APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
JOURNAL CITATION REPORTS® IMPACT FACTOR 1.681 ©2020 Clarivate Analytics

Peer Review File

Article information: http://dx.doi.org/10.21037/apm-20-2429

**Comment 1:** "Background", Lines 33-34:
"Ovarian teratomas are tumors originated from primordial germ cells, and occur frequently in women of childbearing age.".
Here, it should be mentioned that there are reports of malignant ovarian germ cell tumors (MOGCTs) in postmenopausal patients. As such, postmenopausal women with an ovarian mass should be suspected for MOGCTs. Their prognosis is poor, even for patients with early-stage disease.
Recommended reference: Boussios S, et al. Malignant Ovarian Germ Cell Tumors in Postmenopausal Patients: The Royal Marsden Experience and Literature Review. Anticancer Res. 2015;35:6713-6722.

**Reply 1:** we have modified our text as advised.

**Changes in the text:** However, postmenopausal women with an ovarian mass should be suspected for malignant ovarian germ cell tumors (MOGCTs). Their prognosis is poor, even for patients with earlystage disease. (see Page 3 , line 31-33)

**Comment 2:** "Background", Lines 34-36:
"Teratomas could be classified into mature teratomas, immature teratomas, and struma ovariis etc, of which mature teratomas account for approximately 95%-98%.".
The background section should report the classification of the non-epithelial ovarian cancers. They include malignant ovarian germ cell tumors (MOGCTs) and sex-cord stromal tumours, each of which is subdivided into several histological subtypes. MOGCTs are rare accounting for approximately 5% of all ovarian malignancies. Based on histopathology, MOGCTs consist of dysgerminoma, immature teratoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, and mixed MOGCTs, but all are derived from primordial germ cells of the ovary. Ovarian small cell cancers and sarcomas are more rare.
Recommended reference: Boussios S, et al. Ovarian sex-cord stromal tumours and small cell tumours: Pathological, genetic and management aspects. Crit Rev Oncol

JOURNAL CITATION REPORTS IMPACT FACTOR 1.681 ©2020 Clarivate Analytics

Hematol. 2017;120:43-51.

**Reply 2:** we have modified our text as advised.

**Changes in the text:** the non-epithelial ovarian cancers include malignant ovarian germ cell tumors (MOGCTs) and sex-cord stromal tumours, each of which is subdivided into several histological subtypes. MOGCTs are rare accounting for approximately 5% of all ovarian malignancies. Based on histopathology, MOGCTs consist of dysgerminoma, immature teratoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, and mixed MOGCTs, but all are derived from primordial germ cells of the ovary. Ovarian small cell cancers and sarcomas are more rare. (see Page 3 , line 33-39)

**Comment 3:** "Discussion", Lines 107-108:
"Actually, postoperative pathology proved a teratoma with malignant transformation.".
Please, make a comment about the immunohistochemical profile of the ovarian immature teratomas. Expression of sex determining region Y-box 2 (SOX2) has been recognised in primitive neuroectoderm of teratoma. Furthermore, Sal-like protein 4 (SALL4) is positive in some immature teratomas.
Recommended reference: Boussios S, et al. Non-epithelial Ovarian Cancer: Elucidating Uncommon Gynaecological Malignancies. Anticancer Res. 2016;36(10):5031-5042.

**Reply 3:** we have modified our text as advised.

**Changes in the text:** It is reported that expression of sex determining region Y-box 2 (SOX2) has been recognised in primitive neuroectoderm of teratoma. Furthermore, Sal-like protein 4 (SALL4) is positive in some immature teratomas. Immunohistochemistry in this patient indicated P63 expression, suggesting the presence of squamous differentiation. (see Page 5 , line 111-114)

**Comment 4:** "Discussion", Lines 136-139:
"The TMB has the potential to predict the production of tumor neoantigens, thus becoming an important marker for predicting the therapeutic response of some tumors to the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) (PDx)

pathway inhibitors".

Furthermore, it is important to be mentioned that changes in the neutrophil-to-lymphocyte ratio (NLR) may be a useful predicting factor in patients treated with anti-PD-1/PD-L1 agents. Increased NLR has been reported as an independent poor prognostic indicator and its normalisation following treatment has been found to predict survival. Baseline NLR is easily obtainable in daily clinical practice.

Recommended reference: Moschetta M, et al. Dynamics of Neutrophils-to-Lymphocyte Ratio Predict Outcomes of PD-1/PD-L1 Blockade. Biomed Res Int. 2017;2017:1506824.

**Reply 4:** we have modified our text as advised.

**Changes in the text:** Furthermore, changes in the neutrophil-to-lymphocyte ratio (NLR) may be a useful predicting factor in patients treated with anti-PD-1/PD-L1 agents. Increased NLR has been reported as an independent poor prognostic indicator and its normalisation following treatment has been found to predict survival. Baseline NLR is easily obtainable in daily clinical practice. (see Page 6 , line 144-148)

**Comment 5:** "Discussion", General comment:

It would be interesting to incorporate a final paragraph in the discussion, in terms of the research on the mutations. The lack of efficacy of imatinib in malignant ovarian germ cell tumors (MOGCTs) is probably related to the frequent mutations in the KIT enzymatic site, which leads to reduced sensitivity to imatinib blockade. Investigation of CDK4/6 inhibition for the treatment of teratoma is required, based on the preliminary indication of safety and potential clinical benefit. Finally, embryonal carcinoma can originate from the ovaries and invariably express CD30 on their cell membranes. Targetable biomarkers for CAR T-cell therapy are expanding, but tumour rarity and heterogeneity are currently limiting the development of CAR T-cell therapy in MOGCTs.

Recommended reference: Boussios S, et al. Wise Management of Ovarian Cancer: On the Cutting Edge. J Pers Med. 2020;10:41.

**Reply 5:** we have modified our text as advised.

**Changes in the text:** Selecting treatments based on genetic mutations is an option worth exploring, however, past research has shown that the lack of efficacy of

JOURNAL CITATION REPORTS® IMPACT FACTOR 1.681 ©2020 Clarivate Analytics

imatinib in malignant ovarian germ cell tumors (MOGCTs) is probably related to the frequent mutations in the KIT enzymatic site, which leads to reduced sensitivity to imatinib blockade. Investigation of CDK4/6 inhibition for the treatment of teratoma is required, based on the preliminary indication of safety and potential clinical benefit. Finally, embryonal carcinoma can originate from the ovaries and invariably express CD30 on their cell membranes. Targetable biomarkers for CAR T-cell therapy are expanding, but tumour rarity and heterogeneity are currently limiting the development of CAR T-cell therapy in MOGCTs. In this case, based on high TMB and TP53 mutation, we confirmed that the application of Carelizumab achieved a good effect.It is suggested that immunotherapy with PD-1 antibody may be a good option for some cases. (see Page 8-9 , line 202-214)