Highlights in gynaecological cancers

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During this year's ESMO Congress in Munich, which was attended by over 28,000 participants, the vast majority of presentations and communications in the gynaecological cancer domain were devoted or restricted to ovarian cancer. This included at least one major breakthrough and practice-changing study in the first-line treatment of BRCA mutated high grade serous and endometrioid ovarian cancer.

OVARIAN CANCER

FIRST-LINE THERAPY AND PARP INHIBITORS

The most important results presented at this ESMO Congress came from the phase III SOLO-1 trial, presented by Moore *et al.*[1] SOLO_1 is the first trial to evaluate maintenance therapy with a PARP inhibitor (olaparib) in newly diagnosed patients with advanced stage III/IV ovarian cancer and a *BRCA1/2* who were in partial or complete response following surgery and platinum-based chemotherapy. In total, 391 *BRCA*-mutation positive patients (mostly germline, only 2 with somatic mutations) were randomised (2:1) to olaparib (300 mg bid) or placebo. The primary endpoint was investigator-assessed progression-free survival (PFS) according to modified RECIST v1.1. The design of the study is depicted in *Figure 1*.

After a median follow-up of 41 months, the primary progression-free analysis showed a significant reduction in the risk of progression or death with olaparib *vs.* placebo (*Figure 2*). This PFS benefit of olaparib over placebo was seen in all investigated subgroups. At 3 years, there is an unprecedented PFS advantage of >30% (60.4% *vs.* 26.9%) in favour of the olaparib arm. PFS sensitivity analyses, second PFS and time to first subsequent therapy or death support the primary analysis (*Figure 3*), indicating that patients maintain the ability to benefit from subsequent lines of therapy. The overall survival (OS) data are still immature. Health-related quality of life (HRQoL) did not deteriorate in comparison to baseline. Adverse events were mostly low grade. The most common grade ≥3 toxicities with olaparib were anaemia (22%) and neutropenia (8%). Olaparib dose reductions, interruptions and discontinuations occurred in 28%, 52% and 12%, respectively. These outstanding results, who were simultaneously published in the New England Journal of Medicine,[2] underline that olaparib maintenance should be considered as a new standard in first-line responding patients with advanced stage ovarian cancer and a *BRCA1/2* mutation.

BRCA patients make up only 20–25% of ovarian patients, so there is still a large percentage of patients that deserve our full attention to improve outcomes. The next steps are to achieve this magnitude of finding in non-mutated *BRCA* patients.

There are several completed and maturing trials that will evaluate the use of a PARP inhibitor as maintenance in other biomarker subgroups such as homologous recombination repair deficient patients and in all comers. These data should be available in 2019, making it a very exciting year as we will see whether PARP inhibitor use has a meaningful impact on PFS beyond *BRCA*. In addition to this, exciting results are awaited from studies evaluating therapeutic combinations in the front-line treatment of ovarian cancer treatment, including the combination of PARP inhibitors with angiogenesis inhibitors, or with immune checkpoint inhibitors.

PARP inhibitors such as olaparib, rucaparib, niraparib, given as maintenance therapy in platinum-sensitive relapsing ovarian cancer responding to platinum-based chemotherapy showed a significant improvement in PFS, regardless of

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Key words: ovarian cancer, first-line therapy, platinum-sensitive relapse, platinum-resistant relapse, targeted therapy, immunotherapy, PARP inhibitors (olaparib, rucaparib, niraparib), MSI-H endometrial cancer, sex cord tumours, malignant ovarian germ cell tumours.

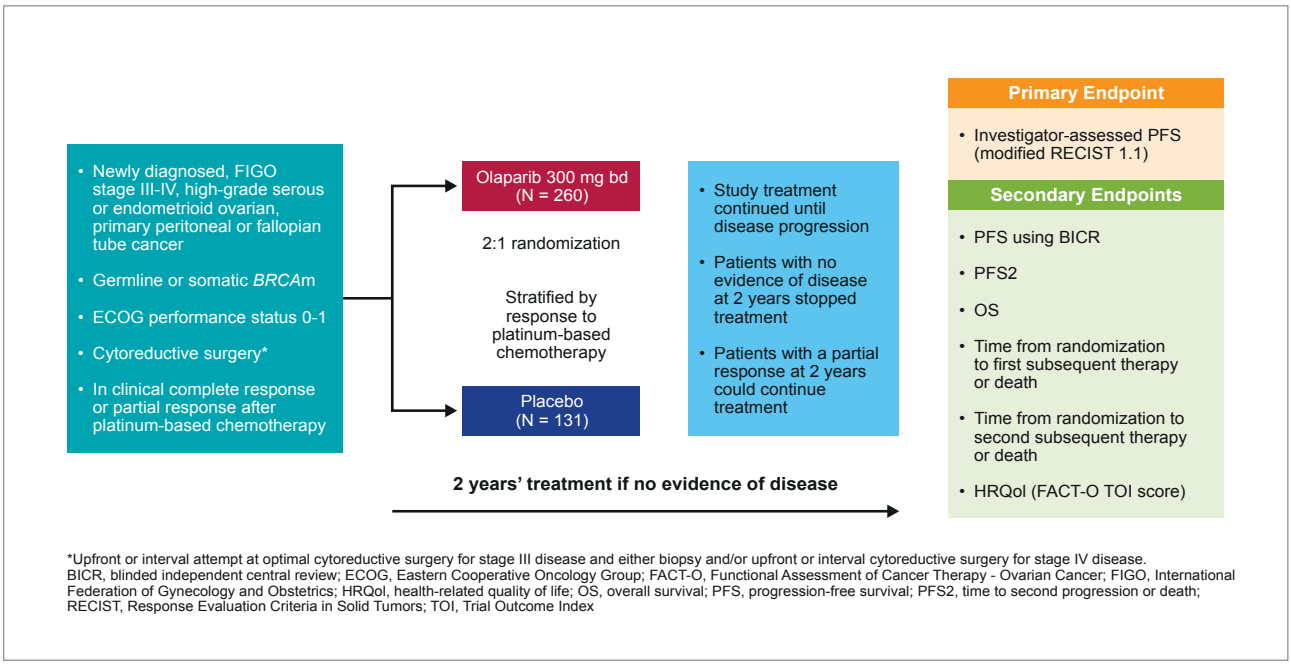

FIGURE 1. Study design of the SOLO-1 trial.[1,2]

BRCA or homologous recombination deficiency (HRD) status. In the phase III ENGOT-OV16/NOVA trial, early dose adjustments of niraparib occurred in 69% of the patients. A retrospective analysis of NOVA indicated that patients with body weight < 77 kg or baseline platelet count < 150 K/µL were more likely to be dose reduced due to haematological adverse events, whereas efficacy was not compromised.

The PRIMA study evaluates niraparib *vs.* placebo as maintenance therapy for patients with high-risk stage III/IV ovarian cancer who are responding to front-line platinum-based therapy. The trial remains blinded for efficacy and safety but was amended to require starting dose of 200mg qd in patients with baseline body weight < 77kg or platelet count < 150 K/µL (initial dosing 300mg qd). After dosing 107 patients post-amendment, in comparison to 466 pre-amendment treated patients, interim safety data from blinded pooled niraparib and placebo arms improved significantly: any grade ≥3adverse event 17.8% *vs.* 48.7%, any serious adverse event 7.5% *vs.* 20.6%, ≥grade 3 thrombocytopenia 5.6% *vs.* 30.7%, ≥grade 3 anaemia 2.8% *vs.* 16.5%.[3]

PLATINUM-SENSITIVE RELAPSE

In patients with platinum-sensitive recurrent ovarian cancer who are suitable for platinum-based retreatment, standard therapies include carboplatin-gemcitabine-bevacizumab (CGB), carboplatin-paclitaxel-bevacizumab (CPB), carboplatin-pegylated liposomal doxorubicin (CD).

The aim of a phase III randomised trial presented at ESMO 2018 was to evaluate whether CD + bevacizumab (CDB) is superior to GC + bevacizumab (CGB).[4] Stratification factors included platinum-free interval, presence or absence of residual tumour, prior angiogenesis inhibition. The intention-to-treat analysis included 682 patients of whom 40% were previously exposed to angiogenesis inhibition. The median PFS was 13.3 months with CDB as compared to 11.7 months with CGB (HR[95%CI]: 0.807[0.680-0.956]; p= 0.0128]. This PFS advantage in favour of the pegylated liposomal doxorubicin (PLD) containing regimen was maintained in the subgroup of patients with previous anti-angiogenic treatment (HR: 0.73; p< 0.05). The OS did not differ significantly between the 2 treatment arms (median OS: 33.5 *vs.* 28.2 months; HR[95%-CI]: 0.833[0.680-1.022]; p= 0.0787]. Global quality of life was slightly better with CDB. Unfortunately, the *BRCA* and homologous recombination repair deficiency status of patients was not known, so it is impossible to know if the benefit with the PLD-based regimen is attributable to a better efficacy in mutated or deficient tumours. Globally the CDB combination may be added to the therapeutic options in this category of patients.[4]

PLATINUM-RESISTANT RELAPSE

Lurbinectedin is a new anticancer agent that blocks transcriptional transactivation, induces DNA double-strand breaks and modulates the tumour microenvironment. This new drug showed activity in platinum-resistant ovarian cancer in a randomised phase II trial in comparison to topotecan. In the phase III CORAIL trial, 441 patients were randomly assigned to receive either lurbinectedin (3.2 mg/m² iv every 3

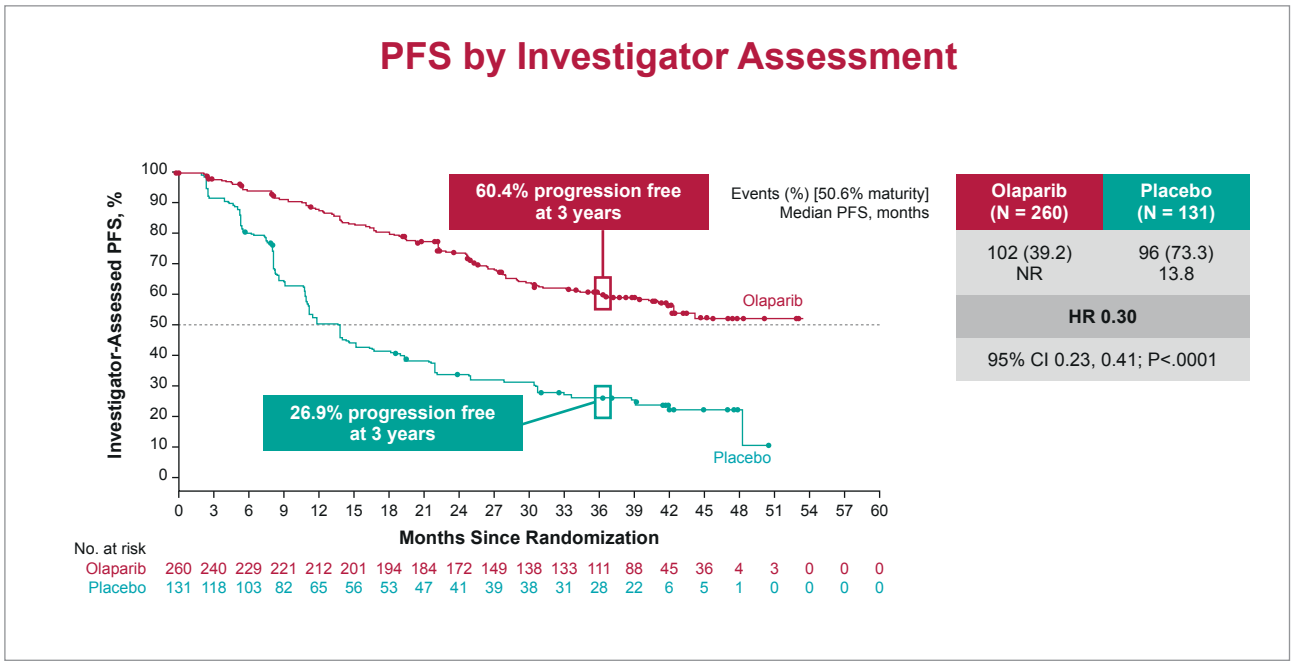

FIGURE 2. PFS by investigator assessment in the phase III SOLO-1 trial.[1,2]

weeks) (Arm A) or investigator choice of PLD (50 mg/m² every 4 weeks) or topotecan (1.5 mg/m²/day for 5 consecutive days every 3 weeks) (arm B).[5] Patients were stratified according to ECOG PS (0 *vs.* ≥1), platinum-free interval (1-3 *vs.* >3-6 months) and the number of prior chemotherapy lines (1-2 *vs.* 3). The objective response rates (ORR) were 14.0% *vs.* 12.2%, with a median PFS 3.5 *vs.* 3.6 months (HR[95%CI]: 1.04[0.84-1.29]) for arm A and arm B, respectively. The primary endpoint of a 30% reduction in the risk of progression or death was not met. There were no significant differences in OS (median 11.2 *vs.* 11.1 months), global quality of life scores and related adverse events, although topotecan accounted for a higher percentage of adverse events than PLD. The differences in the outcome with lurbinectedin in this trial compared to the previous phase II study (ORR: 30%) may be explained to a higher primary resistance rate (58% *vs.* 35%), a lower median platinum-free interval and a lower response rate to prior platinum-based chemotherapy (31% *vs.* 76%). In addition, the phase III trial included a higher percentage of patients who received 3 prior chemotherapy lines (23% *vs.* 12%), enrolled more older patients (>65 years: 43% *vs.* 27%) and included more bevacizumab exposed women (46% *vs.* 12%).

As such, there remains an urgent medical need to improve the outcome in this rather poor prognosis category of recurrent ovarian cancer patients. Progress may come from more targeted therapies, immunotherapy and from personalised therapeutic approaches according to gene expression profiles and druggable molecular aberrations.

The phase II KEYNOTE-100 study showed clinical activity of pembrolizumab monotherapy in patients with advanced recurrent ovarian cancer. A higher PD-L1 expression (combined positive score or CPS ≥ 10%) was associated with a higher response rate (15%). In the same study, associations of response with T-cell-inflamed 18-gene expression profile (T-cell-GEP), homologous recombination deficiency (HRD), and *BRCA* mutation status were also evaluated in the first 100 patients enrolled: in addition to PD-L1 CPS, T-cell-GEP was positively associated with response, but not HRD or *BRCA* status.[6]

Single agent trials of immunotherapy of immune checkpoint inhibitors against PD-1 or PD-L1 have demonstrated only modest effect in recurrent ovarian cancer. In the context of ovarian cancer relapsing within 12 months after the last dose of chemotherapy, a phase II study has been conducted with the combination of bevacizumab 10 mg/kg and nivolumab 240 mg every 2 weeks in 38 patients with 20 partially platinum-sensitive and 18 platinum-resistant relapses. There were 11 partial responses (28.9%), 8 in platinum-sensitive patients and 3 in platinum-resistant patients, as well as 3 disease stabilisations in each group, for a median PFS of 9.4 months.[7]

Another phase II study evaluated the combination of olaparib (300 mg bid orally) and durvalumab (1500 mg iv on day 1 of each 28-day cycle) in 35 heavily pre-treated patients. In this trial, 30 patients had platinum resistant recurrent ovarian cancer, 6 patients harboured a germline *BRCA* mutation (29 were *BRCA* wild-type) and patients received a median of 3.5 prior therapy regimens. Five partial responses were observed in 34 evaluable patients (15%; 2 *BRCA* mutated and 3 *BRCA*

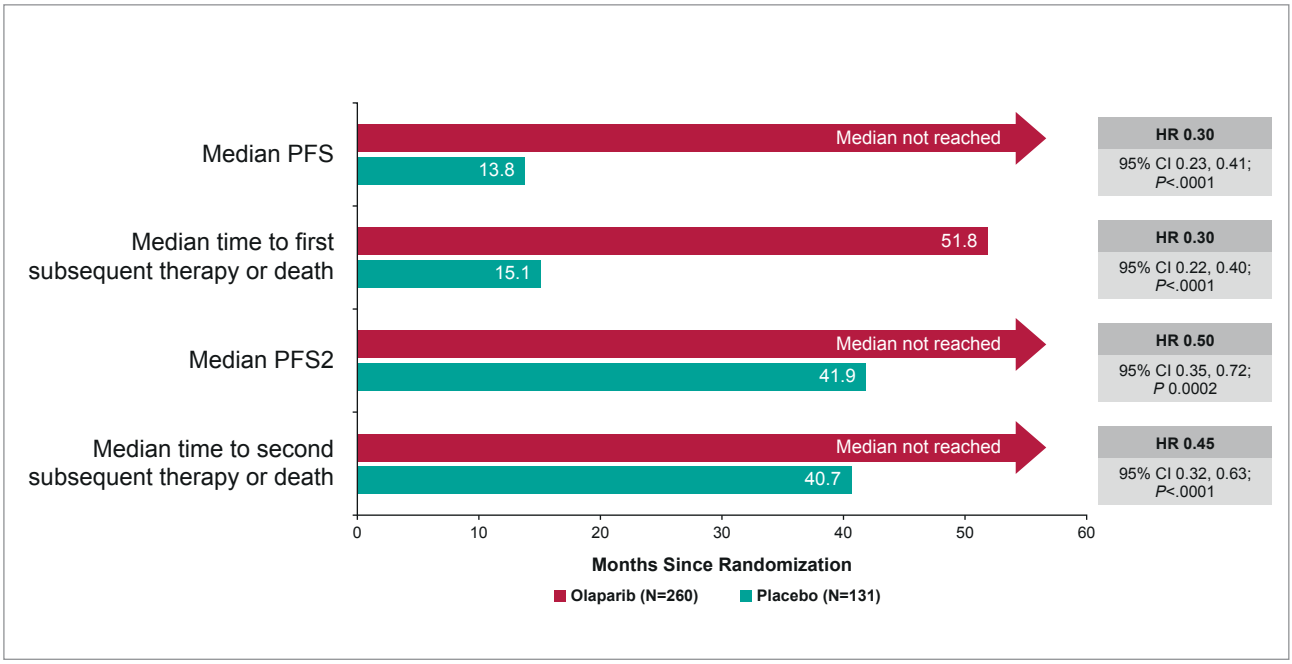

FIGURE 3. Key secondary endpoints of the phase III SOLO-1 trial. No detrimental effect of olaparib maintenance on subsequent treatment effect.[1,2]

wild-type). In addition, 53% of patients experienced disease control for at least 6 months. Unfortunately, this trial did not meet the response rate criteria to pursue the combination.[8]

BRAIN METASTASES

Central nervous system (CNS) metastasis is infrequently reported in patients with ovarian cancer with a rate of approximately 1%. Median time from initial diagnosis to brain metastases is above 2 years and the median OS in this setting is less than 1 year. Positive factors associated with OS are platinum-sensitive recurrence and prolonged interval from initial diagnosis to CNS metastasis. In contrast, a higher number of previous therapy lines and a poor performance status were negatively correlated with survival.[9]

In a retrospective analysis form Yale University on real-world data with regard to brain metastases in 46 out of 4,515 patients, patients with *BRCA* mutated ovarian cancer had a significantly higher risk of developing brain metastases (3%) compared to *BRCA* wild-type tumours (0.6%) with a hazard ratio of 3.84 (p= 0.001). However, OS after brain metastasis did not differ significantly by *BRCA* status.[10]

SURVIVORSHIP AND PSYCHOLOGICAL SUPPORT

OVPSYCH2 is a randomised study prospectively evaluating the impact of a brief course of psychological support on self-reported depression (PHQ9: mild to moderate scores in 58% of the patients), fear of progression (FOP) and quality of life (QoL) following chemotherapy for primary or recurrent ovarian cancer.[11] In total 107 patients were asked to complete PHQ9, FOP-Q-SF, EORTC QLQ C30 and OV28 questionnaires for up to 2 years. Sixty-three of them completed baseline and 3-month questionnaires and were included in the analysis: 31 control, 32 intervention. At 3 months, there was no significant difference between intervention and control as far as PHQ9 (depression score) and global QoL evaluations are concerned. However, there was a significant improvement on FOP-Q-SF scores in the intervention arm, whilst in the control arm, FOP-Q-SF scores deteriorated at 3 months [intervention effect: - 5.2, 95%CI (-8.45-1.9); p = 0.003]. This demonstrates that fear of progression is a prominent concern for patients with ovarian cancer, but that this can be overcome with provision of psychological support immediately after chemotherapy.[11]

Little is known about the rare cohort of long-term survivors (LTS) defined as ovarian cancer diagnosis >8 years ago. The study "Carolin meets HANNA" recruited 310 LTS, of whom 52.1% developed recurrent disease and cancer treatment still ongoing in 38.5%. Current symptoms and side effects from cancer treatment are still present in 53.5% of LTS. The most troubling side effects are alopecia (39.5%), fatigue (37.6%), bone pain (29.8%), polyneuropathy (25.0%) and memory problems (23.8%). Healthy nutrition and physical activity are believed to have a positive impact on the course of the disease: 53.3% of LTS have changed their dietary habits after diagnosis and 66.6% are regularly physically active.[12]

KEY MESSAGES FOR CLINICAL PRACTICE

1. Given the outstanding results in SOLO-1 trial, olaparib maintenance should be considered as a new standard in first-line responding patients with advanced stage ovarian cancer and a ***BRCA1/2*** mutation.
2. In platinum-sensitive recurrent ovarian cancer, the combination of carboplatin-pegylated liposomal doxorubicin (PLD) should be added to other standard combinations
3. Even if active, lurbinectedin has not shown to be superior to PLD or topotecan.
4. Single agent trials of immunotherapy of immune checkpoint inhibitors against PD-1 or PD-L1 have demonstrated only modest effect in recurrent ovarian cancer but may be more effective in combination with angiogenesis inhibition or PARP inhibitors.
5. Fear of progression, a prominent concern for patients with ovarian cancer, can be overcome with provision of psychological support immediately after chemotherapy.
6. MSI-H endometrial cancer was shown to be sensitive to immune checkpoint inhibitors.

MSI-H ENDOMETRIAL CANCER

TSR-042, a humanised monoclonal antibody targeting PD-1 that effectively blocks the interaction with its ligands PD-L1 and PD-L2. It has been evaluated in 25 patients with previously treated MSI-H endometrial cancer. A partial response occurred in 9 patients (53%). TSR pharmacokinetics was dose-proportional. Grade ≥3 adverse events were observed in 11 (44%) patients and treatment-emergent adverse events of any grade in 18 (72%) patients.[13]

These results seem to mirror the good sensitivity of MSI-H ovarian cancer patients to PD-1 inhibition, that was previously shown for pembrolizumab.

MISCELLANEOUS

GESTATIONAL TROPHOBLASTIC NEOPLASIA

For patients with chemotherapy-resistant gestational trophoblastic neoplasia (GTN) the standard treatment consists of historic single agent or polychemotherapy. These regimens are known to be effective in this setting (65-95% hCG normalisation), but come at the cost of considerable toxic. PD-L1 is constitutively expressed in all GTN subtypes. The objective of TROPHIMMUN trial was to assess the efficacy of the anti-PD-L1 monoclonal antibody avelumab given intravenously at the dose of 10 mg/kg every 2 weeks in patients with GTN resistant to single agent chemotherapy.[14] In this cohort of 9 patients, 7 (78%) experienced 62 adverse events: grade 1 (83.9%); grade 2 (14.5%, including 1 hypothyroidism); grade 3 (1 disease-related metrorrhagia). Among the first 6 patients assessed for interim analysis, 3 patients had a normalised hCG level and stopped treatment without any further sign of relapse after 10.7 months of follow-up. This suggests that avelumab might be effective and better tolerated than standard chemotherapy in patients with GTN who are resistant to single agent chemotherapy.[14]

OVARIAN SEX CORD TUMOURS (SCT)

The randomised Alienor/ENGOT-ov7 trial explored weekly paclitaxel (wP) + bevacizumab *vs.* wP alone in patients with relapsing sex cord tumours. The primary endpoint of the trial was the PFS rate at 6 months (PFR-6) and 60 patients (52 granulosa cell tumours, 2 Sertoli Leydig tumours) were included. The PFR-6 was 71% (95%CI: 55-84%) *vs.* 72% (95%CI: 56-87) in the wP and wP + bevacizumab, respectively. Of note, in the wP arm, 50% received bevacizumab alone at cross over. The most frequent adverse events of any grade were: hypertension (78% *vs.* 93%), fatigue (63% *vs.* 78%), neuropathy (56% *vs.* 74%) and proteinuria (13% *vs.* 63%). As such, weekly paclitaxel confirmed to be an active drug in SCT. Bevacizumab added to wP increased the ORR from 25% up to 44%, but failed to significantly improve PFR-6 or PFS.[15]

STAGE I MALIGNANT OVARIAN GERM CELL TUMOURS (MOGCT)

A French rare malignant ovarian tumours network analysed the outcome of 101 patients with stage I MOGCT of whom most will be cured. Active surveillance is associated with an excellent survival outcome in MOGCT. As such, this is the preferred option for immature teratoma. In pure dysgerminoma, the relapse rate was higher than previously reported, emphasising the need to discuss the benefit of not having ad-

juvant chemotherapy with the patient (i.e. balance the avoided risk against the risk of relapse and delayed treatment). Adjuvant chemotherapy remains recommended for all patients with yolk sac tumours.[16]

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