The MITO CERV-2 trial: A randomized phase II study of cetuximab plus carboplatin and paclitaxel, in advanced or recurrent cervical cancer

The MITO CERV-2 trial: a randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer.

Sandro Pignata[1], Giovanni Scambia[2], Domenica Lorusso[3], Ugo De Giorgi[4], Maria Ornella Nicoletto[5], Rossella Lauria[6], Annamaria Mosconi[7], Cosimo Sacco[8], Claudia Omarini[9], Pierosandro Tagliaferri[10], Gabriella Ferrandina[2-11], Saverio Cinieri[12], Antonella Savarese[13], Giorgio Valabrega[14], Carmela Pisano[1], Vanda Salutari[2], Francesco Raspagliesi[3], Barbara Kopf[4], Sabrina Chiara Cecere[1], Giulia Amadio[2], Giuseppe Maltese[3], Marilena Di Napoli[1], Stefano Greggi[1], Simona Signoriello[15], Gennaro Daniele[16], Maria Carmela Piccirillo[16], Ciro Gallo[15], Francesco Perrone[16], on behalf of MITO CERV-2 Investigators (see Appendix).

[1] Dipartimento di Oncologia Uroginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS, Napoli;
[2] Dipartimento per la Tutela della Salute della Donna della Vita Nascente del Bambino e dell' Adolescente, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma;
[3] Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale Tumori – Milano
[4] Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori – IRCSS, Meldola-Cesena;
[5] Istituto Oncologico Veneto IRCCS, Padova;
[6] Università Federico II, Napoli;
[7] Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia;
[8] Ospedale Universitario "S. Maria della Misericordia", Udine;
[9] Oncologia Medica, Azienda Ospedaliero Universitaria Policlinico, Modena;
[10] Oncologia Medica, Università della Magna Grecia, Germaneto (CZ);
[11] Ginecologia Oncologica, Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, Campobasso;
[12] Oncologia Medica & Breast Unit, Ospedale “Senatore Antonio Perrino”, Brindisi;
[13] Oncologia Medica, Istituto Nazionale Tumori Regina Elena, Roma;
[14] Oncologia Medica, Università di Torino, Fondazione del Piemonte per l’Oncologia, IRCCS, Candiolo (TO);
[15] Cattedra di Statistica Medica, Seconda Università di Napoli, Napoli;
[16] Unità Sperimentazioni Cliniche Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS, Napoli; Italy.

Running head: Cetuximab in the treatment of advanced cervical cancer

Address for correspondence
Sandro Pignata
Dipartimento di Oncologia Uroginecologica
Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione G.Pascale, IRCCS
via Mariano Semmola, 80131 Napoli (Italy)
s.pignata@istitutotumori.na.it
phone +390815903637
fax +390815903861

Acknowledgement: The National Cancer Institute of Napoli was the sponsor of the trial. Merck KGaA, Darmstadt, Germany, provided cetuximab free of charge and partial funding.

Previous presentations: Gynecologic Cancer Poster Discussion Session at 2015 ASCO Annual Meeting, and Oral presentation Gynecologic Cancer Session at 2015 AIOM (Associazione Italiana Oncologia Medica) Annual National Meeting.

Disclaimers: This was an academic non-profit trial. The National Cancer Institute of Naples was the sponsor of the trial and it was responsible for trial performing, data collection and analysis. Merck KGaA, Darmstadt, Germany, provided the experimental drug, free of charge, and partial funding. Merck KGaA, Darmstadt, Germany, had no role in data collection, analysis, interpretation of the results, writing of the manuscript and in the decision to publish it. S.P., S.S., G.D., M.C.P., C.G. and F.P. had access to the raw data. The corresponding author had the final responsibility to submit for publication.

Abstract

Background: Cervical cancer cells often express Epidermal Growth Factor Receptor (EGFR). Cetuximab (CET), an anti-EGFR monoclonal antibody, can be safely combined with carboplatin (C) and paclitaxel (P), a standard treatment of advanced or recurrent cervical cancer (ARCC) patients (pts). This is a comparative randomized phase 2 study, testing the addition of CET to CP.

Methods: ARCC pts, <2 previous chemotherapy, ECOG PS≤1, were randomized to CP (C AUC5 + P 175 mg/m², d1q21) for 6 cycles +/- CET (400 mg/m² one week before starting CP, then 250 mg/m² weekly) until disease progression or unacceptable toxicity. Primary endpoint was event-free survival (EFS), i.e. time from randomization to progression, death, definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. With a 4.5 months (mos) expected median EFS and a 6.4 mos predicted EFS (HR 0.70), 0.20 one-tailed α and 80% power, 89 events were required for the final intent-to-treat analysis.

Results: 108 pts were randomly assigned to CP (n=53) or to CP-CET (n=55). A patient in CP arm withdrew the consent and was not analyzed. Median age was 50, 69% were PS 0, 76% had recurrent disease, 91% had distant metastasis and 57% had received previous chemotherapy. After a median follow-up of 23 mos, 102 pts had an event, 97 progressed and 61 died. Median EFS was 4.7 and 6.0 mos (one-tail p=0.43), median progression free survival (PFS) was 5.2 and 7.6 mos (one-tail p=0.20) and median Overall Survival (OS) was 17.7 and 17 mos (one-tail p=0.27), with CP and CP-CET, respectively. There was no difference in the occurrence of severe adverse events, except for skin toxicity.

Conclusion: The addition of CET to CP was feasible but not more active than CP alone in unselected ARCC pts.

INTRODUCTION

Cervical cancer is the fourth most common female cancer worldwide and has the fourth highest cancer-related mortality rate in women, with estimates of 528.000 new cases and 266.000 deaths from the disease per year [1]. Effective screening and prevention programs in developed countries have resulted in a 75% decrease in the incidence and mortality of cervical cancer over the past 50 years [2]. However, in developing countries, cervical cancer accounts for almost 12% of all cancers in females and remains the most common cancer in women in eastern and central Africa.

Surgery and chemo-radiotherapy have a high curative rate in early-stage cervical cancer. However, patients with recurrent or metastatic cancer have limited therapeutic options. The poor long-term results of standard treatment for cervical cancer compel research into new, more beneficial treatment strategies [3]. Cervical cancer cells express the Epidermal Growth Factor Receptor (EGFR) in a very high proportion of cases with increasing levels from intraepithelial disease to invasive carcinoma [4,5]. Expression is present also in metastatic or recurrent cancer more than in localized tumours. High level of expression of EGFR has been correlated with poor prognosis [6,7], despite some contradictory results. Cetuximab, an anti-EGFR monoclonal antibody, has shown efficacy in several epithelial tumor types. In particular, the combination of cetuximab and chemotherapy prolonged survival outcomes as compared with chemotherapy alone, in advanced colorectal [8-10] and head and neck cancer [11].

In preclinical studies, Cetuximab significantly inhibited tumor proliferation in cervical tumor cells lines [5].

From previous experiences, cetuximab can be safely combined with full-dose carboplatin and paclitaxel [12], which is a standard option for treatment of advanced or recurrent cervical cancer patients [13-16].

The possibility of combining cetuximab with full doses of carboplatin and paclitaxel prompted us to evaluate the activity of the addition of cetuximab to carboplatin and paclitaxel in a randomized phase 2 study, comparing the combination to chemotherapy alone.

PATIENTS AND METHODS

Study design

This was a phase II, prospective, open-label, randomized (1:1), multicenter clinical trial, comparing two treatment arms: Carboplatin + Paclitaxel versus Carboplatin + Paclitaxel+ Cetuximab.

Event-free survival (EFS) was the primary end-point, defined as the time from randomisation to progression, death without progression, premature definitive discontinuation of the whole treatment or loss to follow up, whichever occurred first.

Because of the exploratory nature of the study, a so-called relaxed statistical design was chosen for comparison: one-tailed test, significance level equal to 20%, power equal to 80% [17,18]. Assuming a median EFS in the control arm equal to 4.5 months and a median EFS in the experimental arm equal to 6.4 months (corresponding to a Hazard ratio of 0.70), 89 events were required and 108 patients (54 for each arm) were planned (EAST 5 software, Cytel Software, Cambridge, MA, U.S.A.).

Secondary endpoints included progression-free survival (PFS), overall survival (OS), toxicity and objective response rate (ORR). Patient registration and data collection were performed through dedicated electronic CRFs available on the website of the Clinical Trials Unit, National Cancer Institute, Napoli, Italy (http:\\www.usc-intnapoli.net). Randomisation was performed centrally, through the above reported website, by a computer-driven minimization procedure. The number of previous chemotherapy (none vs one), the presence of distant metastases (no vs yes) and the centre, were considered as stratification variables. No blinding procedure was planned.

This study was available in public registries (ClinicalTrials.gov ID: NCT00997009 and EudraCT number: 2009-010099-74).

Study population

Women with advanced or metastatic cervical cancer, untreated or having failed only one previous chemotherapy (with or without concomitant or sequential radiotherapy and with at least 6 months of progression-free interval), not amenable for surgery or radiotherapy, with at least one measurable lesion by the Response Evaluation Criteria In Solid Tumours (RECIST), an ECOG performance status ≤1, and a life expectancy ≥3 months were eligible. Adequate hematopoietic (absolute neutrophils count ≥1,500/mm^3; platelets count ≥100,000/mm^3; hemoglobin ≥9 g/dL), hepatic (SGOT or SGPT≤3 UNL or ≤5 ULN in presence of liver metastases, alkaline phosphatase ≤3 ULN, total bilirubin ≤1.5 UNL), and renal (calculated creatinine clearance ≥ 45 mL/min) function were required.

Exclusion criteria were: a history of heart failure, angina pectoris, myocardial infarction (within 1 year from study entry), uncontrolled hypertension or arrhythmia; active infection requiring antibiotics; previous invasive malignancy within the past 5 years except non-melanoma skin cancer; residual peripheral neuropathy >grade 2 according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; concurrent treatment with other experimental drugs; pregnancy and breast-feeding. The study was approved by Ethics Committees at each participating Institution, and all the patients signed the informed consent before any study related procedure.

Study treatment

Patients were randomly assigned, with a 1:1 ratio, to receive either carboplatin and paclitaxel (standard arm) or carboplatin and paclitaxel plus cetuximab (experimental arm).

Patients in both arms received paclitaxel 175 mg/m^2 (diluted in 250 ml of 0.9% saline and infused intravenously over 3 hours) and carboplatin AUC 5 (diluted in 0.9% saline solution

and infused intravenously over 30 minutes) on day one every 21 days, for a maximum of 6 cycles.

Patients in the experimental arm received cetuximab intravenous infusion, at a starting dose of 400 mg/m^2 over 120 minutes, one week before starting chemotherapy, and further weekly infusion at the dose of 250 mg/m^2 over 60 minutes, until disease progression, prolonged/unacceptable toxicity or patient's withdrawal.

In the experimental arm, a prophylactic premedication with dexamethasone 8 mg intravenously and antihistamine (such as diphenhydramine 50 mg) intravenously was mandatory before the first administration of cetuximab and also strongly recommended before the following weekly doses. In both arms, a prophylactic premedication with dexamethasone 20 mg (or hydrocortisone 250 mg), chlorpheniramine 10 and ranitidine 50 mg intravenously was given before paclitaxel infusion.

In both arms, chemotherapy had to be deferred if absolute neutrophils count $\leq$1,500/mm^3, platelets count $\leq$100,000/mm^3, or organ toxicity grade ≥2 (excluding alopecia and skin toxicity), for up to two consecutive weeks, until recovery. In case of a delay of more than 2 weeks, chemotherapy had to be discontinued. Chemotherapy dose had to be reduced by 20% in case of neutrophils <500/mm^3 for a period of more than 7 days or platelets <50000/mm^3. In case of grade $\leq$2 neurotoxicity paclitaxel dose had to be reduced by 20%, while it had to be definitively stopped in case of grade ≥3 neurotoxicty. In case of chemotherapy delay or stop, cetuximab could continue as planned.

Cetuximab had to be delayed in case of grade ≥3 (according to CTCAE version 3.0) skin toxicities, for up to two consecutive infusions, until toxicity resolved to grade $\leq$2. Cetuximab dose did not change after the first delay, while it had to be reduced to 200 mg/m^2 and 150 mg/m^2 after the second and third occurrence of a grade ≥3 skin toxicity, respectively. Dose reductions were permanent. Patients should have discontinued cetuximab if more than two

consecutive infusions were withheld or on the fourth occurrence of a grade ≥3 skin toxicity despite appropriate dose reduction. Cetuximab infusion rate had to be decreased by 50% after the first occurrence of grade ≤2 allergic/hypersensitivity reaction, while it had to be definitively stopped in case of grade ≥3 allergic/hypersensitivity reaction or on the second occurrence of a grade ≤2 allergic/hypersensitivity reaction despite appropriate infusion rate reduction. In case of cetuximab delay or stop, chemotherapy could continue as planned.

Patient evaluation

Disease assessment included clinical examination, abdomino-pelvic CT scan and chest X-ray, and were performed at baseline and repeated every 3 cycles during chemotherapy and every 3 months thereafter. Objective response was codified according to RECIST [19]. Safety assessment included physical examination, blood tests (haematology and biochemistry) and collection of adverse events history, which were performed at least every 3 weeks during treatment and until 30 days after the last administration of study drugs. Moreover an ECG was performed every three cycles during chemotherapy. Adverse events were coded according to CTCAE version 3.0. Skin toxicity was also graded according to the MASCC (Multinational Association of Supportive Care in Cancer) EGFR inhibitor skin toxicity tool (MESTT©) [20].

Statistical analysis

All the efficacy analyses were done on an intention-to-treat basis. EFS was defined as the time from randomization to progression, death without progression, premature definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. Patients who discontinued the treatment due to symptomatic deterioration in absence of radiologic progression were considered as progressive at the date of symptomatic

deterioration. The whole treatment was considered as prematurely discontinued if all the planned drugs were definitively suspended for reasons different from progression or completion of the planned treatment. A patient was considered as lost to follow-up if at the date of the database lock for the primary analysis she missed the last two consecutive follow-up visits. Patients who did not have an event according to the above definition were censored at the last visit, when the patient was known to be alive and free from progression.

PFS was defined as the time from randomization to progression or death (whichever occurred first) or date of last visit when the patient was known to be alive and free from progression. OS was defined as the time from randomisation to death or date of last follow-up for patients alive. Median follow-up (mFU) was calculated according to the reverse Kaplan-Meier technique [21]. EFS, PFS and OS curves were estimated by Kaplan-Meier product limit method [22] and compared by log-rank test.

ORR was defined as the proportion of complete plus partial responder among patients with at least one target lesion according RECIST. Patients eligible for the evaluation of the response who did not perform the restaging were classified as “not evaluated” and conservatively included among the non-responders. Independent review of radiologic tests was not performed and no formal rules regarding blinding of local radiologists were implemented into the protocol. ORRs between the treatment arms were compared by chi-square test.

All subjects who received at least one dose of study treatment were included in compliance and safety analyses. For each toxicity and each patient, the worst degree ever suffered during treatment was used for the analysis. The whole pattern of toxicity (all grades) was considered for each item and compared between arms by exact Kruskal-

Wallis linear rank test. Statistical analyses were performed using S-Plus version 6.1 (Insightful Corp., Seattle, WA, U.S.A.). Exact tests were performed using Cytel Studio 10 (Cytel Software, Cambridge, MA, U.S.A.).

RESULTS

Patient characteristics

Between February 3, 2010 and May 8, 2013, 108 patients were randomly assigned to standard (n=53) or experimental (n=55) arm (Figure 1). One patient was excluded from analysis because she withdrew consent immediately after randomisation. Therefore, the survival analyses included 107 patients (**Figure 1**). Baseline characteristics of the patients were balanced between the arms (**Table 1**). All 107 patients received at least one dose of the assigned treatment (no case of treatment violation) and, therefore, were included in the compliance and safety analyses.

Treatment compliance

Median number of chemotherapy cycles was 6 (IQR 4-6) in the both arms. Median relative dose intensity (RDI) for carboplatin was 92% (IQR 86%-100%) and 91% (IQR 85%-98%) in the control and experimental arm, respectively. Median RDI for paclitaxel was 90% (IQR 80%-98%) and 89% (IQR 80%-94%) in the control and experimental arm, respectively. Median RDI for cetuximab was 82% (IQR 76%-90%). At least one dose reduction was applied to chemotherapy in 17 (33%) and 21 (38%) patients in the control and experimental arm, respectively. Cetuximab dose was reduced in 4 patients (7%). Overall, 35 (67%) and 34 (62%) patients completed the planned chemotherapy. Chemotherapy was discontinued due to reasons other than completion or progression/death in 3 (6%) and 7 (13%) patients in the control and experimental arm, respectively. Cetuximab was discontinued due to toxicity or refusal by 13 patients (24%); one patient was still on treatment at the time of the analysis (**Table 2**).

Activity analysis

With data locked on March 15, 2015, after a median follow-up of 23 months (95% CI: 20-26), 102 patients had an event for the primary analysis (48 and 54 in the standard and experimental arm, respectively). The event was progressive disease for 83 patients, death without evidence of progression for 2 patients, definitive stop of the treatment for 15 patients and loss to follow-up for 2 patients. Overall, 97 patients progressed (45 and 52 progressions in the standard and experimental arm, respectively) and 61 died (30 and 31 death in the standard and experimental arm, respectively).

Median EFS was 4.7 with the standard treatment and 6.0 months with the experimental treatment and the difference was not statistically significant (HR 0.97, 95% CI: 0.66-1.43; one-tailed log-rank test p=0.43). Median PFS was 5.2 and 7.6 months (HR 0.84, 95% CI: 0.56-1.26; one-tailed log-rank test p=0.20) and median OS was 17.7 and 17 months (HR 0.85, 95% CI: 0.52-1.42; one-tailed log-rank test p=0.27), with standard and experimental treatment, respectively (**Figures 2-4**).

Twenty-one patients (8 in the control arm and 13 in the standard arm) were found ineligible after randomisation, as they did not have measurable disease according to RECIST at baseline assessment. Therefore, 86 (80.4%) patients were eligible for response analysis according to RECIST 1.0, 44 (84.6%) and 42 (76.4%) in the control and experimental arm, respectively. Nineteen patients (43%, 95% CI: 30%-58%) in the standard arm and 16 patients (38%, 95% CI: 25%-53%) in the experimental arm achieved an objective response (Chi square p=0.79) (**Table 3**).

Safety analysis

The worst per patient toxicity according to CTCAE 4.0 distributed per treatment arm, is summarized in **Table 4**. There were no unexpected toxicities. One patient died following a

stroke during standard treatment. There was no difference between treatment arms in the occurrence of adverse events, except, as expected, for diarrhoea (only not severe) and skin toxicity.

Overall, at least one severe (grade ≥3) adverse event was reported in 30 (58%) patients in the control arm and 44 (80%) in the experimental one. As expected, severe skin toxicity was reported only in the experimental arm (9 patients reported a grade 3 skin toxicity, 6 of whom had acneiform skin rash).

Skin toxicity reported according to the MASCC EGFR inhibitor Skin Toxicity Tool (MESTT) is summarized in **Table 5**. Twelve patients reported a severe (all grade 3) toxicity with MESTT in the experimental arms.

DISCUSSION

The addition of cetuximab to carboplatin and paclitaxel in the treatment of patients with advanced or recurrent cervical cancer, did not improve EFS (primary end-point), PFS, OS nor ORR in the MITO CERV-2 trial.

Other three unsuccessful phase 2 trials of cetuximab in advanced cervical cancer were conducted during the same years. A single-arm GOG trial of single agent cetuximab in 35 pretreated patients failed to show any activity, with no objective response reported and an unsatisfactory PFS rate at 6 month [23]. A GINECO trial tested the activity of the combination of cetuximab with cisplatin and topotecan as first-line chemotherapy for advanced disease [24]. This was a single-arm trial with ORR as primary end-point but was stopped early, with 19 enrolled out of 44 planned patients, for an unexpected excess of severe and fatal toxicity (infections and myelotoxicity). Another GOG study, enrolling 76 patients, tested the combination of cetuximab with cisplatin only as first line treatment for advanced recurrent or persistent disease. The combination was well tolerated but not active as predicted. In this study, the investigator collected baseline tumor specimens and found a correlation between a high tumoral EGFR expression and advanced stage and shorter PFS [25].

Our study tested the addition of cetuximab to a doublet chemotherapy scheme including carboplatin and paclitaxel, a combination that has been largely evaluated in lung cancer treatment, and that was therefore considered safe. Indeed, we had no problem of tolerability and the addition of cetuximab increased skin toxicity only.

We chose a randomised comparative design with statistical criteria that, accepting a high alpha error, allow an adequate power to screen a promising treatment, to be evaluated for efficacy in a phase 3 study, with a relatively small sample size. The control arm performed

as expected, with a median EFS of 4.7 months found and a median EFS of 4.5 months anticipated under the null hypothesis. We chose a composite endpoint, EFS, as primary end-point since it includes as event the discontinuation of treatment due to causes different from progression, such as toxicity or patient choice, and it could be relevant for a treatment that is scheduled until progression of disease and has a specific, socially relevant, toxicity. However, the addition of cetuximab did not substantially improve also the secondary outcomes.

Our study enrolled molecularly unselected patients, while it is known that mutations of RAS, an EGFR downstream signalling molecule, are strongly predictive of lack of efficacy of cetuximab in colorectal cancer. In SCCHN patients, RAS mutations, rare at baseline, seem to be involved in the acquired resistance to cetuximab treatment [26]. However, neither RAS or EGFR mutations, nor EGFR gene amplification, were associated with benefit from cetuximab in lung cancer [27], whilst contrasting results were reported for high EGFR protein expression as positive predictive factor [27,28].

We cannot exclude that there might exist cervical cancer molecular subgroups that could be sensitive or resistant to cetuximab treatment. We tried to retrospectively collect tumor samples for an exploratory biomarker analysis, with the aim of identifying molecular alterations predictive of cetuximab clinical activity and, possibly, to optimize its use; but unfortunately, only a very low number of samples were retrieved and we cannot conduct any explorative subgroup analysis.

In previous studies, EGFR was showed to be overexpressed in most of cervical cancers [5] and RAS mutations seemed to be rare or even absent in cervical carcinoma [29]. Therefore, in principle, cetuximab would be active in this tumor. Recently, within a randomised study of radio-chemotherapy plus cetuximab in 78 patients with locally advanced cervical cancer,

a molecular analysis of baseline tumor samples found that no tumor had an EGFR mutation, 4% of tumors only had a KRAS mutation while 22% had a PIK3CA mutation [30]. A complete response was observed in 27% of patients without PIK3CA mutations but in none of the patient with one or more PIK3CA mutations, suggesting a correlation between these mutations and cetuximab resistance.

In conclusion, our trial showed that the addition of cetuximab to carboplatin and paclitaxel was feasible but not more effective than chemotherapy alone and does not deserve phase 3 testing in unselected advanced or refractory cervical cancer patients.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-86, 2015

2. National Cancer Institute at the National Institute of Health. Cervical Cancer Screening (PDQ), http://www.cancer.gov/types/cervical/hp/cervical-screening-pdq#section/_8, 2016

3. Monk BJ, Tewari KS, Koh WJ: Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol 25:2952-65, 2007

4. Fuchs I, Vorsteher N, Buhler H, et al: The prognostic significance of human epidermal growth factor receptor correlations in squamous cell cervical carcinoma. Anticancer Res 27:959-63, 2007

5. Bellone S, Frera G, Landolfi G, et al: Overexpression of epidermal growth factor type-1 receptor (EGF-R1) in cervical cancer: implications for Cetuximab-mediated therapy in recurrent/metastatic disease. Gynecol Oncol 106:513-20, 2007

6. Kersemaekers AM, Fleuren GJ, Kenter GG, et al: Oncogene alterations in carcinomas of the uterine cervix: overexpression of the epidermal growth factor receptor is associated with poor prognosis. Clin Cancer Res 5:577-86, 1999

7. Kim GE, Kim YB, Cho NH, et al: Synchronous coexpression of epidermal growth factor receptor and cyclooxygenase-2 in carcinomas of the uterine cervix: a potential predictor of poor survival. Clin Cancer Res 10:1366-74, 2004

8. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al: Cetuximab for the treatment of colorectal cancer. N Engl J Med 357:2040-8, 2007

9. Van Cutsem E, Kohne CH, Lang I, et al: Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 29:2011-9, 2011

10. Heinemann V, von Weikersthal LF, Decker T, et al: FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 15:1065-75, 2014

11. Vermorken JB, Mesia R, Rivera F, et al: Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359:1116-27, 2008

12. Thienelt CD, Bunn PA, Jr., Hanna N, et al: Multicenter phase I/II study of cetuximab with paclitaxel and carboplatin in untreated patients with stage IV non-small-cell lung cancer. J Clin Oncol 23:8786-93, 2005

13. Sit AS, Kelley JL, Gallion HH, et al: Paclitaxel and carboplatin for recurrent or persistent cancer of the cervix. Cancer Invest 22:368-73, 2004

14. Kitagawa R, Katsumata N, Shibata T, et al: Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. J Clin Oncol 33:2129-35, 2015

15. Tinker AV, Bhagat K, Swenerton KD, et al: Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: the British Columbia Cancer Agency experience. Gynecol Oncol 98:54-8, 2005

16. Long HJ, 3rd: Management of metastatic cervical cancer: review of the literature. J Clin Oncol 25:2966-74, 2007

17. Korn EL, Arbuck SG, Pluda JM, et al: Clinical trial designs for cytostatic agents: are new approaches needed? J Clin Oncol 19:265-72, 2001

18. Rubinstein LV, Korn EL, Freidlin B, et al: Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol 23:7199-206, 2005

19. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-16, 2000

20. Lacouture ME, Maitland ML, Segaert S, et al: A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer 18:509-22, 2010

21. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-6, 1996

22. Kaplan E.L. MP: Non parametric estimation from incomplete observation. J Am Stat Assoc 53:457-81, 1985

23. Santin AD, Sill MW, McMeekin DS, et al: Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 122:495-500, 2011

24. Kurtz JE, Hardy-Bessard AC, Deslandres M, et al: Cetuximab, topotecan and cisplatin for the treatment of advanced cervical cancer: A phase II GINECO trial. Gynecol Oncol 113:16-20, 2009

25. Farley J, Sill MW, Birrer M, et al: Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression: a Gynecologic Oncology Group study. Gynecol Oncol 121:303-8, 2011

26. Braig F, Voigtlaender M, Schieferdecker A, et al: Liquid biopsy monitoring uncovers acquired RAS-mediated resistance to cetuximab in a substantial proportion of patients with head and neck squamous cell carcinoma. Oncotarget, 2016

27. Khambata-Ford S, Harbison CT, Hart LL, et al: Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 28:918-27, 2010

28. Pirker R, Pereira JR, von Pawel J, et al: EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol 13:33-42, 2012

29. Bumrungthai S, Munjal K, Nandekar S, et al: Epidermal growth factor receptor pathway mutation and expression profiles in cervical squamous cell carcinoma: therapeutic implications. J Transl Med 13:244, 2015

30. de la Rochefordiere A, Kamal M, Floquet A, et al: PIK3CA Pathway Mutations Predictive of Poor Response Following Standard Radiochemotherapy +/- Cetuximab in Cervical Cancer Patients. Clin Cancer Res 21:2530-7, 2015

Table 1 : Baseline characteristics

		Carboplatin/Paclitaxel (n =52)	Carboplatin/Paclitaxel + Cetuximab (n=55)
Median age (IQR)		52 (44-62)	47 (41-60)
Previous chemotherapy			
	No	22 (42%)	24 (44%)
	Yes	30 (58%)	31 (56%)
Distant metastasis			
	No	9 (17%)	10 (18%)
	Yes	43 (83%)	45 (81%)
ECOG performance status			
	0	33 (64%)	40 (73%)
	1	19 (36%)	15 (27%)
Histotype			
	Adenocarcinoma	11 (21%)	12 (22%)
	Squamous	41 (79%)	43(78%)
Grade			
	1	1 (2%)	1 (2%)
	2	8 (15%)	20 (36%)
	3	31 (60%)	27 (49%)
	Not known	12 (23%)	7 (13%)

Table 2. Treatment compliance

	Carboplatin/Paclitaxel (n =52)	**Carboplatin/Paclitaxel + Cetuximab (n=55)**
Chemotherapy		
No. of cycles, median (IQR)	6 (4-6)	6 (4-6)
No. of patients		
At least one delay	17 (33%)	21 (38%)
At least one dose reduction	12 (23%)	8 (14%)
Cause of treatment interruption		
Completion	35 (67%)	34 (62%)
Progression or death	14 (27%)	14 (25%)
Toxicity or refusal	2 (4%)	7 (13%)
Medical decision	1 (2%)	0 (0%)
Cetuximab		
No. of weeks, median (IQR)	-	26 (14-35)
Number of patients		
At least one delay	-	27 (49%)
At least one dose reduction	-	4 (7%)
Cause of treatment interruption		
Progression or death	-	41 (74%)
Toxicity or refusal	-	13 (24%)
Still on treatment	-	1 (2%)

IQR: interquartile range

Table 3. Objective response according to treatment arm

	Carboplatin/Paclitaxel (n =44)	Carboplatin/Paclitaxel + Cetuximab (n=42)	P
Responders	19 (43%) 95%CI: 30%-58%	16 (38%) 95%CI: 25%-53%	0.79
CR	5 (11%)	2 (5%)	
PR	14 (32%)	14 (33%)	
Non responders	25 (57%)	26 (62%)	
SD	8 (18%)	14 (33%)	
P	11 (25%)	6 (14%)	
Not evaluated	6*(14%)	6** (14%)	

CR: complete response; PR: partial response; SD: stable disease; P: progression.

* 4 patients underwent, at the restaging, a radiologic exam different than the baseline one; 2 patients did not undergo restaging owing to early clinically assessed PD.

** 2 patients underwent, at the restaging, a radiologic exam different than the baseline one; 4 patients did not undergo restaging owing to early clinically assessed PD (1 patient), early death (1 patient) or early treatment discontinuation (2 patients).

Table 4. Worst per patient toxicity comparison

	Carboplatin/Paclitaxel										Carboplatin/Paclitaxel + Cetuximab										
Grade	**1**		**2**		**3**		**4**		**5**		**1**		**2**		**3**		**4**		**5**		
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P***
Anemia	14	(27)	14	(27)	7	(13)	1	(2)	0	(0)	13	(24)	14	(25)	8	(15)	0	(0)	0	(0)	0,68
Leucopenia	4	(8)	15	(29)	12	(23)	0	(0)	0	(0)	5	(9)	9	(16)	10	(18	5	(9)	0	(0)	0,85
Neutropenia	2	(4)	10	(19)	12	(23)	8	(15)	0	(0)	3	(5)	6	(11)	15	(27)	11	(20)	0	(0)	0,55
Febrile Neutropenia	0	(0)	0	(0)	0	(0)	2	(4)	0	(0)	0	(0)	0	(0)	3	(5)	3	(5)	0	(0)	0,27
Infection	0	(0)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	2	(4)	1	(2)	0	(0)	0	(0)	0,55
Thrombocytopenia	6	(12)	6	(12)	3	(6)	1	(2)	0	(0)	4	(7)	7	(13)	5	(9)	1	(2)	0	(0)	0,86
Hemorrage	4	(8)	1	(2)	2	(4)	0	(0)	0	(0)	2	(4)	3	(5)	0	(0)	0	(0)	0	(0)	0,46
Allergy	0	(0)	1	(2)	1	(2)	0	(0)	0	(0)	1	(2)	1	(2)	1	(2)	1	(2)	0	(0)	0,60
Heart, rhythm	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	2	(4)	1	(2)	0	(0)	0	(0)	0	(0)	0,55
Heart, general	2	(4)	3	(6)	0	(0)	0	(0)	0	(0)	4	(7)	1	(2)	0	(0)	0	(0)	0	(0)	0,81
Thrombosis/embolism	0	(0)	1	(2)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	1	(2)	3	(5)	0	(0)	0,46
Fever	3	(6)	1	(2)	0	(0)	0	(0)	0	(0)	6	(11)	4	(7)	1	(2)	0	(0)	0	(0)	0,07
Fatigue	14	(27)	9	(17)	3	(6)	0	(0)	0	(0)	18	(33)	9	(16)	6	(11)	0	(0)	0	(0)	0,31
Constitutional, other	2	(4)	1	(2)	0	(0)	0	(0)	0	(0)	3	(5)	1	(2)	2	(4)	0	(0)	0	(0)	0,38
Hair loss	0	(0)	16	(31)	0	(0)	0	(0)	0	(0)	8	(15)	15	(27)	0	(0)	0	(0)	0	(0)	0,53
Anorexia	5	(10)	0	(0)	0	(0)	0	(0)	0	(0)	2	(4)	0	(0)	0	(0)	0	(0)	0	(0)	0,26
Constipation	11	(21)	7	(13)	1	(2)	0	(0)	0	(0)	5	(9)	7	(13)	0	(0)	1	(2)	0	(0)	0,22
Diarrhoea	1	(2)	3	(6)	0	(0)	0	(0)	0	(0)	9	(16)	4	(7)	1	(2)	0	(0)	0	(0)	**0,02**
Mucositis	2	(4)	2	(4)	0	(0)	0	(0)	0	(0)	4	(7)	3	(5)	3	(5)	0	(0)	0	(0)	0,11
Nausea	13	(25)	6	(12)	0	(0)	0	(0)	0	(0)	10	(18	7	(13)	0	(0)	0	(0)	0	(0)	0,65
Vomiting	6	(12)	9	(17)	0	(0)	0	(0)	0	(0)	9	(16)	2	(4)	0	(0)	0	(0)	0	(0)	0,18
Liver	4	(8)	1	(2)	0	(0)	0	(0)	0	(0)	6	(11)	1	(2)	0	(0)	0	(0)	0	(0)	0,73
Renal/Genitourinary	4	(8)	2	(4)	1	(2)	0	(0)	0	(0)	4	(7)	2	(4)	2	(4)	0	(0)	0	(0)	0,88
CNS ischemia	0	(0)	0	(0)	0	(0)	0	(0)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1,00
Sensory neuropathy	15	(29)	5	(10)	0	(0)	0	(0)	0	(0)	12	(22)	7	(13)	1	(2)	0	(0)	0	(0)	1,00
Neurology other	3	(6)	3	(6)	1	(2)	0	(0)	0	(0)	3	(5)	2	(4)	0	(0)	0	(0)	0	(0)	0,43
Pain	1	(2)	2	(4)	1	(2)	1	(2)	0	(0)	1	(2)	2	(4)	3	(5)	0	(0)	0	(0)	0,89
Pulmonary	1	(2)	1	(2)	1	(2)	0	(0)	0	(0)	3	(5)	0	(0)	0	(0)	0	(0)	0	(0)	0,74
Dry skin	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	5	(9)	2	(4)	1	(2)	0	(0)	0	(0)	**0,03**
Flushing	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	6	(11)	3	(5)	0	(0)	0	(0)	0	(0)	**0,003**
Nail changes	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	3	(5)	4	(7)	1	(2)	0	(0)	0	(0)	**0,006**
Pruritus	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	6	(11)	1	(2)	0	(0)	0	(0)	0	(0)	0,06
Rash/desquamation	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	5	(9)	10	(18)	1	(2)	0	(0)	0	(0)	0,0520
Rash/acneiform	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	13	(24)	14	(25)	6	(11)	0	(0)	0	(0)	**<0,0001**
Skin, other	1	(2)	1	(2)	0	(0)	0	(0)	0	(0)	12	(22)	4	(7)	0	(0)	0	(0)	0	(0)	0,08

*P value from the Kruskal Wallis exact test

Table 5. Worst per patient skin toxicity according to MASCC EGFR inhibitor skin toxicity tool (MESTT) distributed by arm

	Carboplatin/Paclitaxel							Carboplatin/Paclitaxel + Cetuximab						
Grade	**1**		**2**		**3**		**4**	**1**		**2**		**3**		**4**
	A	**B**	**A**	**B**	**A**	**B**		**A**	**B**	**A**	**B**	**A**	**B**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Papulopustular eruption	0	0	0	0	0	0	_	11 (20)	3 (5)	7 (13)	1 (2)	2 (4)	5 (9)	_
Nail Changes-Nail Plate	0	0	0		0		_	3 (5)	1 (2)	0		0		_
Nail Changes-Nail Fold	0		0		0		_	0		2 (4)		0		_
Nail Changes-Digit tip	0		0		0		_	1 (2)		2 (4)		1 (2)		_
Erythema	1 (2)		0		0		_	18 (33)		8 (15)		2 (4)		_
Pruritus	1 (2)		0	0	0		_	4 (7)		0	0	0		_
Xerosis	1 (2)		0	0	0	0	_	11 (20)		0	0	0	0	_
Hair changes-Alopecia	0		14 (27)	2 (4)	_	_	_	8 (15)		12 (22)	3 (5)	_	_	_
Hair changes-Increased hair	0		0	0	_	_	_	0		3 (5)	1 (2)	_	_	_
Flushing	0	0	0	0	0	0	_	4 (7)	2 (4)	1 (2)	1 (2)	1 (2)	0	_
Hyperpigmentation	0		0	0	0		_	2 (4)		0	0	0		_
Mucositis	3 (6)		0		0		0	3 (5)		3 (5)		3 (5)		0
Taste	0		0		0		_	0		0		1 (2)		_

Figure legends

Figure 1.

Study flow.

Figure 2.

Event-free survival (EFS) curves by treatment arm.

Figure 3.

Progression-free survival (PFS) curves by treatment arm.

Figure 4.

Overall survival (OS) curves by treatment arm.

APPENDIX

List of MITO CERV-2 participating Institutions (town), physicians, research nurses and data managers.

1. Dipartimento di Oncologia Uroginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS (Napoli): Sandro Pignata, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Stefano Greggi, Rosa Tambaro, Laura Arenare, Angela Maria Trujillo, Margherita Tambaro.
2. Dipartimento per la Tutela della Salute della Donna della Vita Nascente del Bambino e dell' Adolescente, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore (Roma): Giovanni Scambia, Gabriella Ferrandina, Vanda Salutari, Giulia Amadio, Mariagrazia Distefano, Rosa Pasqualina De Vincenzo, Caterina Ricci, Antonella Pietragalla, Alessia Di Legge, Michela Panella.
3. Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale Tumori (Milano): Domenica Lorusso, Francesco Raspagliesi, Giuseppa Maltese, Stefano Lepori, Antonino Ditto, Giorgio Bogani, Ilaria Sabatucci, Valentina Chiappa, Cono Scaffa, Mauro Signorelli, Elisa Grassi.
4. Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori – IRCSS (Meldola-Cesena): Ugo De Giorgi, Barbara Kopf, Salvatore Luca Burgio, Cecilia Menna, Vincenza Conteduca, Valentina Gallà.
5. Istituto Oncologico Veneto IRCCS (Padova): Maria Ornella Nicoletto, Alessandra Baldoni, Simona Frezzini, Giulietta Sinigallia.
6. Università Federico II (Napoli): Rossella Lauria, Cinzia Cardalesi.
7. Oncologia Medica, Ospedale S. Maria della Misericordia (Perugia): Annamaria Mosconi, Tella Porrozzi, Fabiana Marchetti.
8. Ospedale Universitario "S. Maria della Misericordia" (Udine): Cosimo Sacco, Claudia Andretta, Roberta Sottile.
9. Oncologia Medica, Azienda Ospedaliero Universitaria Policlinico (Modena): Roberto Sabbatini, Elisabetta Filieri, Pasquale Mighali.
10. Oncologia Medica, Università della Magna Grecia (Germaneto,CZ): Pierosandro Tagliaferri, Angela Salvino.
11. Ginecologia Ongologica, Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Uninversità Cattolica del Sacro Cuore (Campobasso): Gabriella Ferrandina, Aida Di Stefano, Francesca Risi.
12. Oncologia Medica & Breast Unit, Ospedale “Senatore Antonio Perrino” (Brindisi): Saverio Cinieri, Enrica Mazzoni, Ermelinda Ferrara.
13. Oncologia Medica, Istituto Nazionale Tumori Regina Elena (Roma): Antonella Savarese, Paola Malaguti, Agnese Provenziani.
14. Oncologia Medica, Fondazione del Piemonte per l’Oncologia, IRCCS (Candiolo, TO): Giorgio Valabrega, Massimo Aglietta, Celeste Cagnazzo.
15. Cattedra di Statistica Medica, Seconda Università di Napoli (Napoli): Ciro Gallo, Simona Signoriello, Giuseppe Signoriello, Paolo Chiodini.
16. Unità Sperimentazioni Cliniche Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS (Napoli): Francesco Perrone, Maria Carmela Piccirillo, Gennaro Daniele, Jane Bryce, Giuliana Canzanella, Federika Crudele, Manuela Florio, Giovanni De Matteis, Cristiana De Luca, Anna Gimigliano, Fiorella Romano, Antonia Del Giudice, Marilena Martino, Maria Teresa Ribecco, Alfonso Savio, Lucia Sparavigna.