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Small cell cancers: cervix versus ovary

Prof Bergamini: So, welcome, everybody. We are about to talk today about small cell carcinomas of the genital tract, in particular, with a focus on ovarian and cervical small cell carcinomas. Small cell carcinomas are rare tumors characterized by an aggressive disease course and mainly arise in the lung, which is the site of origin of 95% of all small cell carcinomas. 5% are the so-called extrapulmonary small cell carcinoma, which originates outside the lung, mainly in the gastrointestinal tract and in the genitourinary tract. Most importantly, most of the small cell carcinoma belongs to the family of neuroendocrine tumors. Regarding gynecological small cell carcinoma, the most common ones arise in the cervix, even though they can originate from any of the sites of the gynecological tract. So, vulva, vagina, endometrium, and ovary. All the small cell carcinomas of the gynecological tract are of neuroendocrine origin with the exception of small cell carcinoma of the ovary of the hypercalcemic type. So, moving to small cell carcinomas of the ovary, these can be further classified into small cell carcinoma of the ovary of pulmonary type and small cell carcinoma of the ovary of hypercalcemic type. Small cell carcinomas of pulmonary types are extremely rare. Only few cases have been described in literature. So, it's very difficult to draw any final recommendation regarding treatment. They present in women with mean age of 50-years, usually, as bilateral disease. It is difficult also for the pathologist to distinguish a small cell carcinoma of the ovary of pulmonary type, primary of the ovary from small cell carcinomas metastatic to the ovary arising from other sites such as from the lung. The treatment is typically characterized by a multi-modality treatment comprising surgery as for epithelial ovarian cancer. So, primary debulking surgery followed by chemotherapy. They use regimens derived from those applied in lung small cell carcinomas such as cisplatin, carboplatin, and etoposide, alkylating agents, less commonly, or also, paclitaxel and irinotecan. The other peculiar type of small cell carcinoma of the ovary does not belong to the family of neuroendocrine tumor and is small cell carcinoma of hypercalcemic type, which is very peculiar, was first described in 1979 by Scully. And there are fewer than 500 cases reported in literature. It is pathologically characterized by small hyperchromatic cells with scant cytoplasm and brisk mitotic activity. These tumors may present in up to 60% of cases, hypercalcemia, which is related to the common expression of parathyroid-related protein. And it mainly affects young women with a mean age of presentation of 24-years. The clinical presentation is related to the presence of an abdominal mass, usually unilateral, causing abdominal pain and symptoms associated to the enlarged waist or to difficulties in feeding, nausea, vomiting, and weight loss. Usually, these tumors present as unilateral disease or with peritoneal implant with stage III

disease in 45% of cases. The staging system used is that of ovarian cancer according to the last FIGO staging system. And the prognosis of this tumor is very poor with a five-year overall survival for all stages ranging between 30-40% with standard treatment. And initial response to chemotherapy is common, but often, these tumors usually relapse with chemo-resistant disease. Prognostic factors include stage which is the most important prognostic factor, and also, age, high-preoperative calcium levels are associated with a poor prognosis as well as suboptimal cytoreduction. These tumors have been largely studied from the molecular point of view and molecular profiling revealed that these tumors are associated with an inactivating mutation of SMARCA4 gene, which encoded for the SMARCA4/BRG1 protein in 95% of cases. This mutation can be either somatic or germline. And SMARCA4/BRG1 protein is part of a larger complex, remodeling complex called SWI/SNF that makes, basically makes DNA accessible to transcriptional regulators and repressors and plays an important role, so in transcriptional regulation, DNA damage repair, cell differentiation and mitosis. There is another protein called SMARCA2 that is mutually exclusive to SMARCA4 that plays the same role, so it's a tumor suppressor that occasionally can be, the expression of which can be lost in some small cell carcinoma of the ovary of a hypercalcemic type which may retain SMARCA4 expression. The concomitant loss of SMARCA4 and SMARCA2, the loss of the expression of SMARCA2 occurs via epigenetic silencing is considered pathognomonic of small cell carcinoma of the ovary of hypercalcemic type. And the immunostaining of SMARCA2 and SMARCA4 is useful also for the pathologist to distinguish this latter tumor for other forms of small cell carcinoma, for example, small cell carcinoma of the lung. It is important that the pathological diagnosis is made in a referral center by an expert gynecological pathologist as the differential diagnosis of small cell carcinoma of the ovary of a hypercalcemic type include several rare conditions of the ovary such as ovarian granulosa cell tumor, malignant ovarian germ cell tumor, endometrial stromal sarcoma, neuroblastoma, peripheral neuroectodermal tumors, small round cell tumor desmoplastic of the abdomen, lymphoma, and metastases to the ovary from other site such as melanoma or small cell lung cancer, of course. Recently, the International Small Cell Carcinoma HT Consortium has met in order to draw the recommendations on diagnosis management and genetic counseling of patients affected by this disease. And as these diseases characterized by the inactivating mutation of SMARCA4, in this consortium, they concluded to refer all patients affected by this disease to clinical genetic counseling in order to be offered germline testing and in order to activate also surveillance systems, surveillance pathway also for the family. The mutation of SMARCA4 can be germline in up to 40% of cases, even in the case of a silent familiar history which usually occurs. For the family and for patient affected by this disease, the risk of developing other tumor is still to be determined, even though the possibility of performing contralateral oophorectomy in patient’s carrier of a germline mutation, pathologic variant of SMARCA4 gene should be discussed as they might have an increased risk of a second primary malignancy. The treatment consists of a multimodal approach. This conclusion, of course, is not based on prospective studies as given the rarity of this disease, but it's based on retrospective case series often with a heterogeneous management. This is one of the largest series reported to date, including more than 2,050 patients affected by this disease. And as we can see, surgery alone is characterized by a poor prognosis while the best outcome is obtained with the association of surgery, chemo-radiotherapy, and high-dose chemotherapy. For stage I disease, conservative surgery is not recommended given the higher rate of recurrences in patients addressed to fertility-sparing surgery and to date, even in patients who have received conservative surgery, no pregnancies have been obtained most probably due to gonadotoxic effect of chemotherapy and due to the poor prognosis of this disease. So, for stage I, according to this large series of patients, you can see that surgery alone is characterized by the worst prognosis, surgeries plus chemo seems to perform better, but there seems to be no advantage of adding radiotherapy, and the best outcome with 100% overall survival, even though only on 9 patients with stage I disease is obtained with the combination of surgery, chemo, and high-dose chemotherapy with or without radiotherapy. Similarly, for advanced stage disease, the best outcome with an overall survival, five-year overall survival of 71% was obtained with the combination multimodal treatment on 19 patients. Here, you can see that the results plotted for 19 patients with advanced stage disease treated with the combination of treatment. Let's now review what ESMO guidelines, the most recent ESMO guidelines recommends for the

treatment of this rare disease in terms of surgery and adjuvant treatment. For both early-stage and advanced-stage disease, surgery is the first-step of treatment. And here, basically we can apply the principles of cytoreductive surgery of ovarian cancer, of epithelial ovarian cancer, so, with the aim of obtaining optimal cytoreduction. If debulking is not feasible at primary surgery, neoadjuvant chemotherapy can be offered followed by interval debulking surgery and adjuvant chemotherapy. The regimens recommended are regimens based on the combination of cisplatin and etoposide, mainly EP, but also BEP, or more recently, PAVEP have been reported as a very effective regimen. Most importantly, in those patients achieving complete response after first-line therapy, consolidation treatment with high-dose chemotherapy and allogeneic stem cell transplant is recommended as consolidation, while pelvic radiotherapy can be considered in case of, for example, residual disease after chemotherapy and in particular, on the pelvis. Moving to the second-line treatment, the treatment of recurrent disease, we must say that in case of recurrence, the prognosis is very extremely poor with a short-term remission usually achievable with second-line therapy. Regimens recommended in this case include the cyclophosphamide combined with doxorubicin and vincristine. Carboplatin and paclitaxel also with the dose-dense regimen, topotecan. But according to the ISC Consortium recommendation of 2020, they suggested to perform a biopsy in order to characterize the recurrent disease at recurrence. And they also suggest to consider secondary surgical cytoreduction if the conditions are appropriate, but also, to consider other off-label immune-checkpoint inhibitors or other off-label regimens. And also, to consider enrollment in phase I trials on the basis in particular of international collaboration. There are several investigational drugs that are being tested in preclinical and early clinical setting. Here, you can see a summary of these drugs modified from the position paper of the ISC consortium. In particular, FGFR inhibitors and histone deacetylase inhibitors and BETi inhibitors have shown activity in vitro and in xenograft while other agents, in particular, CDK4-6 such as palbociclib inhibitors have shown activity in small cell carcinoma of hypercalcemic-type patients. And this phase II trial, which is a Canadian phase II trial, has recently opened the enrollment also for patient with SMARCA4 mutated tumors such as small cell carcinoma of the hypercalcemic type. Other agents, such as tazemetostat and seclidemstat are currently being tested in phase II basket trial or phase I trials. Interestingly, despite its low-mutational burden, this disease has shown high-degree of tumor-infiltrating lymphocyte rate of infiltration and a high expression also of PD-L1 in macrophages infiltrating the tumor. So, on the basis of these preclinical findings, pembrolizumab has been tested in small cell carcinoma of hypercalcemic type, and in particular, two-phase trials are now active, the AcSe trial and the Pembro Small Cell Carcinoma Hypercalcemic Type trial. The first one is a trial in recurrent rare ovarian cancer tumors using pembrolizumab and the second one is a trial combining chemotherapy and pembrolizumab in advanced-stage disease first-line. So, to conclude this first part, these tumors are rare tumor with an aggressive disease course and poor prognosis. It is very important to refer these cases to expert centers with an expert gynecological pathology review possible. The treatment should be multimodal treatment combining surgery, adjuvant chemo, and also, a high dose chemo in case of a complete response as a consolidation treatment. Several new promising approaches need to be tested and need to be further evaluated in phase I-II trials. And most importantly, international collaborations should be promoted in order to ensure the registration of all new cases in international registry. We will now focus on small cell carcinoma of the uterine cervix which is the most common small cell carcinoma of the gynecological tract and belongs to the family of neuroendocrine tumors of the uterine cervix, which counts for 1.4% of all cervical tumors. According to the WHO classification, neuroendocrine carcinoma can be classified into small cell or larger cell neuroendocrine tumors. The most common ones are the high-grade small cell carcinoma of the cervix. These are characterized by small cells with scant cytoplasm, hyperchromatic nuclei, which typically follow a diffused pattern, more rarely are... they follow a pattern in nest or a trabeculated pattern. And morphological features include apoptosis, nuclear molding, and necrosis. The differential diagnosis includes that of lymphomas and squamous cell carcinoma of the small cell type. Recently, the guidelines on the management of these tumors have been revised by the Gynecological Cancer Intergroup and presented at ESGO 2021. And also, they include a section for pathological diagnosis. These tumors should be, when there is a suspicion of a small cell carcinoma of the cervix, the characterization of neuroendocrine marker should

be performed along with the assessment of the typical morphological features. Keeping in mind that the absence of expression of neuroendocrine markers does not rule out the diagnosis of small cell carcinoma of the cervix, which should be performed by an expert, a gynecological pathologist. This is the immunohistochemistry profile of small type carcinoma of the cervix. You can see that it's pretty different from that of squamous cell carcinoma and adenocarcinoma of the cervix with neuroendocrine markers present in 30 to 50% of cases. Importantly, HPV expression was found in these tumors. HPV was found to be present and possibly it plays a role in the pathogenesis of this disease. Small cell carcinoma of the cervix behave differently from other tumors of the cervix, are a much more aggressive. And typical of these tumors is the tendency to diffuse with distant metastases. So, with the hematogenous spread to the lung, liver, bone, and brain. We used to stage this tumor using the FIGO staging carcinoma of the cervix. And clinically, patients present with symptoms that are typical of all cervical carcinomas such as vaginal bleeding or discharge, or in case of bulky disease, also pelvic pain or pelvic pressure, but also, in case of distance spread of disease, symptoms related to the presence of metastases according to the site of disease. It is common to detect in this case, weight loss. Also, paraneoplastic syndromes can be detected such as SIADH, cushing syndrome, hypercalcemia, or paraneoplastic neurological disorders can be common in this disease clinical presentation. The prognosis, as I said, is very poor, a five-year overall survival of 20-30% for all stages which is around 40% for stage I and II, while it's less than 10% in advanced stage disease. Regarding the prognostic factor, stage is the most important prognostic factor, a pure small cell histology is associated with a poor survival and also the involvement of lymph nodes. So, for clinical staging, physical examination needs to be performed as in all cervical cancer, of course. Imaging is useful both for local staging with pelvic MRI or gynecological ultrasound while for distance staging, PET/CT scan should be performed, or if not available, also, whole body MRI with CT of the chest. While brain MRI, according to the recent guidelines can be performed only if clinically indicated. This allow us to stratify the risk in early-stage disease, up to stage IB2, which means the tumor is limited to the cervix with less than four centimeter in size; from advanced-stage disease ranging from stage IB3 to IVB, in particularly, locally advanced stage, so, with the tumor from stage IB3 to stage IVA which means spread to the local organs, to the pelvic organs. While metastatic stage IVB disease if distant metastases are present according to the FIGO staging system. Again, also for these small cell carcinomas, no prospective studies are available. So, the treatment is mainly based on retrospective series and chemotherapy regimens are based on the management of lung small cell neuroendocrine tumors. Again, from the meta-analyses available, it emerged that multi-modality treatment leads to the better outcome for these patients. So, according to the most recent GCIG guidelines, early-stage disease should be approached by surgery at first, including radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection followed by adjuvant chemotherapy with an EP regimen, in particular, they suggest the combination of cisplatin and etoposide with a three-day regimen and the minimum of five cycles. Carboplatin can be considered instead of cisplatin in case of reduced renal function, impaired renal function. Chemoradiation, instead of chemotherapy alone can be offered in some cases with or without brachytherapy in case of... in presence of some risk factors. Fertility preservation can be considered in stage I disease. In locally advanced disease, concurrent chemoradiation with EBRT with or without brachytherapy, and again, EP chemotherapy should be performed while metastatic disease will be treated with four to six cycles of EP chemotherapy, again, with a three-day regime. According to other series reported in literature, the combination of cisplatin/etoposide is the most used chemotherapy regimens, even though, other regimens have been suggested including the combination of platinum-based chemotherapy and paclitaxel, or the combination of vincristine, cisplatin, and bleomycin. In case of recurrent disease, we must say that, again, in this case, the prognosis is very poor with a median survival of 7 to 8 months. The drugs used in this setting are mainly derived from the regimens used in small cell lung cancer. Usually, single agent chemotherapy is offered including topotecan, paclitaxel, docetaxel, or irinotecan with overall response rate reaching 20% of maximum. And more recently, in 2017, the group from MD Anderson has reported their experience with the combination of topotecan, paclitaxel, and bevacizumab in 13 patients affected by recurrent small cell carcinoma of the cervix. And they compared the outcome with the other traditional regimens in this disease

setting, obtaining median progression-free survival of 8 months in the experimental arm and 4 months in the control arm, so, in those patients not treated with topotecan, paclitaxel, and bevacizumab. According to the GCIG guidelines, in this case, so, in the case of recurrent disease, for those patients who have been already treated with EP chemotherapy in first-line, it is possible to reconsider a rechallenge with platinum-based chemotherapy if the interval from last platinum is acceptable. It is possible to adopt, as we have already shown the combination of topotecan, paclitaxel, and bevacizumab as in the MD Anderson experience or to offer single-agent chemotherapy. In patients not pretreated with etoposide and platinum, it is possible to offer this regimen, also in combination of bevacizumab, given the results. The well-known results of the addition of bevacizumab to platinum-based chemotherapy. Interestingly, recently this year, NGS has been performed on 50 cases of small cell neuroendocrine carcinoma of the cervix that has been published in gynecological oncology and just was performed in order to evaluate the presence of mutation in targetable pathways. And they found, interestingly, KRAS mutation in the KRAS pathway, PIK3CA pathway, TP53, and in a lesser extent, in the HRD system also. Interestingly, also, the use of immune-checkpoint inhibitor is emerging as an alternative strategy in this tumor and the rational of using PD-1 inhibitors, in particular, derives also from the presence of HPV that has been found in up to 50% of the cases of small cell carcinoma of the cervix and possibly this virus might be involved in the pathogenesis of this tumor, and also given the results of pembrolizumab in both small cell lung cancer and in first-line treatment of cervical carcinoma. So, for sure this latter approach needs to be further investigated. So, to conclude, also, small cell carcinoma of the cervix are rare tumors characterized by an aggressive disease course and poor prognosis. In this tumor, a multi-modality treatment, again, is recommended. In case of recurrent disease, single-agent chemotherapy or the combination of topotecan, paclitaxel, bev can be offered. And new approaches with immunotherapy, MEK-inhibitors, PIK3CA inhibitors need to be investigated through international collaboration for clinical research that remains mandatory in these rare tumors. I would like to thank you for your attention. Thank you very much.