AGO 20 - SYNOPSIS

TITLE	**A two-stage multicenter phase II trial of concurrent panitumumab immunotherapy, cisplatin chemotherapy and pelvic radiotherapy for primary cancer of the uterine cervix stage Ib-IIIb**
SPONSPOR	Studienzentrale der AGO
TREATMENT LINE	Primary / adjuvant
DESIGN	Two-step phase II (Bryant & Day design)
DURATION OF STUDY	18 months inclusion period and 1-year follow-up

RATIONALE

Cervical Cancer

Despite a decreasing incidence with currently an age standardized incidence rate of 10.4 new cervical cancer cases per 100.000 women per year in western industrialized countries, there are 600 new cases in Austria of which one third (n≈200) die every year.

In the past few years, a shift in the therapeutic paradigm of cervical cancer now favors to avoid surgery in patients with metastatic lymph node involvement, since it has been shown that these patients benefit from postoperative chemoradiotherapy, which however is strained with much more adverse events than primary chemoradiotherapy. Thus, because of stage (FIGO IIb-IIIb) and / or metastatic lymph node involvement (FIGO Ia-IIa), approximately 55% percent (n≈100), according to the current epidemiologic development of the disease[1], are candidates of primary chemoradiotherapy in Austria. The vast majority of these patients are treated in cancer centers selected as study centers of this clinical trial by the AGO.

Chemoradiation

Two large and outstanding clinical trials of chemoradiotherapy in cervical cancer demonstrated significant improvement of progression-free and overall survival in FIGO stage Ib2, and of progression-free survival in FIGO stage IIb-IVa. A systematic review and meta-analysis in 4,580 patients randomized in 19 clinical trials was able to describe an improvement of overall, progression-free and distant metastasis-free survival. In consequence of these reported data, every radiation therapy with curative intent nowadays is to be delivered as chemoradiotherapy, usually with cisplatin as chemosensitizer.

Despite this success, between 20% and 40% of patients have recurrent disease after 4 years, and 15% to 35% die within 4 years after diagnosis and chemoradiotherapy. Thus, recurrence after chemoradiotherapy is largely fatal, which is in accordance with the clinical experience that salvage chemotherapy in metastasized patients produces response rates ranging from 20% to 30%, and that overall survival of these patients is usually less than 10 months. **In consequence, there is a strong clinical need to improve the therapeutic index of chemoradiotherapy for patients with locally advanced cervical cancer**.

Improvements in progression-free survival are seen as early as 3-6 months, suggesting that some tumors have a primary resistance to cisplatin chemoradiation. Since recurrences are highly likely to be fatal within 5 years, early assessment of progression might serve as a surrogate marker of overall efficacy and may relate to overall survival. Thus, a **primary efficacy endpoint at 4 months** appears clinically justified in a trial setting when supplemented by an overall observation period of 1 year. By a 4-month efficacy assessment, efficacy data will not be compromised or biased by cases with tumor-positive cervical post-treatment biopsies, which will require surgical removal of the uterus approximately 5 weeks after completion of treatment, i.e. roughly 4 months after treatment initiation.

Anti-EGFR target therapy

Because of the minimal degree of success with both primary and salvage chemotherapy regimens in cervical cancer, and because of the poor prognosis of patients with either advanced or progressive disease, interest has increased in targeted therapeutics for the primary treatment of cervical cancer. The epithelial growth factor receptor type-1 (EGFR1, also called HER1) has recently been identified as a promising target for cervical cancer. Both squamous carcinoms and adenocarcinomas of the cervix uteri express EGFR in all stages and

in over 85% of cases, suggesting that cervical cancer would be an ideal target for anti-EGFR treatment; in addition, EGFR expression has been associated with poor prognosis. Interestingly, EGFR expression levels detected by immunohistochemistry do not correlate with response to anti-EGFR treatment. EGFR blockade with anti-EGFR antibodies has shown synergistic effects with cisplatin in human tumor xenografts in vivo. EGFR has further been shown to modulate tumor cell chemosensitivity and radiosensitivity, and is used in chemoradiotherapy protocols in currently recruiting clinical trials in head-and-neck and cervical cancer.
Early reports from the ongoing trials on anti-EGFR treatment mentioned previously on skin related toxicity in head-and-neck cancer and gastrointestinal toxicity in cervical cancer, respectively, require prudent control of treatment related toxicities. With regard to the proposed trail, gastrointestinal perforation (GIP) excessively beyond an inacceptable threshold level of 7.5%, as described for GIP in the use of bevacizumab in ovarian or colorectal cancer, would represent an inacceptably toxic treatment regime. In consequence, an early stopping rule has been implemented in the trial design to control for severe toxicity exceeding 7.5% among the first 11 enrolled patients.

KRAS mutation and anti-EGFR treatment
Point mutations at codon 12 and 13 of the *KRAS* gene have been described for squamous cell (6%) and for adenocarcinoma type (14%) tumors, respectively. The negative predictive effect of *KRAS* mutation on response of metastasized colorectal tumors to Pmab treatment appears well established; such tumors are known to contain rather genetically uniform tumor cell clones due to sharp selection of resistant clones by previous treatments and progression. It is well acknowledged that evolutionarily younger clonal generations show larger genetic variation, and a mutated *KRAS* tumor cell population might not be the predominant clone; in consequence, the tumor lesion might response to anti-EGFR treatment. However, in order to avoid selection of putatively treatment resistant tumor cell clones, we will test for KRAS mutation status of the individual patient tumor, and we will exclude patients with KRAS mutations from study treatment. **In consequence, only patients with wild-type KRAS gene in biopsy samples will receive Pmab monotherapy followed by Pmab-cisplatin chemoradiotherapy.**

As a consequence of recently reported data on the putative negative predictive value of *BRAF* mutations for anti-EGFR treatment in colorectal cancer, we will test all tumors of study patients for *BRAF* mutations, since only inconsistent data exist on the prevalence of *BRAF* mutations in cervical cancer. In addition, E2F transcription factors which are thought to play a critical role in EGFR signaling and growth stimulation will be examined in cases where snap-frozen tumor tissue is available for analysis. Thus, our translational research biomarker approach will provide first insights EGFR signaling in cervical cancer.

Panitumumab (Vectibix), a fully human anti-EGFR antibody
Panitumumab (Pmab) is a fully human IgG_2 monoclonal antibody acquired by the XenoMouse technology. It does not contain murine protein sequences: clinical data indicate that Pmab is well tolerated, does not require premedication and is associated with a very low incidence of induced neutralizing a-Pmab antibodies. It binds EGFR with high affinity ($K_d = 5 \times 10^{11}$ M) and blocks binding of EGF and TGFα, inhibiting EGF-dependent tumor cell activation and proliferation. Pmab binds to EGFR and prevents receptor dimerization, EGFR-tyrosine autophosphorylation, and activation of downstream signaling molecules, thereby resulting in the inhibition of cellular proliferation and tumor growth and in the induction of apoptosis

In a phase I study Pmab was well tolerated with comparable exposure and safety profiles for the weekly, biweekly, and 3-weekly administration schedules at 2.5 mg/kg, 6.0 mg/kg and 9.0 mg/kg, respectively. The overall incidence of CTCAE grade 4 adverse events was 7%. The incidence of skin-related toxicities, the predominant cause of DLT, was dose dependent. No maximum tolerated dose was reached. No human anti-Pmab antibodies were detected. No investigator-determined Pmab infusion-related reactions were reported. Pmab showed single-agent antitumor activity.

In phase II studies, panitumumab monotherapy for the treatment of chemo-refractory

	colorectal cancer was active and well tolerated. An open-label phase III of single-agent Pmab plus best supportive care in chemo-refractory colorectal cancer revealed significantly improved PFS over best supportive care. For the latter indication and except for tumors with *KRAS* mutations, Pmab has received FDA and EMEA approval. **In conclusion, the proposed investigational treatment with concurrent Pmab and cisplatin chemoradiotherapy is a promising candidate experimental arm for a phase III trial with standard of care cisplatin chemoradiotherapy as comparator in patients with wild-type *KRAS*.**
OBJECTIVES AND ENDPOINTS	**Primary Efficacy Objective (Endpoint)** To assess the activity of concurrent Pmab-CRT in $KRAS^{wt}$ patients (*measured* by 4-month rate of progression-free survival of target lesion [i.e. uterine tumor] MRI measures according to RECIST **Primary Safety Objective (Endpoint)** To assess the rate of PRDs and/or GIPs of Pmab-CRT in $KRAS^{wt}$ patients (*measured* by CTCAE grades at 4 months) **Secondary Efficacy Objectives (Endpoints)** • To assess the activity of study treatment in $KRAS^{wt}$ positive and negative patients (*measured* by 4-month ORR according to RECIST) • To assess the activity of concurrent Pmab-CRT in $KRAS^{wt}$ positive and negative patients (*measured* by 12-month rate of progression-free survival of target lesion measures according to RECIST) • To assess the activity of concurrent Pmab-CRT in $KRAS^{wt}$ positive and negative patients (*measured* by 12-month rate of overall survival) **Secondary Safety Objectives (Endpoints)** • To assess the rate of (severe) adverse events during Pmab-CRT in $KRAS^{wt}$ and $KRAS^{mt}$ patients (*measured* by CTCAE grades 4 months after treatment initiation) • To assess the rate of post-treatment (severe) adverse events (*measured* by CTCAE grades 12 months after treatment initiation) • To assess the rate of (severe) adverse events of Pmab monotherapy (*measured* by CTCAE grades after Pmab monotherapy [at d14])
NUMBER OF PATIENTS	**50** female patients
STUDY POPULATION	**Main Inclusion Criteria** • Primary diagnosis of either adenocarcinoma or squamous small-cell or large-cell, keratinizing or non-keratinizing carcinoma of the uterine cervix • Indication for primary chemoradiotherapy (both neoadjuvant and definitive treatment concepts are comprised) in patients with stage FIGO Ib-IIIb without paraaortic lymph node metastases, or with documented clinical indication for primary chemoradiotherapy • Absence of predominant and clinically effective neuroendocrine tumor cell differentiation • Absence of acute life-threatening vaginal hemorrhage (e.g. requiring emergency irradiation, RBC packs transfusion) • Absence of clinical indication for paraaortic field irradiation because of (preferably) histologically confirmed or unambiguous radiologic evidence of paraaortic lymph node metastasis • WHO performance status 0, 1 or 2 • No current or prior malignancy within previous 5 years (other than current ovarian cancer or adequately treated non melanoma skin cancer or in-situ carcinoma of the cervix) • Serum creatinine clearance >50 ml/min (measured or calculated)

TREATMENT	**1 cycle of panitumumab at 6.0 mg/kg IV (d1)** followed by **6 cycles of cisplatin (e.g., Platinol™) at 40 mg/m^2 IV;** **repeated qw (d14, d22, d29, d36, d43, d50)** **3 cycles of concurrent panitumumab at 6.0 mg/kg IV;** **repeated q14d (d14, d29, d43)** **External and intracavitary radiotherapy with a biologic effective dose >75-90 Gy:** • teletherapy of pelvis of >45 Gy with fractions of 1.8-2.0 Gy • high-dose rate (HDR) brachytherapy of 4-6x 4,0-7,0 Gy
STATISTICS & STOPPING RULE	**The Bryant & Day two-step design taking into account toxicity and activity** **STEP1**—accrual of **25** patients: • continue trial if P_{r0} > 95% of patients have a 4-month progression-free survival • **stop** trial if P_{r1} < 85% of patients have a 4-month progression-free survival (i.e., **3 or more patients progress**) • continue trial if P_{t0} < 1.0% of patients experience skin necrosis and/or GIP • **stop** trial if P_{t1} > 7.5% of patients experience CTCAE °4 skin necrosis and/or GIP (i.e. **3 or more patients have CTCAE °4 skin necrosis and/or GIP**) **STEP2**—accrual of remaining **25** patients
TRANSLATIONAL RESEARCH	**Central assessment of wild-type *KRAS* and *BRAF*** Point mutations at codon 12 and 13 of the *KRAS* gene have been described for squamous cell (6%) and for adenocarcinoma type (14%) tumors, respectively. Since Pmab efficacy in colorectal cancer is limited to patients with wild-type *KRAS* and *BRAF,* assessment of mutated *KRAS* and *BRAF* represents important information for the analysis of Pmab efficacy in cervical cancer. Patients with tumor with *KRAS* mutation will be excluded from this trial. Results will be described and correlated with response to study treatment. **EGFR expression** Immunohistochemical EGFR detection using Pmab on pretherapeutic and subsequent samples will monitor the effects of Pmab on carcinoma cells and assess if selection of EGFR-negative clones occurs; results will be described and correlated with response to study treatment. **Proliferation and apoptosis** Ki67 and TRAIL will be determined immunohistochemically in order to monitor the assumed effects of Pmab and chemoradiotherapy on carcinoma cells, i.e. reduced proliferation and increased apoptosis; results will be described and correlated with response to study treatment. **VEGF expression of tumor cells** In a small explorative study on 29 patients, an elevated pretreatment VEGF expression was associated with poor prognosis and poor response to cisplatin-based chemoradiotherapy; results will be described and correlated with response to study treatment. **E2F transcription factors** Preliminary translational research data show that E2F play a central role in EGFR signaling and signal transduction regulation in ovarian cancer models (data in submission for publication). It may therefore be assumed that the transcriptional cell cycle regulator of the E2F family may also play a significant role in cervical cancer. For this purpose, some biopsy material will be snap frozen at sites and tumor validated samples will be analysed for variant transcription levels; results will be described and correlated with response to study treatment.