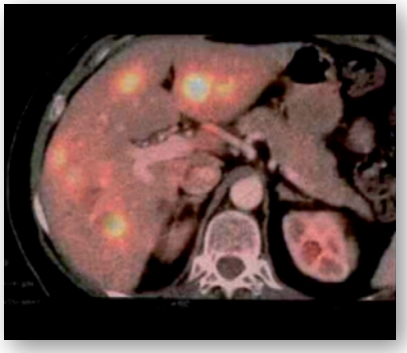

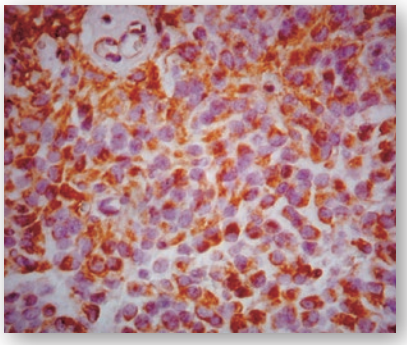

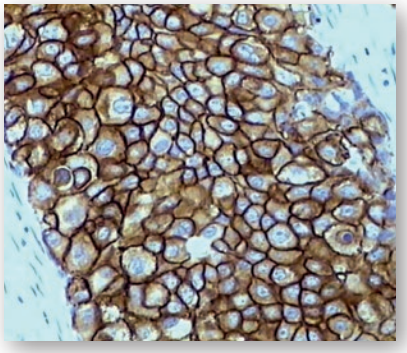

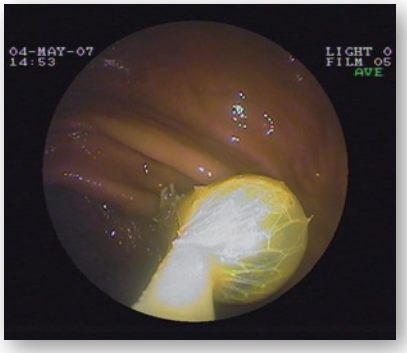

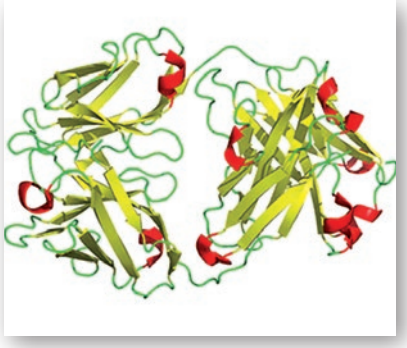

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Wild-type patient unable to receive bevacizumab in first-line who relapsed between 6 and 12 months

Claudia Andreetta

Department of Oncology, Azienda Ospedaliera Universitaria, Udine

Clinical summary

67-year-old patient;
arterial hypertension, prior abdominal aortic aneurysm.

↓

June 2018: hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, lymphadenectomy, omentectomy, peritoneal biopsies. Residual tumor <1 cm.
Histology: high-grade serous ovarian carcinoma, pT3cN1, FIGO stage: IIIC.
No BRCA1/2 mutation.

↓

July 2018: first line with carboplatin AUC5 + paclitaxel 175 mg/m^2 iv q21 - 6 cycles.
Allergic reaction during last cycle.
Bevacizumab was not administered due to the history of aortic aneurysm.

↓

July 2019: Peritoneal progression disease (PD) (progression free interval [PFI] 6-12 months).
Second line with trabectedin + pegylated liposomal doxorubicin (PLD) for 6 cycles with stable disease (discontinued in accordance with patient's wishes).
Reported toxicities: G1 asthenia, G1 nausea, G1 mucositis.

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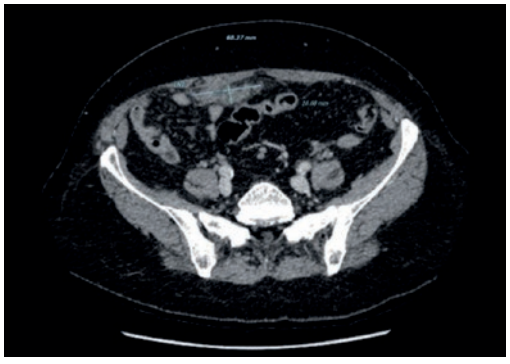
History and clinical characterization

- 67-year-old woman in good health.
- Comorbidities: arterial hypertension, prior abdominal aortic aneurysm (surgically corrected in 2013).
- Home therapy: ramipril 5 mg/day, acetylsalicylic acid 100 mg/day, delorazepam 12 drops/day.
- In May 2018: patient complained of increase in volume of the abdomen, feeling of gastric fullness, and dyspnea on slight exertion.
- The patient's general practitioner indicated first-level diagnostic investigations (abdominal ultrasound and chest X-ray) and referred her to a gynecology outpatient clinic following the finding of peritoneal carcinomatosis and a suspicious ovarian mass.
- Following the gynecology consultation and second-level ultrasound scan, the diagnosis was probable ovarian cancer with peritoneal carcinomatosis; CA-125 2547 IU/mL.

Surgery



- On June 14, 2018: Computed tomography (CT) scan of the chest and abdomen showed nodules of peritoneal carcinomatosis and suspicious right adnexal mass, no pleural, pulmonary, or hepatic lesions.
- On June 28, 2018: hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, lymphadenectomy, omentectomy, and peritoneal biopsies. Residual tumor <1 cm (peritoneal mottling).
- Histopathological diagnosis: high-grade serous ovarian carcinoma pT3cN1, FIGO Stage IIIC. No BRCA1/2 mutation.

First-line therapy

- Between July 27, 2018 and November 23, 2018: first-line therapy with carboplatin AUC5 + paclitaxel 175 mg/m^2 iv q21 regimen, for 6 cycles.
- Carboplatin infusion-related reaction reported during the last cycle, characterized by sweats, hypotension and rash, treated with steroids and antihistamines.
- CA-125 normalized from the second cycle of therapy.
- CT scan of the chest and abdomen after the sixth cycle (December 10, 2018): no evidence of residual disease.

During follow-up:
- On 20/06/2019: CA-125 384 IU/mL.
- On 10/07/2019: Contrast-enhanced CT scan of the chest and abdomen revealed multiple nodules of carcinomatosis in all quadrants of the abdomen.

Comment

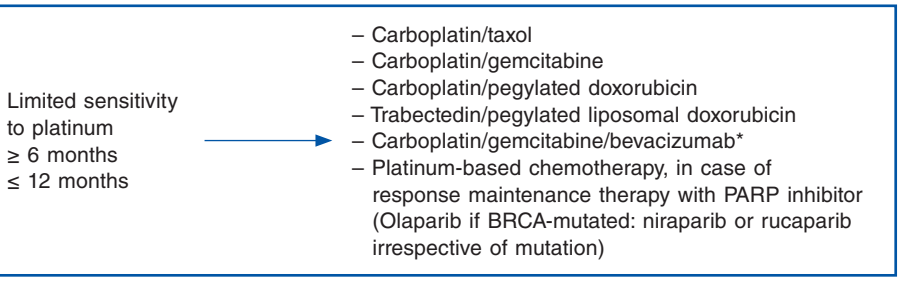
The patient received first-line chemotherapy with carboplatin and paclitaxel every 3 weeks for six cycles. Concomitant bevacizumab was not administered due to the patient's history of aortic aneurysm. The treatment was complicated by a carboplatin infusion-related reaction[1] during the last cycle, which was resolved pharmacologically without requiring hospitalization. The restaging contrast-enhanced CT scan of the chest and abdomen after the sixth cycle showed complete response. Therefore, the patient was referred to clinical and instrumental follow-up, with a finding of biochemical and radiological progression in the peritoneum approximately 7 months after the end of first-line therapy.

Rationale

In the case of recurrence between 6 and 12 months from the last administration of platinum, treatment options are rechallenge with a platinum-based treatment or platinum-free therapy with trabectedin + PLD combination (Box 1)[2].

The choice of treatment at the time of recurrence is currently not based solely on the platinum-free interval but also takes into account other factors, such as the received first-line therapy and its residual toxicity, the BRCA mutational status, and the patient's eligibility for retreatment with platinum. All these factors must be taken into account while defining a sequential therapeutic strategy that allows the use of all available therapies, with the main objective of chronifying the disease.

In favor of platinum rechallenge	In favor of trabectedin + PLD
– The possibility of a response to platinum after a recurrence between 6 and 12 months from the last platinum administration (objective response rate [ORR] of 39-45% reported with platinum rechallenge in patients with PFI 6-12 months treated in 2nd line)[3]	– The early finding (at 7 months) of massive peritoneal carcinomatosis suggests that the patient is unlikely to show platinum-sensitivity if retreated with platinum
– The possibility of starting subsequent maintenance therapy with poly-(ADP ribose) polymerase (PARP) inhibitor in the event of response to the treatment with platinum	– Favors recovery from certain adverse effects of first-line therapy
	– A relapse to the subsequent line of therapy can occur before 6 months, which would prevent the patient from benefiting from this option indicated for platinum-sensitive ovarian cancer. Platinum rechallenge followed by a PARP inhibitor could be used at a later time



* Bevacizumab only if not administered previously

Box 1. *2020 AIOM Guidelines – Treatment algorithm: stage III-IV and limited sensitivity to platinum* (adapted from Gadducci et al., 2020)[2].

In platinum-sensitive disease, trabectedin + PLD regimen is an efficacious and well-tolerated treatment option, as demonstrated by the OVA-301 trial, in which the combination obtained a significant advantage over PLD monotherapy in terms of progression-free survival (PFS) (9.2 vs. 7.5 months; HR: 0.73; 95% CI: 0.56-0.95; p=0.0170) and overall survival (OS) (28.4 vs. 24.1 months; HR 0.78;95% CI: 0.62-0.98; p=0.0319, based on Cox regression analysis after adjustment for key prognostic factors)[4,5].

The survival advantage observed with the combination was larger in the subset of patients who relapse between 6 and 12 months, achieving 6 months difference in OS (22.4 vs. 16.4 months; HR 0.64; 95% CI: 0.47-0.86; p=0.0027) (Fig. 1)[6]. When these patients with limited platinum sensitivity were treated with platinum at the time of relapse to trabectedin + PLD or PLD monotherapy, the survival advantage of the combination increased, reaching a 9-month difference (27.7 vs. 18.7; HR: 0.58; 95% CI: 0.37-0.90; p=0.0153)[7].

These observations led to the design of a randomized Phase III trial comparing trabectedin + PLD vs platinum rechallenge in patients who relapse between 6 and 12 months to one or two previous platinum-based lines. Results from this study have been recently published and showed a similar OS between treatment arms (trabectedin/PLD: 21.5 months vs. carboplatin/PLD: 21.3 months; HR: 1.10; 95% CI: 0.92-1.32; p=0.284), not achieving the primary endpoint of the study but confirming trabectedin+PLD as the alternative platinum-free therapy for platinum-sensitive ovarian cancer patients[8].

Second-line treatment

– From July 25, 2019: patient started treatment with trabectedin + PLD, achieving stable disease and a considerable decrease in CA-125 (Fig. 2).

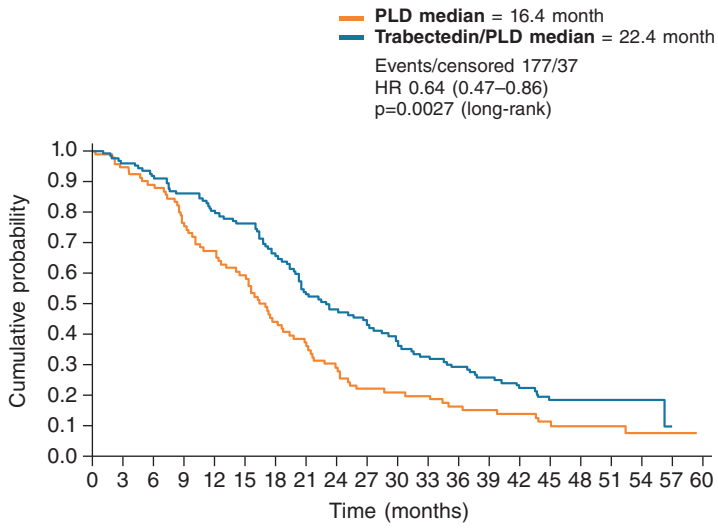


Figure 1. *OVA-301 Study: OS results in patients with limited sensitivity to platinum (PFI 6-12 months)* (adapted from Monk et al., 2012)[6].

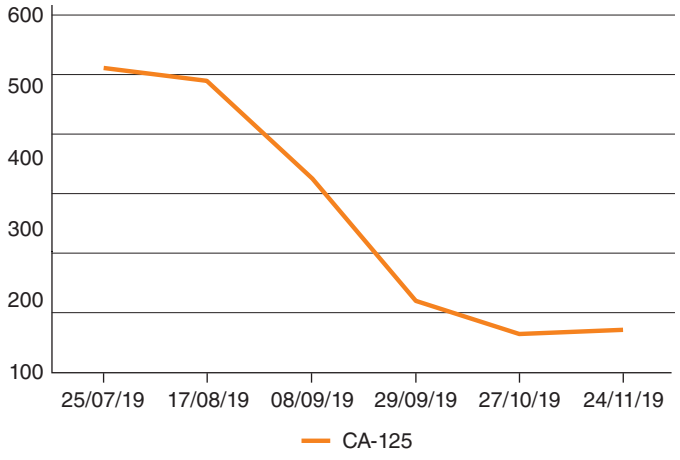


Figure 2. *CA-125 trend during treatment with trabectedin + PLD.*

– The treatment was discontinued after six cycles in accordance with patient's wishes, despite the indication to continue until progression/intolerance.

Comment

The choice of treatment was based on the efficacy data in favor of trabectedin + PLD combination in patients who relapse between 6 and 12 months, as well as the patient's refusal to undergo a carboplatin desensitization protocol[9].

Management of adverse events

– Treatment was generally well tolerated.
– Reported toxicities: G1 asthenia, G1 nausea, G1 mucositis.
– AEs were mild and resolved without requiring therapeutic measures, treatment delays or dose reductions.

Rationale

Table 1 indicates the main AEs reported in the OVA-301 study[4]. Despite being associated with a

Table 1. *Main adverse events in OVA-301 randomized phase III study*

Toxicity	PLD (n=330)				Trabectedin/PLD (n=333)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Hematologic								
Neutropenia	46	13.9	28	8.5	96	28.8	113	33.9
Leukopenia	24	7.3	8	2.4	82	24.6	28	8.4
Thrombocytopenia	6	1.8	2	0.6	34	10.2	27	8.1
Anemia	15	4.5	1	0.3	31	9.3	10	3.0
Febrile neutropenia	6	1.8	1	0.3	15	4.5	8	2.4
Non-hematologic								
HFS	61	18.5	4	1.2	13	3.9	0	0
Mucosal inflammation	19	5.8	0	0	7	2.1	0	0
Stomatitis	16	4.8	1	0.3	3	0.9	0	0
Fatigue	8	2.4	1	0.3	19	5.7	1	0.3
Nausea	8	2.4	0	0	29	8.7	0	0
Vomiting	7	2.1	0	0	33	9.9	1	0.3
AST increase	1	0.3	1	0.3	21	6.3	3	0.9
ALT increase	1	0.3	0	0	95	28.5	8	2.4

	PLD (n=330)		Trabectedin/PLD (n=333)	
Other events of interest	**n**	**%**	**n**	**%**
Alopecia	44	13	40	12
Alkaline phosphatase increase	24	7	68	20
Neuropathy	24	7	34	10
Bilirubin conjugated increase/hyperbilirubinemia	18	5	51	15

Adapted from Monk et al., 2010[4].
HFS: hand-foot syndrome; AST: aspartate transaminase; ALT: alanine transaminase.

higher incidence of Grades 3-4 AEs, the combination treatment has a manageable safety profile without cumulative toxicities. Furthermore, the subsequent patient-reported outcomes analysis did not show that the combination had any effect in terms of a worsening in functional status and symptoms compared to PLD monotherapy[10].

Conclusions

- The first-line therapy in patients with advanced non-BRCA1/2-mutated serous ovarian cancer is based on carboplatin + paclitaxel to which bevacizumab can be added (provided there are no contraindications). Later studies (not available when the first-line treatment for our patient was decided) have shown that maintenance with PARPi (±bevacizumab) represent another valid option for the first-line treatment of these patients[11,12].
- There are two options in the case of recurrence between 6 and 12 months from the last carboplatin administration: rechallenge with platinum-based therapy or platinum-free therapy with trabectedin + PLD.
- Trabectedin + PLD combination represents a valid alternative to platinum-based therapy,

especially when platinum is not the best option due to the early onset of recurrence and to allow for recovery from possible adverse events.

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BRCA mutated patient consecutively treated with bevacizumab, PARP inhibitors and trabectedin + PLD as first, second, and third line

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Clinical summary

39-year-old patient who, at the age of 20, had had multiple myeloma that was treated with chemotherapy, allogeneic bone marrow transplant and radiotherapy on the left wing of ilium, CR ever since.

↓

October 2016 (36 years): oncological history → Appearance of ascitic effusion, pelvic mass and increase in CA-125.

↓

Peritoneal carcinomatosis from high-grade serous ovarian carcinoma
No germline BRCA1/2 mutation.

↓

November 2016: cytoreductive chemotherapy with carboplatin and paclitaxel iv - 4 cycles with RP.

↓

April 2017: hysterectomy with salpingo-oophorectomy, sigmoidectomy, pelvic peritonectomy, omentectomy, pelvic and peri-aortic lymphadenectomy, removal of right diaphragmatic peritoneum.
Histology: high-grade serous ovarian carcinoma, FIGO stage: IIIC. No post-surgical residue.

↓

May 2017: chemotherapy with carboplatin and paclitaxel – 4 cycles with CR; from second cycle combination with bevacizumab discontinued after 7 administrations due to rectovaginal fistula, which was treated surgically.

↓

August 2018: Peritoneal progression of disease.

↓

October 2018: ileocecal resection, pelvic and abdominal peritonectomy, removal of peritoneal nodules.
No macroscopic residue.
Histology: high-grade serous ovarian carcinoma. Positive somatic BRCA1/2 mutation test.
Subsequently, from December 2018, second-line chemotherapy with carboplatin and PLD – 6 cycles with CR → maintenance therapy with olaparib.

↓

January 2020: Peritoneal and hepatic progression of disease. PFI 6-12-month: third-line chemotherapy with trabectedin + PLD – 4 cycles, ongoing.

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History and clinical characterization

- 39-year-old patient.
- Family cancer history: paternal grandmother diagnosed with breast cancer > 60 years.
- Personal history: at the age of 20, diagnosed with multiple myeloma treated with chemotherapy according to the vincristine, doxorubicin, dexamethasone regimen for 4 cycles, followed by allogeneic bone marrow transplant (after conditioning with cyclophosphamide and busulfan) and radiotherapy on the left wing of ilium, the site of an osteolytic lesion, complete response (CR) ever since.
- October 2016 (36 years): oncological history → Appearance of ascitic effusion, pelvic mass and increase in CA-125: 2095 kU/L.

Surgery

- On 29/10/2016: diagnostic laparoscopy → Peritoneal carcinomatosis from high-grade serous ovarian cancer.
- No germline BRCA1/2 mutation.
- Between November 2016 and March 2017: patient received debulking chemotherapy with carboplatin + paclitaxel iv q21 regimen for 4 cycles, obtaining biochemical response, and partial response (PR) on the restaging computed tomography (CT) scan.
- On 11/04/2017: patient underwent surgery for hysterectomy and salpingo-oophorectomy, sigmoidectomy, pelvic peritonectomy, omentectomy, pelvic and peri-aortic lymphadenectomy, and removal of right diaphragmatic peritoneum.
- Histopathological diagnosis: high-grade serous ovarian cancer, FIGO Stage IIIC.
- No post-surgical residue.

Comment

The patient had a diagnostic laparoscopy to assess the actual extent of the peritoneal disease and the optimum surgical approach. A germline BRCA1/2 mutation test was performed given the familiarity for breast cancer and the patient's young age.

In 2016, it was not possible to perform a somatic BRCA1/2 test or a test for homologous recombination deficiency; on the other hand, PARP-inhibitors were not available in Italy outside of clinical trials at that time. After 4 cycles of neoadjuvant chemotherapy, the disease showed PR on CT scan and CA-125 test; therefore, the patient had optimal surgery with no macroscopic post-surgical residue.

First-line therapy

- From May 19, 2017 to September 15, 2017: chemotherapy with carboplatin + paclitaxel q21 was administered for a further 4 cycles in combination with bevacizumab from the second cycle.
- October 2017: restaging CT scan negative for metastases; CA-125 31 kU/L.
- October 2017: patient continued maintenance therapy with bevacizumab.
- March 2018: due to the finding of a rectovaginal fistula, the patient underwent an ileostomy and discontinued maintenance therapy with bevacizumab (total of 7 administrations). Referred for clinical and instrumental follow-up.
- July 2018: Intervention of recanalization.

Comment

Maintenance therapy with bevacizumab was complicated by the appearance of a rectovaginal fistula requiring a temporary ileostomy and the discontinuation of treatment.

Vaginointestinal fistulae are serious adverse events that are potentially associated with the anti-angiogenic action of bevacizumab and their risk increases in case of intestinal resections during prior surgical procedures. The measures to be implemented for their prevention are careful patient selection and adequate timing between surgery and the start of treatment with bevacizumab[1-3].

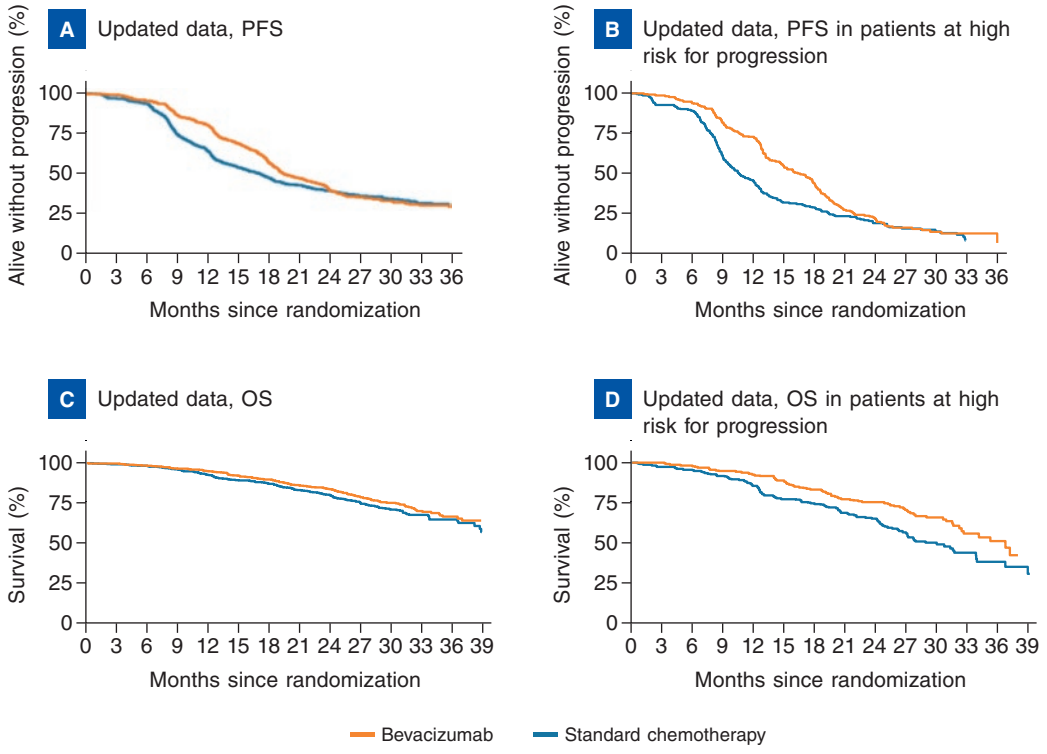
Rationale

According to the results of the GOG 218[2] and ICON7[1] studies performed in advanced ovarian cancer, adding bevacizumab to first-line therapy with carboplatin + paclitaxel brings significant advantages over chemotherapy alone in terms of PFS. A *post hoc* analysis revealed OS in high-risk subgroups (Box 2)[1,4].

The most frequently reported toxicities associated with bevacizumab in first-line include grade ≥ 2 hypertension, grade ≥ 3 proteinuria, grade ≥ 3 thromboembolic events, and grade ≥ 2 gastrointestinal events (Table 2)[2].

Second-line treatment – 1

- August 2018 (11 months after the end of first-line chemotherapy): following an increase in CA-125 (123 kU/L), the patient underwent instrumental restaging by means of:
  - CT scan of the chest and abdomen: negative.



Box 2. *PFS and OS results from ICON7 study* (adapted from Perren et al., 2011)[1].

Table 2. *Bevacizumab selected adverse events reported at GOG 218 study*

Event	Bevacizumab initiation (n=607)	Bevacizumab throughout (n=608)	Control (n=601)
	Number of patients (percent)		
Gastrointestinal events (grade ≥ 2)	17 (2.8)	16 (2.6)	7 (1.2)
Hypertension (grade ≥ 2)	100 (16.5)	139 (22.9)	43 (7.2)
Proteinuria (grade ≥ 3)	4 (0.7)	10 (1.6)	4 (0.7)
Pain (grade ≥ 2)	252 (41.5)	286 (47.0)	250 (41.6)
Neutropenia (grade ≥ 4)	384 (63.3)	385 (63.3)	347 (57.7)
Febrile neutropenia	30 (4.9)	26 (4.3)	21 (3.5)
Venous thromboembolism	32 (5.3)	41 (6.7)	35 (5.8)
Arterial thromboembolism	4 (0.7)	4 (0.7)	5 (0.8)
Wound disruption	22 (3.6)	18 (3.0)	17 (2.8)
CNS bleeding	0	2 (0.3)	0
Non-CNS bleeding (grade ≥ 3)	8 (1.3)	13 (2.1)	5 (0.8)
Reversible posterior leukoencephalopathy syndrome	1 (0.2)	1 (0.2)	0

Adapted from Burger et al., 2011[2].
CNS: central nervous system.

- PET scan with fluorodeoxyglucose (FDG) – September 2018 – finding of uneven increased tracer up-take in the right iliac fossa.

– On October 26, 2018: the patient underwent surgery for ileocecal resection, pelvic and abdominal peritonectomy, removal of peritoneal nodules. No macroscopic post-surgical residue. Histology: high-grade serous ovarian carcinoma.
– Somatic BRCA1/2 test positive (pathogenetic variant C5 BRCA1).

Comment

The patient was eligible for upfront debulking surgery due to a PFI >6 months, her good performance status (PS) (ECOG 0) and the limited spread of the disease.

Rationale

As reported by the AGO DESKTOP III/ENGOT-ov20 study[5], patients presenting a first recurrence after 6 months from the end of the previous platinum-based treatment and a positive AGO *(Arbeitsgemeinschaft Gynaekologische Onkologie)* score (ECOG PS 0, ascites ≤ 500 mL, complete resection during initial surgery), obtain significant advantages in terms of PFS and OS if they undergo debulking surgery, followed by chemotherapy rather than chemotherapy alone:

– Median PFS was 14 months without and 19.6 months with surgery (HR: 0.66, 95%CI 0.52-0.83, p<0.001)[5].
– Median OS of 53.7 months with and 46.2 months without surgery (HR 0.76, 95%CI 0.59-0.97, p=0.03)[6].

The benefit in terms of survival resulting from secondary surgery becomes even greater when complete cytoreduction is achieved (median 60.7 vs. 46.2 months)[6].

Second-line treatment – 2

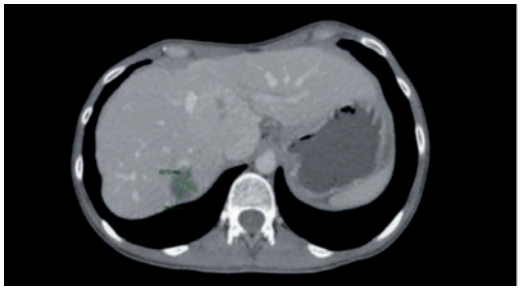
– Between December 17, 2018 and June 07, 2019: patient received chemotherapy with carboplatin and PLD iv q21 for 6 cycles.
– Due to an allergic reaction to carboplatin, from the second cycle the patient continued treatment with the Castells desensitization protocol[7].
– At the end of the chemotherapy, the patient had instrumental restaging with a contrast-enhanced CT scan of chest and abdomen, which was negative for recurrence; CA-125 10 kU/L.
– From July 25, 2019: maintenance therapy with olaparib.

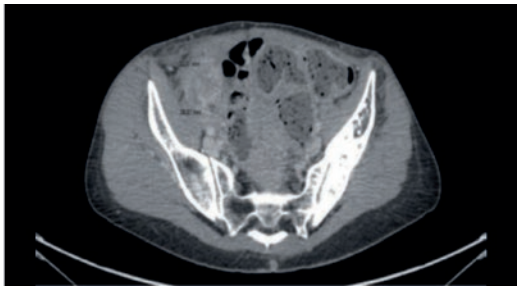
Comment

According to the 2019 ESMO-ESGO Consensus Conference[8], the time elapsed since the previous line of therapy indicates that the patient's recurrence can be considered potentially platinum-sensitive. The absence of residual disease after secondary debulking along with data supporting subsequent maintenance with a PARP inhibitor in the event of a complete or partial response after 4-6 cycles of platinum[9-11] were additional factors that led clinicians to select a new exposure to a platinum-based regimen. Carboplatin + PLD combination was chosen based on its toxicity profile[12], in particular, due to the lower incidence of hematological toxicity compared to the combination with gemcitabine[13], and also taking into account the pretreatment received for allogeneic bone marrow transplant that the patient received in her youth.

Third-line treatment

– From December 2019: gradual increase in CA-125 (6 months after the end of platinum chemotherapy).
– January 2020: contrast-enhanced CT scan of the chest and abdomen: finding of peritoneal carcinomatosis in the Glissonian capsule and in the pelvic cavity and appearance of suspicious hepatic lesions.
– Between January 25, 2020 and April 17, 2020: third-line chemotherapy with trabectedin + PLD for 4 cycles (treatment on going at the time this case was written up).





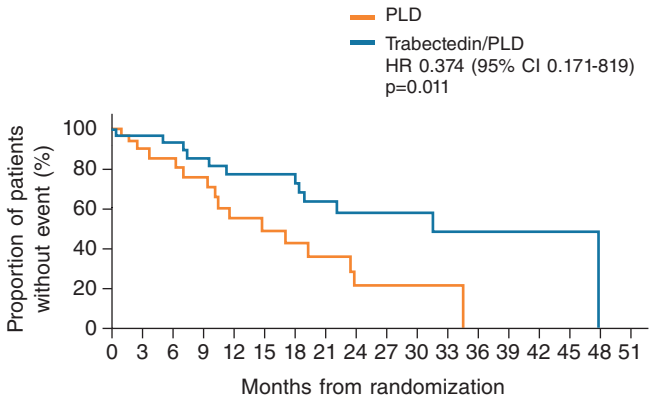


Figure 3. *OS in patients with BRCA mutation and PFI 6-12 months* (adapted from Monk et al., 2020)[15].

Rationale

Options for patients who relapse after first-line exposure to bevacizumab and PARPi (olaparib) are likely to be limited to platinum- or non-platinum-based regimens without maintenance therapy. A key strategy to delay platinum resistance and improve prognosis of recurrent disease is to alternate treatments with different mechanisms of action. The multiple mechanisms of trabectedin and its complementarity with platinum allow intercalation between platinum regimens in potentially platinum-responsive patients with recurrent disease[14].

The recent randomized phase III OVC 3006 study[15] compared OS of patients with platinum-sensitive recurrent ovarian cancer receiving third-line treatment with trabectedin + PLD vs PLD monotherapy. A clinically relevant benefit was obtained with the combination in the subgroups of patients with[15]:

- PFI 6-12 months (median OS 24.8 vs. 17.4 months; HR=0.69, 95% CI 0.48-1.01).
- BRCA1/2 mutation (median OS 34.2 vs. 20.9 months; HR=0.54, 95% CI 0.33-0.90).

In BRCA mutated patients with a PFI 6-12 months, an enhanced benefit was observed with trabectedin + PLD (Fig. 3)[15].

These data support the results of retrospective case series and are consistent with the findings of the randomized phase III OVA-301 study. Trabectedin + PLD resulted in a significant PFS and OS advantage in both subgroups of patients according to the *post hoc* analyzes performed:

- PFI 6-12 months (results with trabectedin + PLD vs. PLD, respectively)[16]:
  - Median PFS 7.4 vs 5.5 months; p=0.0152.
  - Median OS 22.4 vs 16.4 months; p=0.0027.
- BRCA1 mutation (results with trabectedin + PLD vs. PLD, respectively)[17]:
  - Median PFS 13.5 vs. 5.5 months; p=0.0002.
  - Median OS 23.8 vs. 12.5 months; p=0.0086.

The possibility of PLD rechallenge has been a controversial aspect in the treatment of ovarian cancer due to the scarcity of published data. A pre-defined exploratory analysis was conducted to assess the impact of prior PLD therapy in patients who participated in the OVC 3006 study[18]. Prior treatment with PLD in patients treated with trabectedin + PLD did not increase toxicities (Table 3) or negatively influence survival or response rates (Table 4)[18]. Higher ORR, PFS, and OS values were achieved with trabectedin + PLD over PLD monotherapy regardless of prior PLD administration.

The efficacy and safety of trabectedin + PLD in advanced lines of recurrent ovarian cancer (≥ third-line) have also been evaluated in real life studies. In a retrospective analysis of 34 heavily pretreated platinum-sensitive patients (3 median number of previous lines)[19], trabectedin + PLD showed an activity comparable to that observed in second-line studies such as the randomized phase III OVA-301 study[20] (Table 5).

Therefore, the activity of trabectedin + PLD appears to be unrelated to the number of previous lines, being maintained when administered as third or further line[19]. In such advanced lines of ovarian cancer, the safety profile of the treatments acquires special relevance. No new safety signals were reported with the administration of trabectedin + PLD in the third or subsequent lines (Table 6)[19], showing a safety profile as expected based on previous second-line evidence.

Table 3. *Safety of trabectedin + PLD vs PLD by prior PLD therapy use*

Safety	Trabectedin+PLD (n=289) Prior PLD		PLD monotherapy (n=287) Prior PLD	
	Yes (n=19, 6.6%)	No (n=270, 93.4%)	Yes (n=20, 7%)	No (n=267, 93%)
Grade 3/4 treatment related adverse events (AEs), n (%)	18 (94.7)	225 (84.3)	14 (70)	166 (63.4)
Gastrointestinal AEs	5 (26.3)	50 (18.7)	5 (25)	50 (19.1)
Hematologic AEs	10 (52.6)	152 (56.9)	3 (15)	75 (28.6)
Skin AEs: Palmar-plantar erythrodysesthesia	0	10 (3.7)	2 (10)	31 (11.8)
Cardiac AEs	0	3 (1.1)	1 (5)	1 (0.4)

Adapted from Monk et al., 2020[18].

Table 4. *Efficacy of trabectedin+PLD vs PLD by prior PLD therapy use*

Efficacy	Trabectedin+PLD (n=289) Prior PLD			PLD monotherapy (n=287) Prior PLD		
	Yes (n=19, 6.6%)	No (n=270, 93.4%)	HR (95% CI)	Yes (n=20, 7%)	No (n=267, 93%)	HR (95% CI)
ORR (%)	52.6	45.6	1328 (0.468-3.819)	35	36	0.959 (0.313-2.692)
PFS (months)	7.1	7.5	0.853 (0.435-1.671)	5.6	7.4	1.212 (0.688-2.135)
OS (months)	34.2	22.1	0.844 (0.409-1.740)	28.9	20.9	0.713 (0.349-1.458)

Adapted from Monk et al., 2020[18].

Table 5. *Trabectedin + PLD efficacy by treatment line*

Efficacy	N	Previous lines Median (range)	Cycles median (range)	ORR (%)	Median PFS (months)	Median OS (months)
Retrospective study[19]	34	3 (2-10)	5 (1-16)	32.4	6.1	16.3
OVA-301 phase III trial[20]	218	1	6 (1-21)*	35.3	9.2	27.0

Adapted from Nicoletto et al., 2015[19].
*Data only reported in the whole population included at the randomized Phase III trial OVA-301 including 115 patients with a PFI lower than 6 months and 218 patients with a PFI beyond 6 months. Appendix Table A1, online only: http://ascopubs.org/doi/full/10.1200/JCO.2009.25.4037.

Conclusions

- Surgery can be offered to suitable ovarian cancer patients with first recurrence after 6 months (with positive AGO-Score), as it has shown significant efficacy benefits with acceptable morbidity.
- The efficacy and safety of trabectedin + PLD in advanced lines of recurrent ovarian cancer (≥ third-line) have been evaluated in clinical trials and real life studies:
  - A clinically relevant benefit was observed with trabectedin + PLD over PLD monotherapy as third-line treatment of patients

Table 6. *Treatment-related AEs (worst grade per patient; n=34) reported with trabectedin + PLD in heavily pre-treated ovarian cancer patients*

	NCI-CTCAE grade			
	1/2		3	
	n	%	n	%
Alanine aminotransferase increase	–	–	1	2.9
Anemia	1	2.9	1	2.9
Asthenia	6	17.6	–	–
Fever	1	2.9	–	–
Intolerance to antiemetics	1	2.9	–	–
Mucositis	3	8.8	2	5.9
Myalgia	1	2.9	–	
Nausea/vomiting	12	35.3	5	14.7
Neutropenia	5	14.7	1	2.9
Pancreatitis	1	2.9	–	–
Phlebitis	1	2.9	–	–
Sensorial peripheral neuropathy	2	5.9	–	–
Thrombocytopenia	1	2.9	–	–

Adapted from Nicoletto et al., 2015[19].
NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

with BRCA mutation and/or PFI of 6 to 12 months.
- Trabectedin + PLD activity and safety profile appear to be unrelated to the number of previous lines, remaining unchanged in heavily pre-treated patients.

– PLD rechallenge is a valid therapeutic choice for relapsed ovarian cancer patients, since efficacy is not affected and there is no increased toxicity.

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Heavily pre-treated BRCA-mutated patient who relapsed between 6 and 12 months during fourth-line therapy

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Clinical summary

38-year-old patient, good general health. The family history includes mother and maternal aunt with breast cancer.

↓

April 2013: Computed tomography (CT) finding of pelvic mass associated with ascites. Hysterectomy with salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy, appendectomy, multiple peritoneal biopsies, peritoneal washing. No residual tumor. Histology: high-grade serous cancer with stage IIB due to spread to the intraperitoneal pelvic tissues. Germline BRCA1 mutation. Between May and September 2013 chemotherapy with carboplatin AUC5 + PLD 30 mg/m^2 – 6 cycles → Follow-up.

↓

June 2016: Peritoneal PD with omental cake and ascites (PFI > 12 months) → From July to September 2016 second-line chemotherapy with carboplatin AUC4 + gemcitabine 1000 mg/m^2 + bevacizumab 15 mg/kg – 6 cycles with PR → Bevacizumab maintenance therapy.

↓

July 2017: Peritoneal and abdominal lymph node PD (PFI > 12 months) → Between September 2017 and January 2018 third-line chemotherapy with carboplatin AUC4 – 4 cycles with PR → Maintenance with olaparib 400 mg PO BID.

↓

October 2018: Peritoneal and abdominal lymph node PD (PFI 6–12 months) → Between October 2018 and February 2019 fourth-line chemotherapy with trabectedin 1.1 mg/m^2 + PLD 30 mg/m^2 – 6 cycles with PR → Continued for a further 3 cycles, reducing the dose of PLD to 20 mg/m^2.

↓

May 2019: Peritoneal PD associated with lymph node SD → Fifth-line chemotherapy with carboplatin AUC4 iv q21 - 3 cycles (allergic reaction during third cycle) with PR → Therapeutic break.

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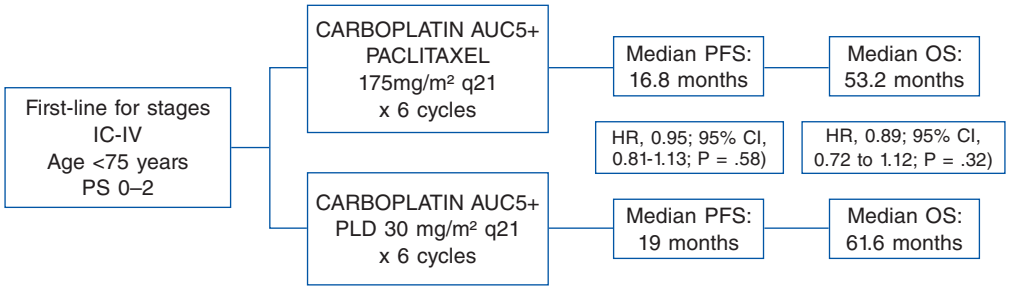
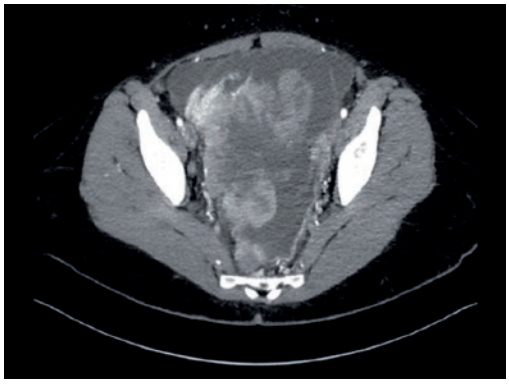


Box 3. *MITO-2 study design and primary outcomes[1].*

History and clinical characterization



- 38-year-old patient, good general health.
- Single, nulliparous, works in the administration department of a local health authority.
- Cancer familiarity:
  - Mother: breast cancer.
  - Maternal aunt: breast and bowel cancer.
  - Paternal uncle: bowel cancer.
- April 2013: CT finding of pelvic mass associated with ascites; CA-125 >1000 IU/mL.

Surgery and first-line treatment

- The patient underwent surgery for hysterectomy with salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy, appendectomy, multiple peritoneal biopsies, and peritoneal washing. No residual tumor. Histology: high-grade serous carcinoma, Stage IIB due to spread to the intraperitoneal pelvic tissues.
- Finding of germline BRCA1 mutation, exon 17.
- From May to September 2013: chemotherapy with carboplatin AUC5 + PLD 30 mg/m^2 for six cycles (180 mg/m^2 in total).
- Continued follow-up until June 2016 (3 years).

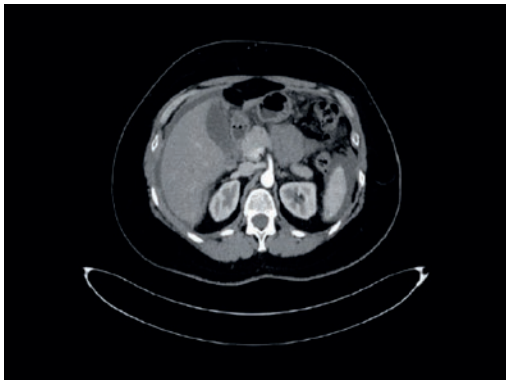
Comment

The choice of systemic treatment for this patient took into account her age, disease stage, and her staunch refusal to receive therapies causing hair loss.

Rationale

The use of carboplatin + PLD in this setting is supported by the results of the randomized MITO-2 study[1], which compared this combination with standard carboplatin + paclitaxel in patients with Stage IC-IV ovarian cancer (Box 3). The investigational arm was not seen to be superior in terms of PFS or OS to the control arm; however, the comparable efficacy results allow considering carboplatin + PLD a valid alternative for patients who are not eligible for the standard treatment. Furthermore, the randomized Phase III CALYPSO study[2] showed superior PFS benefit with carboplatin + PLD over carboplatin + paclitaxel in patients with platinum-sensitive recurrent ovarian cancer (median PFS 11.3 vs. 9.4 months, respectively; HR, 0.821; 95% CI, 0.72-0.94; p=0.005)[2].

Second-line treatment



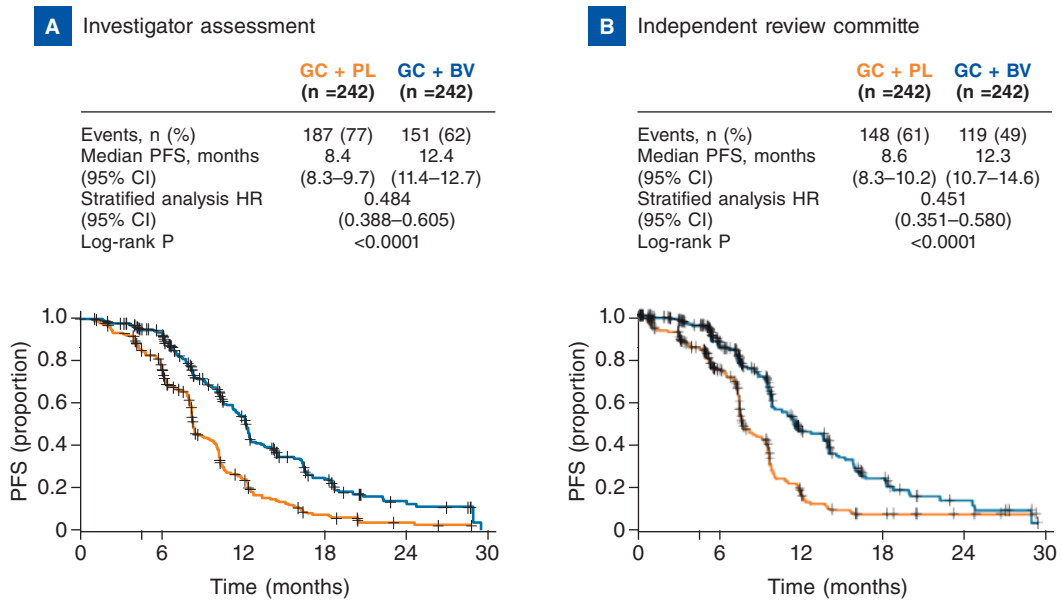


Figure 4. *OCEANS Study: PFS* (adapted from Aghajanian et al., 2012)[3].

- June 2016: the restaging CT scan showed recurrence of peritoneal disease with omental cake and ascites; CA-125 >1000 IU/mL.
- Between July and September 2016: second-line therapy with carboplatin AUC4 + gemcitabine 1000 mg/m^2 + bevacizumab 15 mg/kg for six cycles.
- The CT performed at the end of the chemotherapy showed partial response; CA-125 500 IU/mL.
- From September 2016: the patient continued with bevacizumab maintenance therapy.

Comment

Taking into account the general good health of the patient, the time elapsed since the end of the first-line therapy and the initial debulking surgery, clinicians initially considered the possibility of a secondary debulking surgery. However, the presence of abundant ascites and the spread of the disease, which made optimal debulking unlikely, led to the decision not to perform surgery.

Since bevacizumab had not been administered previously, and in the absence of contraindications regarding its use, a new administration of platinum-based chemotherapy with the antiangiogenic agent in maintenance was decided.

Rationale

Carboplatin + gemcitabine with bevacizumab in maintenance is indicated for the treatment of the first platinum-sensitive recurrence, on the basis of the results obtained in the randomized Phase III OCEANS study, which demonstrated an advantage in terms of PFS (Fig. 4) and ORR with the addition of bevacizumab over the arm receiving chemotherapy alone[3].

Third-line treatment

- July 2017: after ten cycles of bevacizumab maintenance therapy, the CT scan showed progression of disease in the peritoneum and abdominal lymph nodes; CA-125 1200 IU/mL.
- From September 2017 to January 2018: the patient received third-line chemotherapy with carboplatin AUC4 for four cycles.
- The post-treatment CT scan showed partial response; CA-125 600 IU/mL.
- January 2018: started maintenance therapy with olaparib 400 mg PO BID.

Comment

As recurrence occurred a long time after the end of the last systemic treatment and in the absence

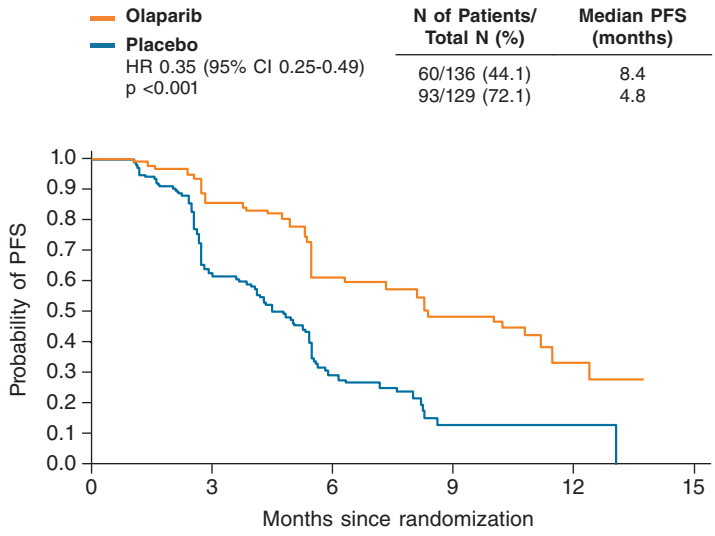


Figure 5. *19 Study: PFS in the total population* (adapted from Ledermann et al., 2012)[4].

of significant residual toxicities, the patient was considered eligible to receive another platinum-based treatment. The partial response observed after four cycles of chemotherapy allowed the initiation of maintenance therapy with the PARP inhibitor olaparib, a treatment that was highly recommended for this patient due to the presence of the BRCA1 germline mutation.

Rationale

Olaparib was approved as maintenance therapy for platinum-sensitive recurrence in BRCA-mutated patients on the basis of the results of the 19 Study, a Phase II clinical trial evaluating the efficacy and safety of the PARP inhibitor compared to placebo in patients with platinum-sensitive high-grade serous ovarian cancer who had had a partial or complete response to their most recent platinum-based regimen[4]. The study achieved its primary endpoint, showing a statistically significant improvement in PFS with olaparib over placebo in the total study population (HR=0.35; 95% CI 0.25–0.49; p<0.00001) (Fig. 5). In the BRCA-mutated patient subgroup (n=136), treatment with olaparib was seen to afford a greater benefit, with a statistically significant improvement in PFS of 6.9 months (HR=0.18; 95% CI 0.10-0.31; p<0.00001; median: 11.2 vs 4.3 months)[4].

Fourth-line treatment

– October 2018: after 9 months of maintenance therapy with olaparib, the CT scan showed progression disease affecting peritoneum and abdominal lymph nodes.
– Between October 2018 and February 2019, the patient received chemotherapy with trabectedin 1.1 mg/m^2 + PLD 30 mg/m^2 every 3 weeks for 6 cycles.
– At the end of the sixth cycle, the CT scan showed PR in all disease sites; decrease in CA-125.
– Considering the response and good tolerance, it was decided to continue with a further three cycles, reducing PLD dose to 20 mg/m^2. The dosage was reduced not to exceed the maximum cumulative dose of anthracycline and not to risk problems of cardiological toxicity.

Comment

At the time of recurrence, the patient was in good general condition, with no occlusive symptoms. Given the limited platinum sensitivity obtained after three previous platinum-based therapies, fourth-line therapy with trabectedin + PLD was proposed. Recently revealed evidence showing the possibility of retreatment with PLD without decreased efficacy or increased toxicity[5,6] further supports the use of trabectedin + PLD in this patient who had received prior PLD.

Rationale

The randomized Phase III OVA-301 trial demonstrated the superior efficacy of trabectedin + PLD

Table 7. *OVA-301 and NIMES-ROC studies: Efficacy with trabectedin + PLD*[7,10]

Study	OVA-301 phase III[7]	NIMES-ROC phase IV[10]
N (platinum-sensitive)	218	218
Median age	56 years	61 years
Previous lines	1 previous line in 100% of patients	≥ 2 previous lines in 72.5% of patients
Median PFS	9.2 months	9.46 months
Median OS	27 months	23.56 months
ORR	35.3%	37.2%

Table 8. *Summary of real-life studies with trabectedin + PLD in context with OVA-301 phase III trial: Efficacy outcomes in platinum-sensitive ovarian cancer*

	N	Trabectedin+PLD treatment	Cycles Median (range)	ORR (%)	Median PFS (months)	Median OS (months)
Phase III: OVA-301[7,11]	218	2nd line in 100% of patients	6 (1-21)*	35.3	9.2	27.0
REAL LIFE						
Single-center[12]	34	≥ 3rd line in 100% of patients	5 (1-16)	32.4	6.1	16.3
OVA-YOND[13]	77	≥ 3rd line in 66.2% of patients	6 (1-21)	31.2	6.3	16.4
PROSPECTYON[14]	91	≥ 3rd line in 48.3% of patients	6 (1-9)	38/48#	6.0/5.9#	1-year 81%/87%#
NIMES-ROC[10]	218	≥ 3rd line in 72.5% of patients	6 (1-24)	37.2	9.46	23.56

*Data only reported in the whole population included at the randomized phase III trial OVA-301 including 115 patients with a PFI lower than 6 months and 218 patients with a PFI beyond 6 months[7]. Appendix Table A1, online only: http://ascopubs.org/doi/full/10.1200/JCO.2009.25.4037
#Results in partially-sensitive patients / fully-sensitive patients.
NE: not evaluated.

over PLD monotherapy as second-line therapy for platinum-sensitive ovarian cancer[7]. An enhanced survival advantage of 6 and 11 months was observed with the use of the combination in patients with PFI 6-12 months and in patients with BRCA1 mutation, respectively[8,9].

The use of trabectedin + PLD beyond second-line therapy of platinum-sensitive ovarian cancer has been assessed in several studies, being the most recent one the international, prospective, observational Phase IV NIMES-ROC study[10]. Median PFS was 9.46 months (95 % CI: 7.9-10.9) whereas median OS was 23.56 months (95% CI: 18.1-34.1). An ORR of 37.2% and a disease control rate of 64.2% were achieved. Although 74.1% of patients were enrolled from the third to the fourth-line of therapy[10], efficacy results were consistent with those of the OVA-301 Phase III trial[7] (Table 7), supporting the use of trabectedin + PLD in heavily pre-treated patients with platinum-sensitive ROC.

The consistency between the results of the NIMES-ROC study (performed in advanced lines)[10] and the phase III trial OVA-301 (performed in second line)[7,11] is also observed when considering other real-life studies previously performed with trabectedin + PLD[12-14]. Table 8 describes the efficacy outcomes observed with trabectedin + PLD in platinum-sensitive ovarian cancer, putting in context different real life studies with OVA-301 phase III trial.

An important consideration with late-line treatment is whether the safety profile of the proposed regimen is compatible with such an advanced line of therapy[15]. The combination of trabectedin + PLD was well tolerated in the intensively treated population included in the NIMES-ROC study[10] (Table 9) and, in fact, the incidence of adverse effects was slightly lower than in the pivotal clinical study OVA-301[7]. This is probably due to the greater experience in the use of trabectedin, in terms of both

Table 9. NIMES-ROC study: Trabectedin + PLD safety profile

Key safety findings	n (%)
Most common Grade 3/4 AEs	
Neutropenia	66 (30.3%)
Anemia	14 (6.4%)
Thrombocytopenia	12 (5.5%)
Asthenia	11 (5%)
AEs leading to trabectedin discontinuation	10 (4.6%)
AEs leading to PLD discontinuation	11 (5%)
Deaths attributed to treatment-related AEs	0 (0%)
Unexpected AEs	0 (0%)

Adapted from Pignata et al., 2020[10].

management of dose adjustments, where necessary, and corrects pre-medication with dexamethasone. Tapering dexamethasone course has been associated with improved tolerability in terms of hepatotoxicity, myelotoxicity, and asthenia. For instance, in addition to intravenous dexamethasone 30 min before treatment, dexamethasone can be given orally the day before treatment and in a tailored decreasing dose during the following 4 days to avoid rebound effects[16].

Trabectedin + PLD safety profile has been shown to be compatible with long-term exposure. In fact, there were no pre-defined limits to the number of trabectedin + PLD cycles administered in clinical trials and the treatment continued while clinical benefit was noted[17]. In the OVA-301 trial, the combination has been administered as second-line treatment for six or more cycles in 52% of patients, having been used for up to 21 cycles with no signs of cumulative toxicities[7]. Of note, trabectedin + PLD is compatible with long-term exposure even when administered in very advanced lines. Nearly 60% of patients in the NIMES-ROC study received ≥ 6 cycles of trabectedin + PLD, having provided clinical benefit for up to 24 cycles[10].

Fifth-line treatment

- May 2019: instrumental restaging showed peritoneal PD associated with lymph node SD.
- The patient was considered suitable for re-treatment with carboplatin AUC4 iv q21.
- During the third cycle, the patient experienced a hypersensitivity reaction to carboplatin.
- In the light of the partial response seen on the CT, it was decided to refer the patient for a therapeutic break.

Conclusions

- Patients with BRCA mutation have been seen to benefit more from chemotherapy, not merely in terms of palliation but also in terms of survival.
- The presence of BRCA mutation in patients with ovarian cancer is usually accompanied by a better prognosis, allowing treatment with multiple lines of therapy. Therefore, designing the correct sequence of treatment becomes even more important for patients to benefit from all available therapies.
- Carboplatin + PLD is a valid first-line alternative for ovarian cancer patients who are not eligible for standard treatment and does not prevent PLD rechallenge in later lines.
- The treatment of ovarian cancer patients with limited sensitivity to platinum (PFI between 6 and 12 months) is controversial and platinum is not always the best treatment option, especially for those patients who have received several consecutive platinum-based lines.
- Trabectedin + PLD combination maintains its activity and safety profile when used in ≥ 3rd lines, allowing to offer a platinum break to intensely pre-treated patients while benefiting from an effective and generally well-tolerated regimen.

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