</td>
<td>51.8 %</td>
<td>0.71 [0.54, 0.95]</td>
</tr>
<tr>
<td>Chang 2000</td>
<td>21/68</td>
<td>12/52</td>
<td>-</td>
<td>9.0 %</td>
<td>1.38 [0.69, 2.74]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.65 [0.53, 0.80]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Favors NACT-S** | **Favors RT**

NACT & RS vs RS

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer (Review)

- Better OS and PFS for NACT/RS vs RS
- Fewer local recurrences
- Fewer distant recurrences
- More radical resections
- Less N+
- Less parametrial involvement

**INCLUSION CRITERIA**
- FIGO IB2, IIA, IIB
- PS 0-2
- Age 18-75
- Squamous
- Adenocarcinoma
- Adenosquamous

**STRATIFICATION**
- FIGO
- Institution
- Age 18-50 vs 50-75
- Histology:
  - Squamous vs
  - Adenocarcinoma vs
  - Adenosquamous

**ENDPOINTS**
- **Primary:** OS
- **Secondary:**
  - PFS
  - Toxicity
  - QoL

---

**RANDOM**

Cisplatin based chemotherapy:
- Min. total dose of 225 mg/mq
- 25 mg/mq per week
- Final dose no later than 8° week

Chemo-radiotherapy
- CDDP 40 mg/mq (6 week) + EBRT 45-50 Gy

**Radical hysterectomy**
SNAP 01: IP vs TIP
Optimal response: 23% vs 48%

TIP more active but more toxic

SNAP 02: TP vs TIP
Optimal response: 27% vs 42%

FIGO IB2-IVA

TIP seems to be the best combination but it is more toxic

IFO 5 g/mq
CDDP 75 mg/mq
Paclitaxel 175 mg/mq

IFO 5 g/mq
CDDP 75 mg/mq
Paclitaxel 175 mg/mq

IFO 5 g/mq
CDDP 75 mg/mq
Paclitaxel 175 mg/mq

IFO 5 g/mq
CDDP 75 mg/mq
Paclitaxel 175 mg/mq

5yrsOS: 78%

Buda A et al 2005
Lissoni AA et al 2009
WHICH TYPE OF NACT?

Our experience

Op rate 81-100%
CR= 10%, PR= 67% SD 19% PD 4%
RR cumulativo circa 77%

<table>
<thead>
<tr>
<th></th>
<th>PTS N°</th>
<th>PTS FIGO STAGE</th>
<th>NACT SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ob Gyn 1988</td>
<td>33</td>
<td>IB-IIIB</td>
<td>CIS+BLEO+MTX</td>
</tr>
<tr>
<td>Cancer 1991</td>
<td>75</td>
<td>IB-IIIB</td>
<td>CIS+BLEO+MTX</td>
</tr>
<tr>
<td>Gynecol Oncol 1996</td>
<td>42</td>
<td>Ib2-IIib (adenok)</td>
<td>CBM, CB, CE</td>
</tr>
<tr>
<td>Eur J Cancer 1998</td>
<td>130</td>
<td>Ib2-III</td>
<td>CDDP/BLEO/MTX</td>
</tr>
<tr>
<td>JCO 2002</td>
<td>210</td>
<td>IB2-IIIB</td>
<td>CDDP-BASED</td>
</tr>
<tr>
<td>Ann surg oncol 2007</td>
<td>18</td>
<td>IVa</td>
<td>CDDP/Pacl</td>
</tr>
<tr>
<td>Gynecol Oncol 2011</td>
<td>46</td>
<td>IB2-IIIB</td>
<td>TOPO+CIS</td>
</tr>
<tr>
<td>Oncology 2015</td>
<td>22</td>
<td>IB2-IIIB</td>
<td>CDDP +TXL DD</td>
</tr>
</tbody>
</table>
OTHER OPTIONS

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy
  - followed by surgery
  - followed by chemo/radiation
A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer

46 pts

Pts characteristics
- Locally advanced cervical cancer (stage IB2-IVA)
- Squamous, adeno- or adenosquamous carcinoma
- Age >18y
- ECOG 0-1
- Adequate bone marrow function
- Adequate renal function
- Normal liver function

NACT
Carboplatin (AUC2) + Paclitaxel 80 mg/m2 weekly FPR 6 cycles

CRT
40 mg/Mq of weekly Cisplatin + 50.4 Gy in 28 fractions plus brachytherapy

Clinical Response (12 weeks after NACT)
- CR 2 pt (4%)
- PR 30 pt (65%)
- SD 10 pt (22%)
- PD 2 pt (4%)
- No data 2 pt (4%)

Response
After 12 weeks post all treatments
- CR 29 pt (63%)
- PR 10 pt (22%)
- SD 2 pt (4%)
- PD 2 pt (4%)
- No data 3 pt (7%)

5 YRS PFS 68%
5 YRS OS 67%

RR: 39%

McCormack et al. Br J Cancer 2013
INTERLACE - Phase 3 trial

Randomize

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

Standard CRT

Standard CRT : 40—50.4Gy in 20-28 fractions plus Intracavity brachytherapy to give min total EQD2 dose of 74-80Gy to point A/volume. Weekly cisplatin 40mg/m² x 6 weeks

Weeks 7 – 13
Standard CRT

Follow-up
3 monthly for 2 years; 6 monthly for 3 years
TREATMENTS IN LACC

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy followed by chemo/radiation
- Neoadjuvant chemotherapy followed by surgery
TREATMENTS IN LACC

- Chemo/radiation
- Chemo/radiation followed by surgery
- Chemo/radiation-chemotherapy
- Neoadjuvant chemotherapy followed by chemo/radiation
- Neoadjuvant chemotherapy followed by surgery

CHEMOTHERAPY IS MANDATORY!
TREATMENT

EARLY STAGES

33.7% Early

EARLY STAGES

STADIO IA1-IA2-IB1

RS or RT

LOCALLY ADVANCED STAGES

62.4% Locally Advanced

LOCALLY ADVANCED STAGES

STADIO IB2-IIA-III-IVA

?

ADVANCED/META STATIC DISEASE

2.7% Metastatic Disease

ADVANCED/META STATIC DISEASE

STADIO IVB

?
PROGRESS IN SURVIVAL IN ADVANCED AND RECURRENT CERVICAL CANCER

GOG 64 Cisplatin

GOG 110 Cisplatin + Ifosfamide

GOG 169 Cisplatin + Paclitaxel

GOG 149 Cisplatin + Topotecan

GOG 179 Cisplatin + Ifosfamide + Bleomycin

GOG 240 Cisplatin + Paclitaxel + Bevacizumab
KEY QUESTIONS

WHICH Platinum doublet?

Carboplatin or cisplatin?

Nonplatinum doublet?

Which role for TARGET THERAPY in CC?
WHICH Platinum doublet?
GOR 204

Primary Stage IVB or recurrent/persistent carcinoma of the cervix

- measurable disease
- GOG performance status 0-1
- ANC ≥ 1500/µl
- platelets ≥100,000/µl
- serum creatinine ≤ 1.5 mg/dl
- no CNS disease
- no past or concomitant invasive cancer
- no prior chemotherapy (unless concurrent with radiation)

**Regimen 1**
Paclitaxel 135 mg/m2 + CDDP 50 mg/m2 p1q 21

**Regimen 2**
Vinorelbina 30 mg/m2 + CDDP 50 mg/m2 p1q 21

**Regimen 3**
Gemcitabine 1000 mg/m2 p1,8q 21+
CDDP 50 mg/m2 p1q 21

**Regimen 4**
Topotecan 0.75 mg/m2 p1,2,3q 21+
CDDP 50 mg/m2 p1q 21

**ALL REGIMENS**
Quality of life Assessment:
Baseline
Before cycle 2
Before cycle 5
9 mo. after study entry at follow-up visit

**WHICH PLATINUM DOUBLET?**

BJ Monk et al 2009
Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study

Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta, Cecelia H. Boardman, Jo Benda, and David Cella

GOG 204

Responders
CR
PR
Non responder
Total

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS+PAC</td>
<td>29</td>
<td>74</td>
<td>103</td>
</tr>
<tr>
<td>CIS+VIN</td>
<td>23</td>
<td>85</td>
<td>108</td>
</tr>
<tr>
<td>CIS+GEM</td>
<td>20</td>
<td>92</td>
<td>112</td>
</tr>
<tr>
<td>CIS+TOP</td>
<td>22</td>
<td>89</td>
<td>111</td>
</tr>
</tbody>
</table>

JCO, 2009
WHICH Platinum doublet?

Carboplatin or cisplatin?
Accrual: 253 pts

**TP**
Tax135 mg/m² p1q21 + Cis 50 mg/m² p2q21

**TC**
Tax175 mg/m² + AUC5 p1q21

### Toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cis(%)</th>
<th>Car(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>85.5</td>
<td>76.2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>16</td>
<td>7.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>31.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Other GI</td>
<td>6.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>7.9</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0</td>
<td>4.8</td>
</tr>
</tbody>
</table>

KEY QUESTIONS

WHICH Platinum doublet?

Carboplatin or cisplatin?

Nonplatinum doublet?

Which role for TARGET THERAPY in CC?
Mechanistics
Tumor Hypoxia and Viral Oncogenes Drive Angiogenesis

HPV E6 → p53 degradation → ↑ TSP-1 → ↑ VEGF → angiogenesis

Anti-VEGF therapy

Displacement of HDAC1, HDAC4, HDAC7
pRb inactivation
p21-Rb pathway dysregulation

Bevacizumab activity in cervical cancer was demonstrated in a phase II single-agent study (GOG 227C)
Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

Accrual: 452 pts

Eligibility
- Metastatic, persistent or recurrent CC
- No candidate for curative therapy

Objectives
1. Cisplatin + paclitaxel VS Paclitaxel + Topotecan
2. Chemo + Bevacizumab VS Chemo alone

Cisplatin 50 mg/m2 + Paclitaxel 135/175mg/m2 p1q21
Cisplatin 50 mg/m2 + Paclitaxel 135/175mg/m2 + BEVA 15 mg/Kg p1q21
Topotecan 0.7 mg/m2 p1,2,3q21 + Paclitaxel 175mg/m2 p1q21
Topotecan 0.7 mg/m2 p1,2,3q21 + Paclitaxel 175mg/m2 p1q21 + BEVA 15 mg/kg p1q21

Krishnansu S Tewari et al 2014
GOG-240
TOPOCIS vs CISTAXOL

- Topotecan + paclitaxel shown to not be superior or inferior to cisplatin + paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>Cis + Pac (n=229)</th>
<th>Topo+Pac (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>81 (35)</td>
<td>93 (42)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>HR=1.20 (98.74% CI, 0.82–1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (1-sided)=.880</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regardless of prior cisplatin

GOG-240
CHEMO vs CHEMO+VEBACIZUMAB

WITHOUT significant deterioration in health-related quality of life.

Penson, Lancet Oncology, 2015
<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Chemo Alone (n=220)</th>
<th>Chemo + Bev (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cycles, median (range)</td>
<td>6 (1-50)</td>
<td>7 (1-40)</td>
</tr>
<tr>
<td>Grade 5 AE(s)</td>
<td>3 (1.3)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Gl events, non-fistula (grade ≥2)</td>
<td>97 (44)</td>
<td>115 (53)</td>
</tr>
<tr>
<td>Gl fistula (grade ≥2)</td>
<td>1 (0.5)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Gl perforation (grade ≥2)</td>
<td>0 (0)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>GU fistula (grade ≥2)</td>
<td>1 (0.5)</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Hypertension (grade ≥2)</td>
<td>4 (1.8)</td>
<td>55 (25)</td>
</tr>
<tr>
<td>Proteinuria (grade ≥3)</td>
<td>0 (0)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Pain (grade ≥2)</td>
<td>63 (29)</td>
<td>72 (33)</td>
</tr>
<tr>
<td>Neutropenia (grade ≥4)</td>
<td>58 (26)</td>
<td>80 (36)</td>
</tr>
<tr>
<td>Febrile neutropenia (grade ≥3)</td>
<td>12 (5.5)</td>
<td>12 (5.5)</td>
</tr>
<tr>
<td>Thromboembolism (grade ≥3)</td>
<td>4 (1.8)</td>
<td>18 (8.2)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CNS (any grade)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gl (grade ≥3)</td>
<td>1 (0.5)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>GU (grade ≥3)</td>
<td>1 (0.5)</td>
<td>6 (2.7)</td>
</tr>
</tbody>
</table>

Even patients with target lesions contained within a previously irradiated field experienced sustained clinical benefit from bevacizumab which was a unique finding and a departure from previous studies that had suggested that these lesions are chemoresistant.
MITO (MULTICENTRE ITALIAN TRIALS IN OVARIAN CANCER) - CERV2 TRIAL: A RANDOMIZED PHASE II STUDY OF CARBOPLATIN AND PACLITAXEL +/- CETUXIMAB, IN ADVANCED AND/OR RECURRENT CERVICAL CANCER

**PFS**

- **Patients**: CP: 52, CP + CET: 55
- **Events**: CP: 45, CP + CET: 52
- **Median PFS (95% CI)**: CP: 5.2 (4.5 - 7.8), CP + CET: 7.8 (5.6 - 9.0)
- **Unadjusted HR**: 0.84 (95% CI: 0.56-1.26)
- **Log-rank p**: 0.20

**OS**

- **Patients**: CP: 52, CP + CET: 55
- **Events**: CP: 30, CP + CET: 31
- **Median OS (95% CI)**: CP: 17.7 (11.0 - 31.6), CP + CET: 17.0 (12.5 - NA)
- **Unadjusted HR**: 0.85 (95% CI: 0.52-1.42)
- **Log-rank p**: 0.27
Ongoing Trial: Phase II, randomized, double blind and placebo controlled trial

Figo IVB/recurrent disease

Randomize

Carboplatin AUC5 + Paclitaxel 175mg/m² + Nintenanib 200 mg Bid
Weeks 1-6

Nintenanib until progression

Carboplatin AUC5 + Paclitaxel 175mg/m² + Placebo Bid
Weeks 1-6

Placebo until progression

Primary End-point: PFS
Secondary End-point: OS, Toxicity, Patient Health status
OBJECTIVES:
- Primary: to assess the safety and antitumor activity by objective response rates (ORR) at the end of cycle 4 of ipilimumab in recurrent CC

- Secondary: to assess the antitumor activity of ipilimumab by disease stabilization and PFS
In locally advanced cervical cancer radio-chemotherapy is the standard
NACT role will be defined by the EORTC trial of NACT/surgery vs chemo-RT
CTRT followed by should be further investigate
In metastatic disease cisplatin/paclitaxel plus bevacizumab is the new standard
Platinum doublets are better than nonplatinum doublets
Carboplatin may replace cisplatin in patients pretreated with the drug
Grazie per l’attenzione