Gynecologic Oncology Reports 40 (2022) 100942

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Impressive and durable clinical responses obtained with dabrafenib and trametinib in low-grade serous ovarian cancer harbouring a BRAF V600E mutation

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ARTICLE INFO

Keywords
Low-grade serous ovarian cancer
BRAF mutation
Dabrafenib
Trametinib
Combination treatment

ABSTRACT

Low-grade serous ovarian cancer (LGSOC) is now considered a different entity from high-grade serous ovarian cancer. The chemoresistance inherent to this type of ovarian cancer narrows the therapeutic options, especially in the recurrent setting. It is thought that the mitogen-activated protein kinase (MAPK) pathway plays a significant role in the pathogenesis of these tumours, and about 2 to 20% of LGSOC harbour a BRAF mutation. Here we present a case report of two patients with a BRAF V600E mutation that achieved sustained clinical responses with combination treatment with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).

1. Introduction

Serous carcinoma is the most common type of epithelial ovarian cancer. In 2004, the International Federation of Gynaecology and Obstetrics (FIGO) introduced a new grading system, which classifies serous ovarian cancer into low- or high-grade subtypes. This new approach has stimulated research in this field and highlighted the distinct epidemiology, molecular biology and clinical behaviour of low-grade serous ovarian carcinoma (LGSOC) compared to high-grade serous ovarian carcinoma (HGSOC). LGSOC are rarer tumours, representing less than 10% of all serous ovarian carcinomas, usually diagnosed at a relatively younger age (median 43 years old), with a more indolent clinical course, longer overall survival, relative chemoresistance and responsiveness to endocrine therapy (Gershenson, 2016).

Genomic profiling studies also support that LGSOC is a different entity from HGSOC (Gershenson, 2016). LGSOC is believed to progress in a step-wise manner from serous cystadenoma or adenofibroma to serous borderline tumour, and finally to LGSOC (Hollis and Gourley, 2016). LGSOC generally arises from a previously diagnosed borderline serous tumour or occasionally as de novo cancer (Gadducci and Cosio, 2020). In contrast, it is nowadays thought that HGSOC originates from the fallopian tube epithelium and not from the ovarian surface epithelium has it was previously assumed. So, HGSOC is supposed to evolve from an occult intraepithelial carcinoma in the fimbrial region of the fallopian tube, called serous tubal intraepithelial carcinoma, with latter involvement of the ovary, or through the implantation of normal fimbrial epithelium on the ovarian surface, that leads to a cortical inclusion cyst formation, that can undergo malignant transformation (Kurman, 2013).

It is thought that the mitogen-activated protein kinase (MAPK) pathway plays a significant role in the pathogenesis of borderline serous tumours and LGSOC. Multiple studies showed that LGSOC often present activating mutations of genes involved in this molecular pathway, such as KRAS, BRAF, ERBB2 and NRAS (Gadducci and Cosio, 2020). BRAF mutations occur in 2 to 20% of cases (Gershenson et al., 2020), being more common in borderline serous tumours and early stage LGSOCs than in the advanced disease, which are found only in about 5% of the cases (Gershenson, 2016; Gadducci and Cosio, 2020). Compared to HGSOC, LGSOC have a much lower frequency of p53 mutations or expression, greater oestrogen and/or progesterone receptor expression, and rarely harbour BRCA mutations (Gershenson, 2016).

Given the known low response rates of LGSOC to chemotherapy and the understanding of the importance of the MAPK pathway in the pathogenesis of this distinct and rare entity, the search for more effective systemic therapies, such as MEK or BRAF inhibitors has gained interest.

To our knowledge, to date there are 3 reported cases in the literature of patients with recurrent BRAF V600E mutation-positive LGSOC treated with BRAF inhibitor that presented sustained response

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https://doi.org/10.1016/j.gore.2022.100942
Received 4 January 2022; Received in revised form 16 February 2022; Accepted 18 February 2022
Available online 23 February 2022

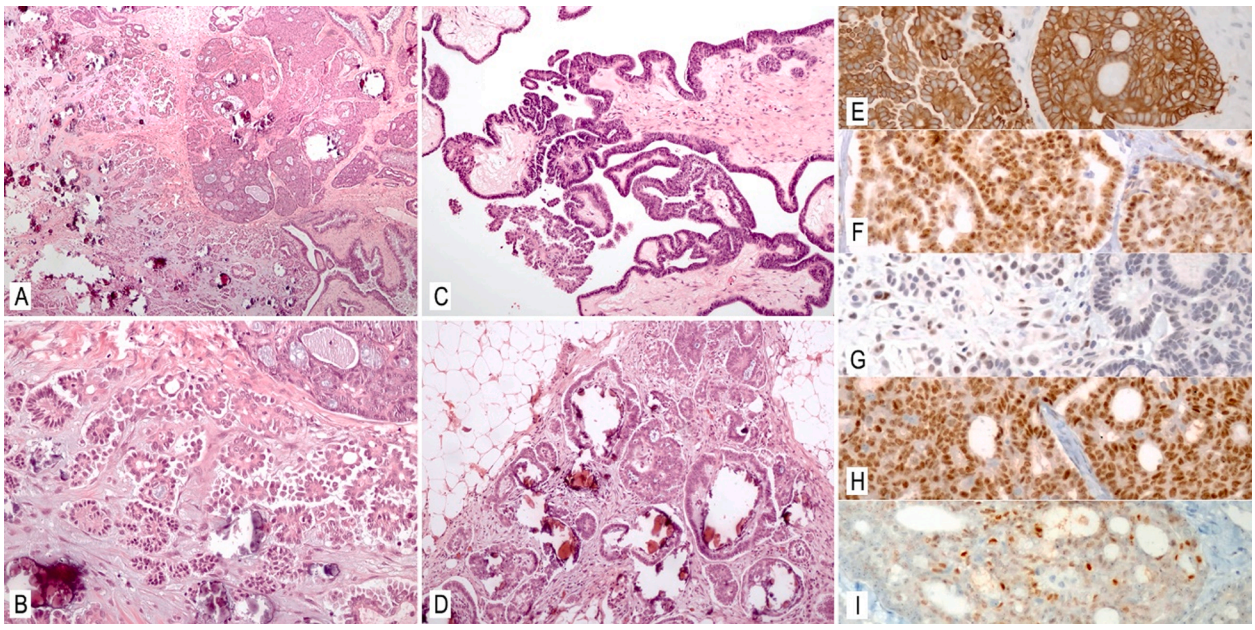

Fig. 1. Low grade serous ovarian carcinoma histological features. A, B - Ovarian tumour showing areas of micropapillary and cribriform pattern, with numerous psammomatous calcifications (H&E, 40x and 200x, respectively). C – Borderline serous tumour areas. D – Peritoneal invasion. E to I – Immunohistochemical profile showing diffuse staining for CK7 (E) and WT1 (F), wild type p53 (G), diffuse ER (H) and focal PR (I) expression.

(Moujaber et al., 2018; Combe et al., 2015), and two cases of patients that received combination therapy with BRAF and MEK inhibitor and showed complete clinical response (Mendivil et al., 2018; Tholander et al., 2020).

We present a case report of two patients with LGSOC harbouring a BRAF V600E mutation that achieved sustained clinical responses with combination treatment with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).

2. Case report 1

This patient was diagnosed in April 2014, at the age of 59 years old, with LGSOC FIGO stage IIIC (Fig. 1).

The diagnosis was made due to persistent pelvic pain, heartburn and early satiety. An exploratory laparotomy showed ascites, peritoneal carcinomatosis with omental cake, bilateral involvement of both ovaries by tumoral masses and the uterus adherent to rectum and bladder, precluding the performance of a hysterectomy. Bilateral salpingo-oophorectomy and omentectomy were performed, with evidence of gross macroscopic disease at the end. Patient was offered postoperative chemotherapy with carboplatin and paclitaxel, having received 8 cycles till November of 2014, with normalization of CA 125, but residual measurable disease on CT-scan. Because of the good response on CT-scan, she underwent a second cytoreductive surgery in January 2015, consisting of anterior rectal resection, hysterectomy, en bloc *retro*-vesical pelvic peritonectomy, parietocolic and subdiaphragmatic bilateral peritonectomy, omentectomy, right ileo-colectomy and splenectomy. However, at the end of surgery miliary retroperitoneal disease remained. Afterwards, given the residual disease and consequential grade 2 peripheral sensory neuropathy, it was decided to continue with chemotherapy with pegylated liposomal doxorubicin. However, due to grade 2 infusion reaction, chemotherapy was changed to topotecan, having completed 7 cycles in January 2016, with stable disease on CT-scan. The patient started letrozole and maintained it for about two years, when it was switched to megestrol acetate due to disease progression. In 2019, disease progressed again. At that time, genetic analysis of the primary tumour revealed an activating p.V600E BRAF mutation, thus, she started a combination treatment with dabrafenib 150 mg orally twice daily, and trametinib 2 mg orally daily. Treatment had to be interrupted twice due to urinary sepsis and renal dysfunction, which prompted two dose reductions (to 75 mg twice daily and 1 mg daily, for dabrafenib and trametinib, respectively). The patient noted significant clinical improvement, with normalization of CA 125 in five months (418 U/mL to 24 U/mL), and radiological partial response after eight months of treatment (Fig. 2). Two and a half years of treatment later, the patient maintains sustained partial response, with good performance status and treatment tolerance, and good quality of life.

3. Case report 2

In 2005, at the age of 30 years old, this patient underwent staging surgery with hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy and omentectomy, and was diagnosed with FIGO stage IA ovarian serous borderline tumour, remaining in regular follow-up after. Eleven years after, in 2016, she noticed progressively growing bilateral supraclavicular nodes. PET/CT scan revealed multiple adenopathies above the diaphragm (cervical, supraclavicular, axillary and mediastinal). Excisional biopsy of a cervical adenopathy confirmed metastasis of LGSOC (Fig. 3). Tumour markers CA 125 and CA 19.9 were elevated, 83.69 U/mL and 103.6 U/mL, respectively. Given the absence of symptoms and the indolent nature of the disease, the patient was started on endocrine therapy with anastrozole in April 2017. She maintained this treatment till May 2018, whereupon she presented with lymph node disease progression in the PET/CT scan, with gradual increase of tumour markers. Endocrine therapy was altered to megestrol acetate, but four months later, she became more symptomatic, with cough and tightness sensation on the cervical region. Genetic analysis of the previously excised adenopathy showed an activating p.V600E BRAF

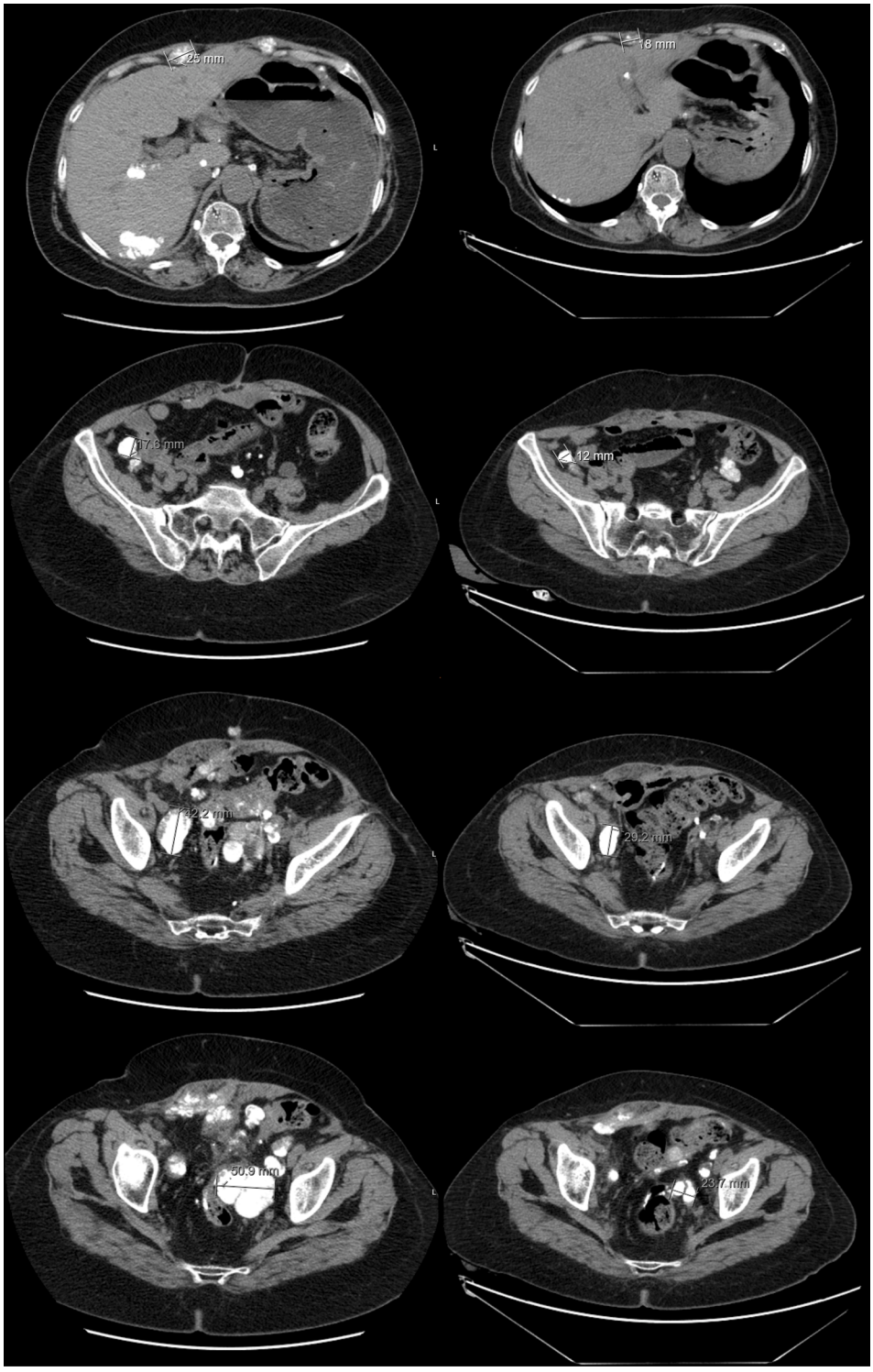

Fig. 2. CT scans at baseline (left column) and eight months after treatment initiation (right column) with dabrafenib/trametinib, demonstrating partial radiological response at the level of calcified peritoneal implants on the abdomen and pelvis.

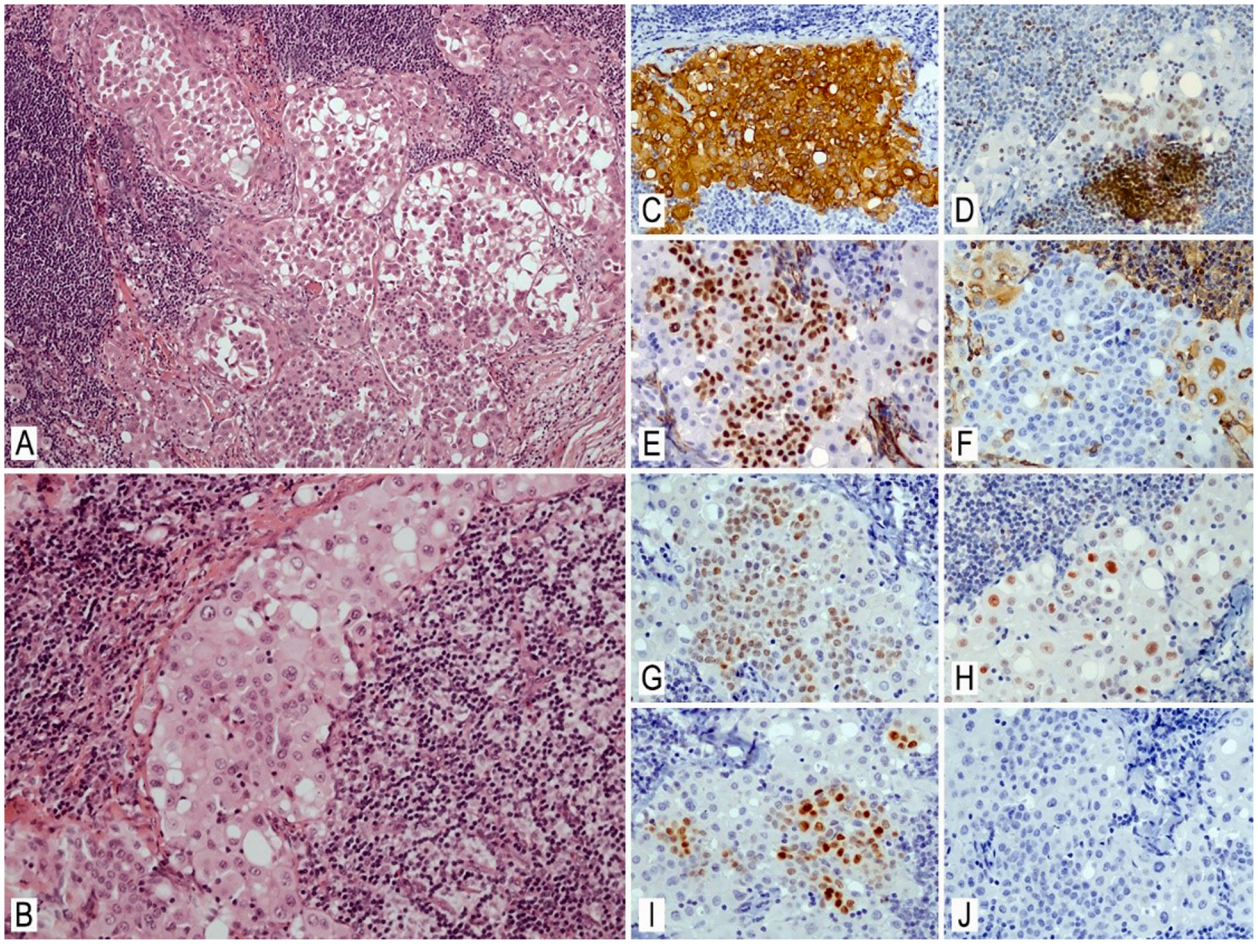

Fig. 3. Histological features of low-grade serous carcinoma metastasis in the patient's cervical lymph node. A, B – Lymph node parenchyma and sinuses occupied by tumour cells with a solid nest and micropapillary arrangement (H&E, 100x and 200x, respectively). C to J – Immunohistochemical profile. Given the metastatic location and large period of time since diagnosis of the ovarian primary, a large panel of antibodies was performed for differential diagnosis. It showed diffuse expression of CK7 (C), multifocal PAX-8 (D) and WT1 (E), focal vimentin (F), multifocal ER (G) and PR (I), wild-type p53 (H) and negative GCDFP-15 (J). Tumour cells were also negative for CK20, CDX-2, TTF-1, p63, HMB45 and mammaglobin (not shown), thus excluding a lung, breast, melanocytic or gastrointestinal primary.

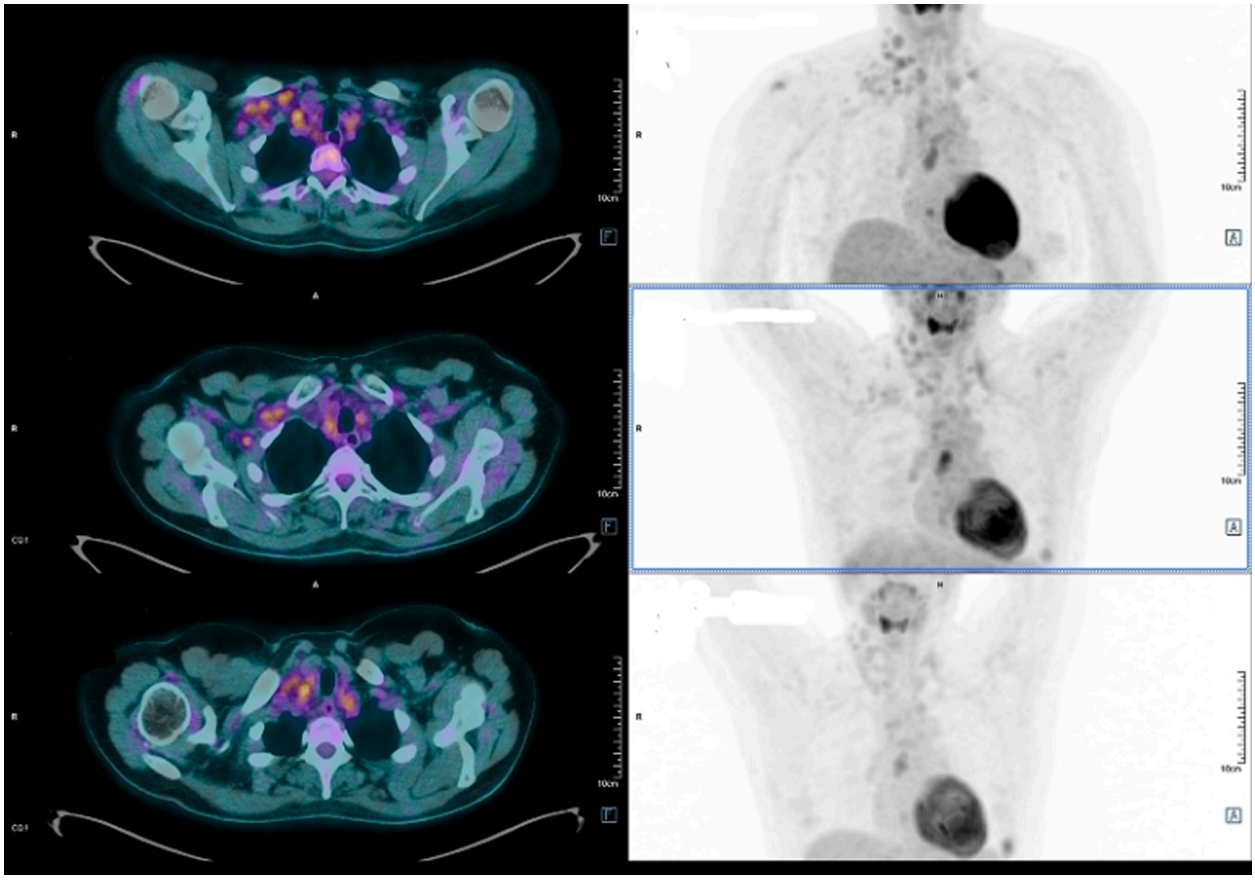

Fig. 4a. PET-Scan at the beginning of treatment with dabrafenib and trametinib, showing moderate 18F-FDG uptake in multiple and bilateral cervical, supra and infra-clavicular and axillary adenopathies.

mutation. So, the patient was started on combination treatment with dabrafenib 150 mg orally twice daily, and trametinib 2 mg orally daily, on November 2018. Due to grade 2 nausea and fatigue, dose was reduced to 100 mg twice daily and 1.5 mg daily, respectively, with better tolerance afterwards. She presented partial response one month after treatment, and complete metabolic response four months after (Figs. 4a and 4b), and tumour markers declined to normal levels (CA 125 dropped from 169.4 U/mL to 9 U/mL). To date, the patient still maintains complete response, with good treatment tolerance and performance status ECOG 1, and good quality of life.

4. Discussion

Regardless of the more indolent nature of the LGSOC compared to the HGSOC, with more prolonged survival, this advantage dissipates after ten years of disease, with similar survival rates between the two entities (Gadducci and Cosio, 2020). The chemoresistance inherent to this type of ovarian cancer, narrows the therapeutic options, especially in the recurrent setting. Moreover, the rarity of this neoplasia hampers the search for novel treatment agents in clinical trials because of the difficulty in recruiting and meeting accrual.

Concerning the use of MEK inhibitors, there are two clinical trials with conflicting results. The MILO/ENGOT-ov11 was a phase III trial, that intended to evaluate the efficacy of Binimetinib compared to physician's choice of chemotherapy, and that was discontinued due to futility (Monk et al., 2020). In contrast, the GOG 0281, a phase II/III trial, aimed to compare trametinib to the standard of care, met its primary endpoint, demonstrating a prolonged progression free survival with the use of trametinib in comparison to physician's choice (13 months vs. 7.2 months; HR 0,48; $P < .001$). In this trial, patients must have recurred or progressed following at least one platinum-based chemotherapy regimen and may not have received all of the five choices in the "standard therapy" arm, allowing both chemotherapy and endocrine therapy (Gershenson et al., 2019). These results have led to the inclusion of trametinib in the therapeutic options for LGSOC by the National Comprehensive Cancer Network guidelines. It is important to highlight that, the studies made so far, weren't able to find a suitable predictive biomarker for MEK inhibitor sensitivity (Gershenson et al., 2020). In relation to the BRAF mutation status as a way to select patients to receive treatment with BRAF inhibitors, a basket trial involving vemurafenib reported an anecdotical case of improved response in a patient with LGSOC with V600E BRAF mutation (Combe et al., 2015; Hyman et al., 2015), and two patients, also with BRAF V600E mutation, included in phase I clinical trials presented durable clinical responses with treatment with dabrafenib (in third line) (Moujaber et al., 2018; Falchook et al., 2012), and lifirafenib (in second line) (Moujaber et al., 2018). Moreover, we found two case reports of heavily pretreated patients with advanced LGSOC with an activating BRAF mutation that showed a complete and sustained response with combined treatment with dabrafenib and trametinib (Mendivil et al., 2018; Tholander et al., 2020).

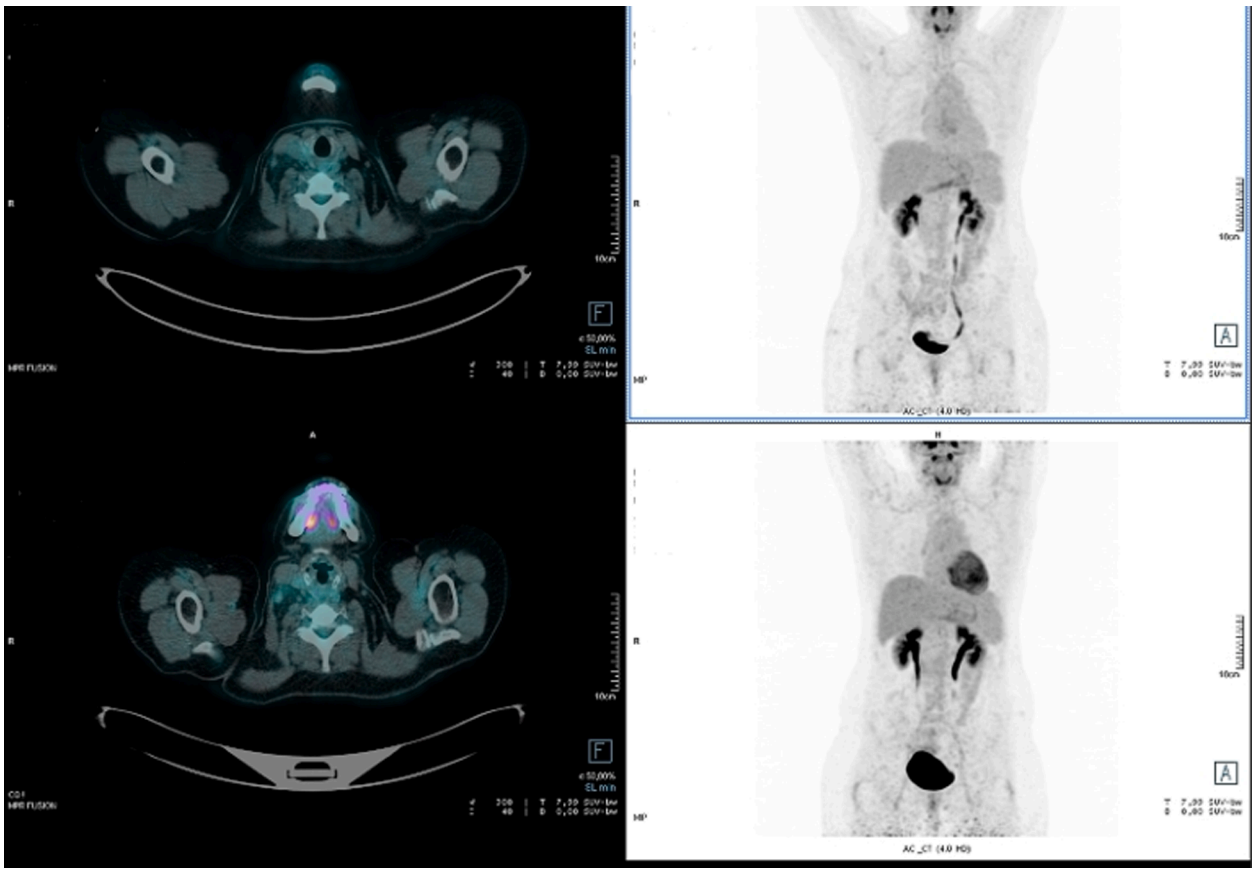

Fig. 4b. PET-Scan after 4 months of treatment with dabrafenib and trametinib, without 18F-FDG uptake, revealing complete metabolic response.

It is important to highlight that the rational of paring dabrafenib/trametinib in our patients was supported at that time by the evidence of better clinical responses with this treatment when compared to a BRAF inhibitor alone in patients with advanced BRAF mutated melanoma, as shown by two phase III clinical trials by Robert et al. (2014) and Long et al. (2014). Nowadays, the positive results of GOG 0281 with the use of trametinib in monotherapy in patients with LGSOC, regardless of the BRAF mutational status, raises the question about the pertinence of combination treatment. However, the use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumour cell lines in vitro and prolonged inhibition of tumour growth in BRAF V600 mutation positive tumour xenografts compared with either drug alone (Tafinlar® Prescribing Information, Mekinist® Prescribing Information). Also, the combination of both drugs helps to mitigate the limitations of the use of BRAF inhibitor alone, by delaying tumour acquired resistance and decreasing the incidence of secondary malignancies, which develop due to a paradoxical activation of MAP-kinase signalling and increased cell proliferation in BRAF wild-type cells (Bowyer et al., 2015). So, regarding BRAF mutated LGSOC, to date it is not clear whether combination therapy with BRAF and MEK inhibitors is superior, or if trametinib monotherapy might be sufficient.

Our clinical cases illustrate the natural history of LGSOC and the impressive and durable clinical responses to combination therapy with dabrafenib and trametinib in tumours harbouring V600E BRAF mutation. It is interesting to notice, that the response was achieved regardless on where the molecular alteration was tested, meaning either in the primary or in the metastasis. Also, the treatment was overall well tolerated, and the response was maintained even after dose reductions.

5. Conclusion

LGSOC represents the challenge that is managing a rare cancer with scarce therapeutic options. Given the prevalence of BRAF mutations in this type of tumour, it might be relevant to consider genetic testing earlier in the course of advanced disease. It may provide new treatment opportunities for patients with a known chemoresistant tumour, by identifying potential actionable targets, and avoid potential toxicities associated with chemotherapy. Here we demonstrate that striking clinical responses can be achieved in BRAF mutated LGSOC treated with combined BRAF and MEK inhibitor treatment. It is imperative to continue to design studies for these patients, in order to find the most effective treatment.

Patient's consent

Obtained.

Funding statement

The authors state that they have not received any funding for this study.

CRediT authorship contribution statement

Bárbara Lima: Conceptualization, Writing – original draft, Writing – review & editing. **Miguel Henriques Abreu:** Conceptualization, Writing – review & editing. **Susana Sousa:** Conceptualization, Writing – review & editing. **Carla Bartosch:** Resources, Writing – review & editing. **Deolinda Pereira:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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