Low-grade serous ovarian cancer – a rare disease with more therapeutic options

Whilst high-grade serous cancers most commonly arise from the fimbrial end of the tube, having as marker gene p53 mutations, low-grade serous cancers are a different entity and should be seen distinct. Due to their slow growth and in parts development from serous borderline tumors, they show different genetic alterations and often marked estrogen-receptor expression (ER). This fact is now commonly used also therapeutically.

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Low-grade serous ovarian cancer (LGOC) is a rare histological subtype and biologically distinct from high-grade serous ovarian cancer (HGOC) and all other established types of ovarian carcinoma (endometrioid, clear cell, mucinous). Only approximately 5–10% of all ovarian cancers are of low-grade serous type, the exact prevalence is still unknown. Retrospective analyses, however, indicate unique pathological, epidemiological, clinical and biological features and recent reviews therefore presume that, although thus far mostly treated in a similar manner, LGOC seems to be a separate disease and not a precursor lesion of HGOC (1). In 2004 and lately again in 2012, the MD Anderson Cancer Center has provided a simpler and more prognostic grading system of serous ovarian cancer than the previous Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) system, now distinguishing only low-grade (mild or moderate atypia with ≤ 12 mitoses / 10 HPF) from high-grade (severe nuclear atypia > 12 mitoses / 10 HPF) (2, 3). The tumor marker CA125 is of less predictive value in LGOC as compared to HGOC (4). Estrogen receptor (ER) expression appears to be higher in LGOC than in HGOC (58 vs. 43%), however, different immunohistochemical techniques and cut-off values make comparisons difficult (5). Gershenson et al. described that only the Dako platform (Agilent, Santa Clara, CA) revealed a significant difference in ER expression between LGOC and HGOC (1).

Epidemiologically, patients with LGOC are generally diagnosed at a younger age (median 55 years). The overall incidence is estimated at 0,5: 100 000/year. Unlike in patients with HGOC, there is no family history association, e.g. BRCA 1–2 mutation carriers are not at increased risk for LGOC (4).

Biologically, LGOC show KRAS (19–55%), NRAS (25%) and BRAF (5%) mutations and are therefore more similar to borderline tumors (17–40%, WT 23–48%) than to HGOC (all < 1%). Moreover, LGOC show p53 mutations in only 8% of the cases, HGOC, in contrast, are p53 mutant in > 95% (see also *Table 1* [4]). Similar to ER-positive breast cancer patients, women < 35 years of age affected by LGOC have a rather poor prognosis (1).

Like HGOC patients, LGOC patients usually present at diagnosis with advanced FIGO stage. Tumor progression, however, appears to be slower and survival is longer with 97 months median overall survival (OS) compared with 57 months in HGOC patients (4, 6) *(Table 1)*.

In spite of these clear distinctions between HGOC and LGOC, primary treatment strategies in both diseases have thus far been generally similar: a maximal surgical cytoreduction effort followed by adjuvant chemotherapy with carboplatin and paclitaxel. The value of hormonal maintenance therapy (HMT) in patients with LGOC is currently under debate as Gershenson et al. showed in a retrospective analysis a significant longer progression-free survival (PFS) in

ABSTRACT

Low-grade serous ovarian cancer

LGOC is a distinct entity, often being diagnosed in young patients. Response to chemotherapy is poor and alternative treatment options need to be developed. Most promising so far is endocrine treatment.

Keywords: Low/high grade, epithelial ovarian cancer, serous

Table 1
Clinico-pathological Characteristics Low-/High-Grade serous Ovarian Cancer

Characteristics	LGOC	HGOC
Median age (years)	55	63
Frequency (% of all ovarian neoplasms)	3–9	90
Presumed precursor	serous borderline	STIC fallopian tube
CA-125	not predictive	predictive
Positive family history	rare	10%
Chemosensitivity	rare	90%
Clinical course	slow	fast
Median PFS (months)	92	35
Median OS (months)	97	57
Gene mutations (%)		
– BRAF	5	< 1
– KrasP53	19–55	< 1
– P53	8	> 95
– BRCA	1–5	15

Source: adapted from (4, 7)

patients with stage II–IV LGOC who received HMT after primary treatment. In this study of 70 patients who received HMT and 133 patients who were observed only, the median PFS was longer in patients who were clinically disease-free but also in patients with persistent disease. After adjusting for disease status, median OS was significantly longer in the patient group who received HMT.

Several small series suggested a benefit of endocrine therapy in LGOC patients, suggesting that there are subgroups of patients with a specific tumor biology that respond very well to endocrine therapy (8, 9). The rationale for endocrine treatment is based on the high ER/PR expression as a predictive marker, since ovarian cancer is partly driven by the estrogen-pathway (10). Gershenson et al. recently (1, 11, 7) presented a retrospective analysis of endocrine maintenance therapy (with diverse regimens, including anastrozole, letrozole and tamoxifen) for LGOC. For patients receiving endocrine maintenance therapy (n = 70) after platinum-based adjuvant chemotherapy, PFS was significantly improved as compared to patients under observation only (n = 133, 64.9 months; 95% Confidence Intervall [CI]: 43.5 to 86.3; versus 26.4 months; 95%-CI: 21.8 to 31.0, p < 0.001) (1). Most patients received treatment with letrozole (54%) or tamoxifen (28%). In 2012, the same authors described a high clinical benefit rate in a retrospective analysis obtained from medical records ranging from 1989 until 2009 covering 64 patients with recurrent LGOC. In spite of the limitation of these data, patients receiving different regimens of endocrine maintenance therapy for relapse showed a response rate of 9% and stable disease of 62% (7). This is of major significance as – similar to ER-positive breast cancer patients – LGOC affects mostly younger women with a rather poor prognosis (1).

A recent systematic review and meta-analysis of phase II trials of hormone treatments in ovarian cancer demonstrated in 53 trials with 2490 patients that in this pre-treated patient cohort there was a summary clinical benefit rate (SCBR) of 41% (95%-CI: 0.33–0.49) using hormonal therapy in advanced ovarian cancer patients (12). The SCBR was even better in ER and/or PR positive cancers (ORR: 46%; 95%-CI: 0.34–0.57) and in platinum sensitive patients (ORR: 55%; 95%-CI: 0.28–0.80). Paleari and colleagues concluded that the findings are «hampered by the heterogeneity of trials encompassing nearly 40 years» and that «RCTs (ran-

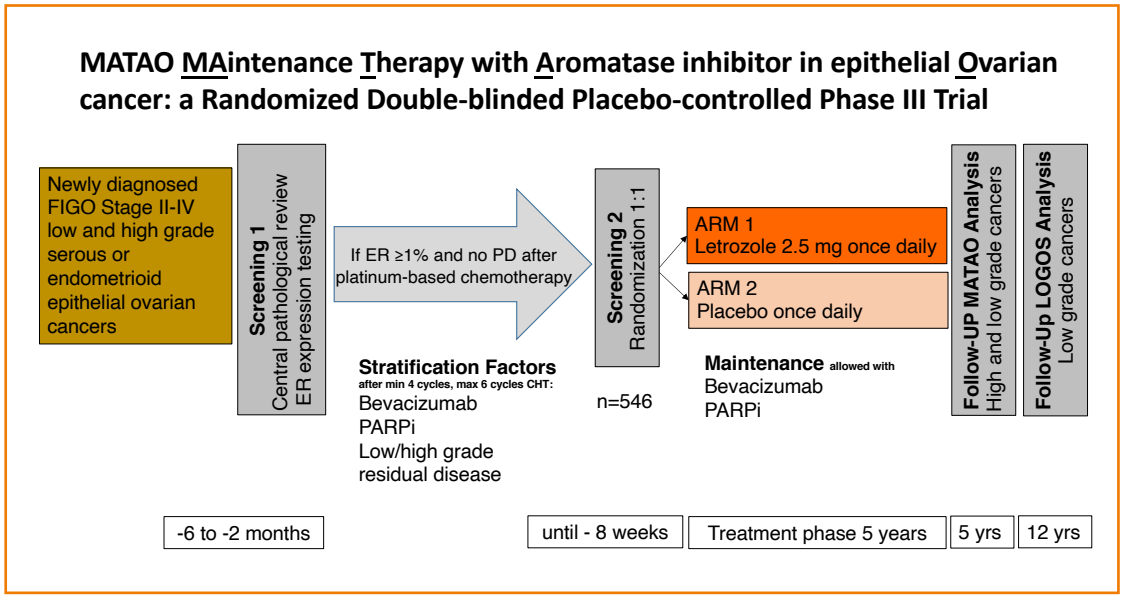

Figure 1: Schematic representation of MATAO study design, covering the maximum time schedule per patient depending on the differences in histopathological grading. Source: V. Heinzelmann, Swiss-GO Trial Group

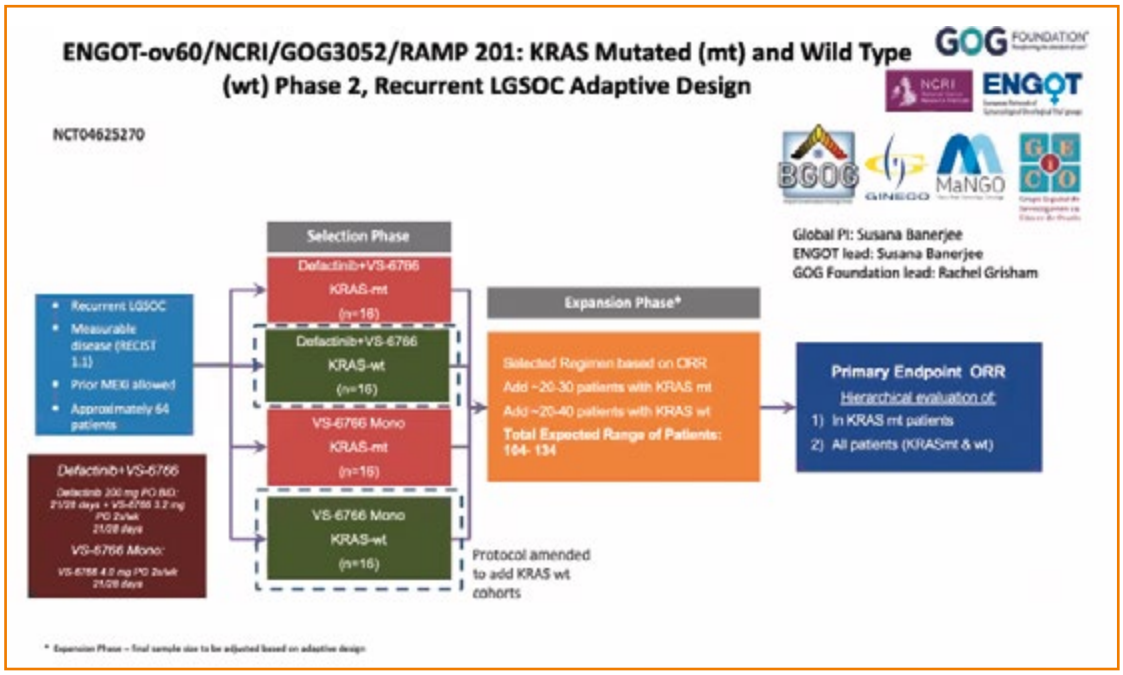

Figure 2: Schematic representation of RAMP 201 study design. PI Banerjee, NCRI, NCT04625270, www.clinicaltrials.gov

domized clinical trials) in the first line treatment of advanced hormone receptor positive EOC (epithelial ovarian cancer) are warranted».

Our own research (13) clearly demonstrates in several large and independent cohorts that the ER receptor and ER protein are markedly present in primary LGOC / HGOC. Moreover, ER protein expression marginally alters during disease progression and acquired chemoresistance. Heinzelmann et al. found in LGOC / HGOC patients a significantly prolonged PFS in patients who received letrozole maintenance therapy (after 24 months: 60% in the letrozole group vs. 38.5% in the control group; p = 0.035) and the same effect was seen in HGOC patients pre-treated with bevacizumab (after 12 months: 87.5% had no recurrence when taking letrozole vs. 20.8% in the control group; p = 0.026).

It is remarkable that endocrine treatment has only been used in the relapsed setting of ovarian cancer and that its role in primary or maintenance treatment has not been studied. Although, for more than 40 years, tamoxifen and later aromatase inhibitors have been studied in smaller cohorts and studies. A literature review covering over 50 trials including retrospective analysis, demonstrated a clinical benefit rate ranging from 0 to 95% when focusing on the most commonly used drugs, tamoxifen and aromatase inhibitors. These ambiguous results are probably caused by the extreme heterogeneous patients characteristics and the fact that these patients received the treatment, mostly, in the later lines (14).

These data were hypothesis-generating for the MATAO trial *(figure 1)*, which is the first Swiss Gynecological Oncology Trial in ENGOT, the European Network of Gynecological Oncology Trial Groups. MATAO is conducted by the Swiss-GO Trial Group and is currently open for recruitment (Principal Investigator [PI]: Viola Heinzelmann-Schwarz; NCT04111978) *(Box)*. The primary objective in this study is to evaluate the efficacy of letrozole maintenance therapy after standard surgical and chemotherapy treatment as measured by PFS compared to no maintenance therapy (placebo) in patients with newly diagnosed ER positive epithelial ovarian cancer (histologic subtype: serous or endometrioid of low-/high-grade, including fallopian tube

Swiss MATAO trial

The Swiss MATAO trial is conducted by the Swiss-GO Trial Group. The trial started recruitment in October 2020 and has so far recruited 50 patients in 13 Swiss centres. For further information and inquiries please contact info@matao.ch or visit the the website:

www.swiss-go.ch

Take Home Messages

- Low-grade serous ovarian cancers are a rare disease and should be treated within clinical trials.
- The major backbone of treatment is maintenance with endocrine treatment.
- The MATAO trial, our first ENGOT Swiss trial, is examining low- and high-grade ovarian cancers for maintenance treatment with endocrine therapy, recruitment is open until 2024.
- New trials are ongoing examining the role of MEK inhibitors in later lines, in combination with endocrine treatments.

and primary peritoneal cancer) of FIGO Stage II–IV, with or without residual disease and with or without concomitant anti-VEGF and/or PARP inhibitor medication, whose cancer has not progressed by the end of adjuvant chemotherapy treatment.

PI Amanda Fader et al. in the US are performing a similar trial in LGOC only, hereby randomizing these patients to one arm with chemotherapy followed by letrozole and the other arm receiving no chemotherapy but only letrozole (NCT04095364). This trial is currently performed by GOG and has recruited around 40 patients so far.

Beside endocrine therapy, MEK inhibitors have emerged as treatment option in LGOC patients, hereby targeting the molecular mutations observed. Previously, the GOG/ENGOT-ov11/MILO trial has examined binimetinib, a MEK inhibitor, in LGOC within a multinational, randomized, open-label phase III study versus physician's choice chemotherapy (15). Although not meeting its primary end point, the MEK inhibitor showed marked activity. It was suggested that KRAS mutation might predict response and be used to select ideal candidates as a predictive marker. For this reason, at present, a phase II trial using a dual RAF/MEK Inhibitor Alone and in Combination with Defactinib (FAK Inhibitor) is examined in recurrent LGOC within the ENGOT-ov60/NCRI/GOG-3052 trial (PI Susana Banerjee, NCT04625270) *(see figure 2)*. Hereby, stratification by KRAS mutation is incorporated. The trial has just started recruitment of the first 5 patients in the US, ENGOT submissions are underway and sites expected to open June/July 2021.

Patients with LGOC reflect a rare subset of epithelial ovarian cancers where optimal treatment is not as yet defined. Therefore, patients should be treated in centres with enough experience and access to trials.

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