M-TRAP: Safety and Performance of Metastatic Tumor Cell Trap Device in Advanced Ovarian Cancer Patients.

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Abstract

Objective

Despite radical surgery and chemotherapy, most patients with ovarian cancer die due to disease progression. M-Trap is an implantable medical device designed to capture peritoneal disseminated tumor cells with the aim to focalize the disease. This trial analyzed the safety and performance of the device.

Methods

This first-in-human prospective, multi-center, non-blinded, single-arm study enrolled 23 women with high-grade serous advanced ovarian cancer. After primary or interval debulking surgery, 3 M-Trap devices were placed in the peritoneum of the abdominal cavity. 18-months post-implantation or at disease progression, devices were initially removed by laparoscopy. The primary safety endpoint was freedom from device and procedure-related major adverse events (MAEs) through 6-months post-implantation compared to an historical control. The primary performance endpoint was histopathologic evidence of tumor cells capture.

Results

Only one major adverse event was attributable to the device. 18 women were free of device and procedure related MAEs (78.3%). However, the primary safety endpoint was not achieved ($p=0.131$), primarily attributable to the greater surgical complexity of the M-Trap patient population. 62% of recurrent patients demonstrated tumor cell capture in at least one device with a minimal tumor cell infiltration. No other long-term device-related adverse events were reported. The secondary performance endpoint demonstrated a lack of disease focalization.

Conclusions

The M-Trap technology failed to meet its primary safety objective, although when adjusted for surgical complexity, the study approved it. Likewise, the devices did not

demonstrate the anticipated benefits in terms of tumor cell capture and disease focalization in recurrent ovarian cancer.

Introduction

Epithelial ovarian cancer encompasses a heterogeneous group of cancers and presents a significant cause of gynecologic cancer death for women. Ovarian cancer accounts for 4% of all cancers in women, with nearly 300.000 new cases diagnosed worldwide in 2018, and is the eighth most common cause of cancer death in women [1]. While ovarian cancer in early stages is highly treatable, approximately 75% of diagnosed women have FIGO stage III-IV [2], when the disease has already spread and is much more difficult to manage. Complete cytoreductive surgery, together with chemotherapy, is currently the standard therapy. This complex primary debulking surgery (PDS) is one of the most relevant prognostic factors [3,4], and consist of an extensive and technically challenging procedure that can result in up to 11% of major complications and can have a mortality rate of 0.3% to 5.7% [5]. As an alternative, neoadjuvant chemotherapy followed by interval debulking surgery (IDS) can be carried out in patients who are unlikely to be completely cytoreduced due to the extent of disease, advanced age or comorbidities.

Despite radical surgery and chemotherapy, most patients with advanced ovarian cancer develop recurrence and die due to progressive disease [6,7]. The 5-year survival rate ranges from 30-50% [1]. Based on the poor survival outcomes of this population, there is a clear unmet clinical need to introduce new strategies to improve the management of patients undergoing cytoreductive surgery. The M-Trap (Metastatic Tumor Cell Trap) medical device represents one of these promising strategies. M-Trap is an implantable device designed to capture actively disseminating tumor cells, and to transform a systemic disease into a focalized disease where surgery and chemotherapy have proven efficacy [8]. M-Trap biomimetic is comprised of a non-resorbable scaffold with a Type I collagen coating. In preclinical studies, implantation of the M-Trap generated a foreign body reaction with an initial inflammatory effect characterized by multinucleated giant and polymorphonuclear cells progressively transforming into a fibrous

connective tissue response, with the migration and proliferation of fibroblasts, neovascularization and deposition of collagen. The combined adhesive capabilities of the reticulated M-Trap device coated with collagen further supported by the sustained foreign body reaction, generated an artificial pre-metastatic niche that served as a preferential niche for tumour cell homing, remodeling the pattern of tumour dissemination. Surgical removal of the biomimetic device with the captured tumor cells resulted in significantly improved outcomes [9].

On the basis of preclinical data, the MTRAP-2016-01 clinical trial was designed to evaluate i) the safety of the M-Trap device, based on device and procedure-related major adverse events (MAEs) compared to historical controls [10], and ii) M-Trap performance, as determined by histological evidence of tumor cell capture. Secondary objectives included the collection of long-term safety data to support device safety and post-market surveillance and to assess disease focalization.

Material and methods

Study design

The MTRAP-2016-01 study (NCT03085238) is a prospective, multi-center, non-blinded, single-arm study that enrolled patients with advanced ovarian cancer with FIGO (International Federation of Gynecology and Obstetrics) stage IIIC PDS and residual tumor ≤1cm, or stage IIIC or Stage IV disease after neoadjuvant chemotherapy prior IDS and complete resection or residual tumor ≤1cm. The study was conducted at eight tertiary gynecologic oncology reference centers in Spain, between March 2017 and July 2019. The study was approved by the Ethical and Clinical Research Committee of the Vall d'Hebron Campus Hospital MTRAP2016-01, which complies with the standards of good clinical practice (CPMP/ICH/135/95), the Spanish Royal Decree (RD) 223/2004, and the Declaration of Helsinki of 1975. Included patients were duly informed, and they freely provided written informed consent. Inclusion and exclusion criteria are available in Supplementary Material.

Outcomes

The primary endpoint was to demonstrate the safety of the M-Trap device, as measured by freedom from device- and procedure-related MAEs through 6-months post-implantation, defined as severe complications based on the Clavien–Dindo scale [11], as well as the Comprehensive Complication Index (CCI) [12], with non-inferiority to historical controls [10]. Adverse events are described in Supplementary Material. The primary performance endpoint was histopathologic evidence of tumor cell capture after device explant.

Secondary safety endpoints included the incidence of other device-related and all other AEs long-term. Corresponding number and percentage of patients were categorized by: total number of AEs/SAEs; total number of device-related AEs/SAEs; total number of unanticipated device-related AEs/SAEs; total number of procedure-related AEs/SAEs; total number of device

deficiencies. Overall mortality rate was also presented. Secondary performance endpoints included semi-quantitative scoring of disease focalization.

Procedure

Patients underwent PDS or IDS by laparotomy, following the institution's standard protocols. A Peritoneal Carcinomatosis Index (PCI) was documented pre- and post-debulking. Up to three M-Trap devices were surgically implanted in the right and left paracolic gutters and behind segment 6 of the liver within the patient's peritoneal cavity at the time of surgical resection. These anatomical locations were selected taking into account the transcoelomic metastasis process, the most common form of ovarian cancer metastasis [13] and an easier access for subsequent removal by laparoscopy (see Supplementary Fig. S1 for M-Trap description). The mesh was placed and secured using six points of a non-absorbable suture (Supplementary Fig. S2). Eligible patients underwent a complete screening assessment and test program within 21 days before the surgery, considering the study subject's baseline, and at each follow-up visit at 1, 3, 6, 9, 12, 15 and 18 months at the gynecologic oncology units (Supplementary Table S1). After completion of carboplatin/paclitaxel-based standard chemotherapy, M-Trap devices were initially removed via minimally invasive surgery (laparoscopy) under one of the following cases: at the final 18-month post-implantation time point, in the presence of an adverse event necessitating device removal or after disease progression as defined by objective RECIST 1.1 and CA-125 criteria [14,15]. A single-use specimen retrieval system (Endobag™) was used to recover the extracted devices. Occurrence of any device- or procedural-related AEs during the removal were recorded. Semi-quantitative scoring scale of disease focalization was based on direct visual assessment, CT scan and ultrasound performed at the time of device removal (Supplementary Table S2). Pathology examination of the explanted devices was performed as

described (Supplementary Material). Also, any ascites present, peritoneal washings and a minimum of two peritoneal biopsies from designated locations were obtained.

Statistical Analysis

Statistical analyses were generated using SAS® version 9.4. The primary safety endpoint was analyzed using a unilateral one sample test for binomial proportion at the 5% level in comparison to historical control population derived from Patankar et al. (2015) [10]. The exact bilateral 95% CI was calculated. Statistical test for the primary safety endpoint: H0: M-Trap freedom MAEs incidence ≤90% - Non-inferiority margin (25%), Versus HA: M-Trap freedom MAEs incidence >90% - Non-inferiority margin (25%). A modified primary analysis was also performed using a freedom from MAEs incidence rate adjusted for the surgical complexity of the study population. Total number of extended procedures was split into four classes: 0, 1, 2, 3 and more. The primary and secondary performance endpoints were assessed with exact one-sided 90% CIs.

Results

Study design

Twenty-three (23) patients, from the initially 35 enrolled in the study, were treated with M-Trap devices, as 11 patients did not meet the eligibility criteria, (6 not high grade serous ovarian carcinoma patients, 1 patient with residual tumor >1cm, 1 patient with residual tumor R0 and 3 stage IIb patients) and 1 patient withdrew her consent to the study. Baseline characteristics and physical findings of the patients included in the study indicated an 80% of Stage IIIC ovarian carcinomas, a mean PCI score of 22.5 and around a 65% of IDS surgical procedures (Table 1). Among the 23 enrolled patients, the median follow-up was 489 days (Q1-3 = 305-563 days) for the 19 patients who completed the study. A summary of patient disposition resulting from the trial is presented in Fig. 1.

Surgeries including omentectomy (100%), unilateral/bilateral salpingo-oophorectomy (96%), hysterectomy (87%), diaphragm peritonectomy (74%), pelvic (61%) and para-aortic (65%) lymph node dissection, large bowel resection (48%), and pelvic peritonectomy (39%) among other procedures, are shown in Supplementary Table S3. All women had three M-Trap devices successfully implanted into the abdominal cavity, except in one case where only two M-Trap devices were placed because the third place was required for a colostomy. There were no device malfunctions or deficiencies. Five (21.7%) device removals were planned per protocol after 18 months' follow-up and 15 (65.2%) device removals were planned because of disease progression defined by objective RECIST and CA-125 criteria. One device was removed because of a device-related AE, and one device was removed for a MAE unrelated to the device. One patient died, and the three devices were removed post-mortem, as described in Table 2. Most devices (66%) were easy to locate and 50% were easy to remove laparoscopically. Of the three locations, M-Trap devices behind segment 6 of the liver were the most difficult to find and retrieve (Supplementary Table S4). No AEs were reported during the device removal

procedure. M-Trap devices were removed from 21 of the 23 women at a median of 16.0 months (Q1-3: 7-18 months) after implantation. 14 of the 15 patients with recurrent disease had their device removed, at a median time of 6.5 months (Q1-3: 5.5-7.0 months) after implantation for platinum-resistant patients and 16.0 months (Q1-3: 14.0-18.0 months) for platinum-sensitive patients. The mean PFS was 569.7 days (range 406-733.4 days) (Supplementary Fig. S3).

Safety analysis of the M-Trap clinical trial

The primary safety endpoint, freedom from device and procedure-related MAEs through 6 months is presented in Table 3, using both measures together, Clavien-Dindo Scale and the CCI. It was analyzed using an historical control freedom from MAE incidence rate of 90% [10]. Eighteen women were free of device and procedure related MAEs at 6 months (78.3%); thus, the primary safety endpoint was not achieved (95% CI–56.3% to 92.5%; P=0.1309). The safety analysis in the Patankar [10] historical control study assessed complications through 30 days. The results showed that 87% of the women were free of device and procedure-related MAEs at 30 days, which was statistically significant (95% CI–66.4% to 97.2%; P=0.018) (Table 3). One major device-related adverse event occurred and resulted in device removal (enterocutaneous fistula).

Further analysis demonstrated that the surgical complexity of the M-Trap patient population was significantly greater than historical controls, as measured by the number of extended procedures during the debulking surgery. When the analysis was adjusted for surgical complexity based on the Patankar [10] definition, results demonstrate statistical significance, and the study passes its primary safety endpoint (P<0.0001), at both 6 months and 30 days (Supplementary Table S5 and Table S6).

Secondary safety endpoints included the incidence of other device-related AEs and all other AEs long- term. No unanticipated M-Trap device-related AEs or SAEs occurred. Eleven women had a total of 30 SAEs during the trial (Supplementary Table S7).

Performance analysis of the M-Trap devices

Tumor cells were captured in 58% of implanted devices (Supplementary Table S8). The results showed that tumor cells were captured in at least one device in 48% of all patients. Overall, 62% of recurrent patients who successfully underwent device removal demonstrated tumor cell capture in at least one device (8 of 13 patients). Mean tumor cell infiltration into the M-Trap devices removed from these 13 recurrent patients was 1.7%.

The secondary performance analysis demonstrated a lack of clinical efficacy in the population of recurrent patients, with no evidence of disease focalization. In 14 of the 15 recurrent patients, disease focalization scores were reported, 5 patients (35.7%) had no evidence of disease focalization (score V), 8 patients (57.1%) had only minimal disease focalization (score IV), and 1 patient had moderate disease focalization (score III). No women had >50% of recurrent disease in the M-Trap device.

At the time of M-Trap device removal, seven women (33%) had ascites, and in five (83%) of these cases malignant cells were present. Malignant cells were found in peritoneal washings in 7 (43.8%) of the 16 women without ascites. Abdominal and pelvic tissue biopsies were taken from 21 women. Most tumors were in the left (n=6, 26%) and right abdominal gutter peritoneum (n=7, 30%).

Immunohistochemistry was performed on explanted devices to assess the cellular immune response. There was marked presence of macrophages (CD68 cells), moderate presence of CD3 T-cells and mild presence of CD20 B-cells at all three device locations. Immunohistochemistry for CK AE1/AE3, CK7, ER, P53, WT1, CD31 and D240 was performed to characterize tumor

252 cells captured by the device (Fig. 2). The tumor cells responses ranged from nil to marked to
253 CK AE1/AE3, CK7, ER, P53, and WT1. When considering the complete population, response
254 was minimal since both recurrent and non-recurrent patients were considered in calculation of
255 the mean and median (which was 0, showing no epithelial tumor cells infiltrating the device).
256 CD31 and D240 showed positively stained vessels, primarily with no infiltrating tumor cells.
257 Infiltrating tumor cells were only detected in 5 devices.

Discussion

The M-Trap clinical study evaluated the safety and efficacy of the M-Trap medical device in advanced ovarian cancer, with a clear necessity of new treatment options that can extend the survival. The target patient population included those with high risk of recurrence within the group of stages III-IV (high PCI, large tumor burden, PDS and IDS with residual tumor, among others). The selection of this very high-risk population was based on achieving a relevant number of recurrences during the 18-month study follow-up period to evaluate the safety and efficacy objectives of the trial. For the stage III-IV patient population, literature shows that the median OS ranges from 24-50 months [3,17-21], while PFS is only 12-21 months [16-18,22]. Of the 23 subjects included, 15 patients underwent device removal due to disease progression within the 18-month study duration (65.2%), with a median PFS rate similar to that published despite including patients with a very high risk of recurrence.

Regarding the primary safety objective, a total of five MAEs occurred in the M-Trap patient population, one was device-related and four were related to the debulking procedure. The safety profile reported in this trial was based on Patankar definition [10], which states that the number of extended surgical procedures is the strongest risk factor for complications. Using this definition, one woman enrolled in the study underwent one extended procedure. The remaining subjects underwent more than one extended procedure, as follows: two procedures n=8; three procedures n=5; four procedures n=6; five procedures n=3. Further analysis demonstrated that the surgical complexity of this population was significantly greater than historical controls; in addition, the historical stratification was based on a retrospective cohort representing a bias compared to the retrospectively conducted M-Trap study. This complex PDS is one of the most relevant prognostic factors [3,4], and consist of an extensive and technically challenging procedure with frequent complications. In fact, it can result in up to 11% of major complications and can have a mortality rate of 0.3% to 5.7% [5]. When the analysis was adjusted for surgical

complexity, results demonstrated statistical significance, and the study passed its primary safety endpoint ($P<0.0001$). The secondary safety analysis revealed no other device-related adverse events. Procedure-related events were anticipated and considered normal and acceptable after major abdominal surgery [5].

Regarding the performance endpoints, the study demonstrated histological evidence of tumor cell capture. Overall, 62% of recurrent patients demonstrated tumor cell capture in at least one device. Mean tumor cell infiltration into the M-Trap devices removed from these 13 recurrent patients was only 1.7%. Though there was no prespecified criteria for the primary performance objective, the device did not meet expectations for histological evidence of tumor cell capture. Nevertheless, and although the secondary performance analysis showed a lack of clinical efficacy, the PFS non-inferiority data in a context of very high-risk population with complex surgeries might indicate a residual benefit of the limited disease focalization. Further confirmation of this clinical benefit might result from a relevant improvement of the tumor cell capture efficacy of the M-Trap devices by new technical developments and/or by the selection of a more appropriate patient population.

This may also be related to the preclinical studies where we assessed the tumor cell capture efficacy of the M-Trap device in murine models of advanced ovarian cancer mimicking a recurrent disease. Tumor cells capture by the devices and the consequent focalization of peritoneal carcinomatosis had a significant benefit in survival outcomes, which was even improved in the group of animals in which devices were removed [9]. The immunohistochemistry of explanted devices demonstrated an expected inflammatory response to the device, characterized by a marked presence of macrophages, moderate presence of CD3 T-cells, and mild presence of CD20 B-cells at all three device locations. To this regard, we could not find significant differences between the explanted devices from the patients and from the preclinical models [9]. On the contrary, it is likely that preclinical studies did not reflect the

extensive surgeries performed in the target patient population selected for this study, resulting in numerous intraperitoneal adhesions develop that could be preventing tumor cells to reach the devices. In addition, the very rapid process of epithelialization of the deperitonized areas completely covering the devices could be further impairing tumor cell capture. This vast re-epithelization process occurring in the whole peritoneal cavity upon the extensive debulking surgery could be also generating additional niches for the homing of disseminating tumor cells, thus actively competing and decreasing the effectiveness of the M-Trap devices. Our group is already working on modified M-Trap devices incorporating pharmacological and non-pharmacological elements to prevent local re-epithelization and support the accessibility of tumor cells. Alternatively, the clinical evaluation of this focalization strategy could be primarily evaluated in patients with R=0 primary surgeries where the absence of residual disease and low tumor burden could be a more appropriate clinical scenario for M-Trap technology. This would also circumvent the incapacity to assess the presence of microscopic or residual disease in patients at the time of surgical implantation of the M-Trap devices that does not permit in comparison to the preclinical models to discriminate between already disseminated disease and actively disseminating disease during the clinical trial period. Likewise, the fact that the preclinical studies have been conducted in immunocompromised mice models represents an additional drawback that impedes to evaluate the contribution of the immune system. Complementary appropriate preclinical studies to address these issues should be conducted in large animal models (i.e., porcine models) before any new clinical trial.

Our study has some limitations. Although the selection of patients allowed results in a shorter period of time, it led to an increase in the number of surgical procedures. This inclusion criterion may have contributed negatively to the primary safety endpoint of the study, as defined by the absence of MAEs through 6-months post-implantation compared to an historical control, regardless of whether they are device or procedure related.

Conclusion

The MTRAP-2016-01 clinical trial failed to meet its primary safety objective, although this failure was primarily attributable to the greater surgical complexity of our M-Trap patient population, rather than risks inherent to the device itself, as only one major adverse event was attributable to the device.

M-Trap did not demonstrate the anticipated benefits in terms of tumor cell capture and disease focalization. Based on the results of the clinical study, no clinical benefit was demonstrated when using the M-Trap device as directed in women with high-grade serous advanced ovarian cancer at high risk of recurrence. Further studies with modified M-Trap devices and a selection of patients at primary surgeries with no residual disease and low tumor burden are required before ruling out the possible benefit of M-Trap in tumor cell capture and disease focalization of peritoneal carcinomatosis.

Conflict of interest statement: L.A.-A. and M. A are currently employees of Nasasbiotech, a substantial equity owner in MTrap Inc.; Nasasbiotech has received corporate funding from MTrap Inc. to perform some of the studies.

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Table Legends

Table 1. Summary of baseline characteristics and physical examination of the 23 patients.

Table 2. Reasons for M-Trap device removal.

Table 3. Non-Inferiority of freedom from device and procedure-related MAEs at 30 days and 6 Months.

Figure Legends

Fig. 1. Clinical trial patient disposition.

Fig. 2. Histological staining of M-Trap device captured tumor cells. Positive staining for CK AE1/AE3, CK7, WT1, ER and p53. (Nuclei: blue; tumor cells: brown; 20X). CD31 positive IH showing vascular invasion (nuclei: blue; endothelial cells: brown; 20X), a moderate inflammatory infiltrate (CD3+ T cells), several multinucleate giant cells (CD68+) near the implanted device and moderate cytotoxic T cells infiltrating the device (CD8+) (nuclei: blue; inflammatory cells: brown; 20X). M-Trap device (*), tumor cells (→), multinucleated giant cells (⇦), vascularization (→), vascular invasion (∇). Scale bar: 100 μm.

Table 1. Summary of baseline characteristics and physical examination of the 23 patients.

Characteristics/Physical Examination	**n = 23**
Mean Age (years ± SD [range])	59.4 ± 9.5 [39-76]
Ovarian Cancer Stage (n (%))	IIIC = 18 (78.3) IVA = 1 (4.3) IVB = 4 (17.4)
ECOG Performance Status (n (%))*	Grade 0 = 16 (69.6) Grade 1 = 7 (30.4)
Menopausal Status (n (%))	Pre-menopausal = 2 (8.7) Post-menopausal = 18 (78.3) Hysterectomy = 3 (13.0)
Gynecological Examination: Nodules/bumps in cul-de-sac (n (%)) Body Mass Index (Kg/m^2); Mean ± SD Blood Pressure (mmHg); Mean ± SD	 No = 12 (52.2) Yes = 11 (47.8) 25.8 ± 3.7 126.7 ± 16.6 / 73.8 ± 9.5
Smoking Status (n (%))	Non-smoker = 15 (65.2) Current smoker = 4 (17.4) Past-smoker = 4 (17.4)
PCI score at baseline (n; Mean (Q1-3))	n=13; 22.5 (19-29)
CA-125 biomarker at baseline (U/ml); Median (Q1-3))	Overall=159.0 (49.7-412.0) PDS=795.7 (322.5- 1827.0) IDS=74.0 (17.1-159.0)
Surgical procedure (n (%))	PDS= 8 (34.8) IDS=15 (65.2) - With 3 rounds chemotherapy= 11 (73.3) - With 4 rounds chemotherapy= 4 (26.7)

*ECOG: Grade 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.

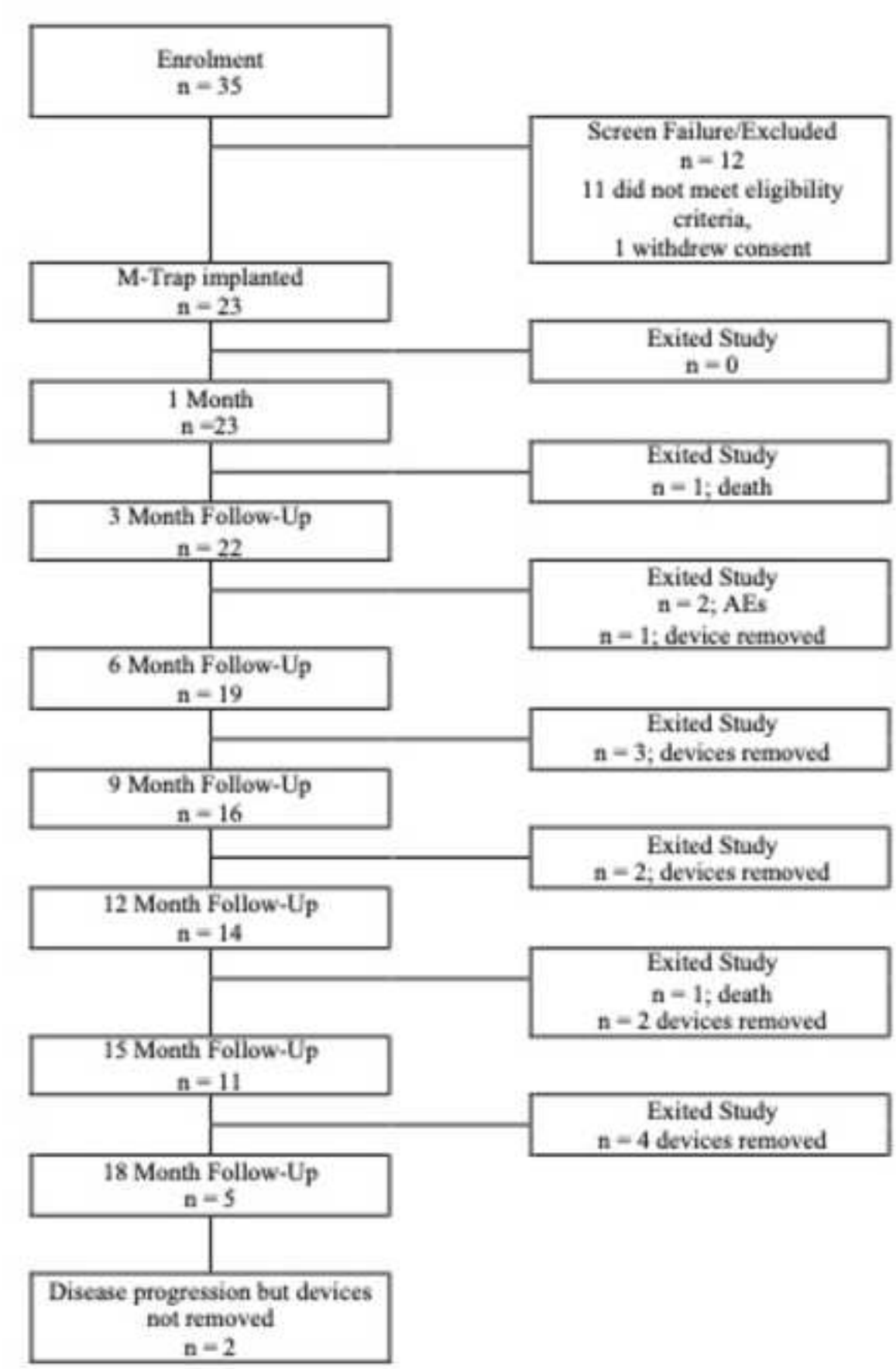
Table 2. Reasons for M-Trap device removal.

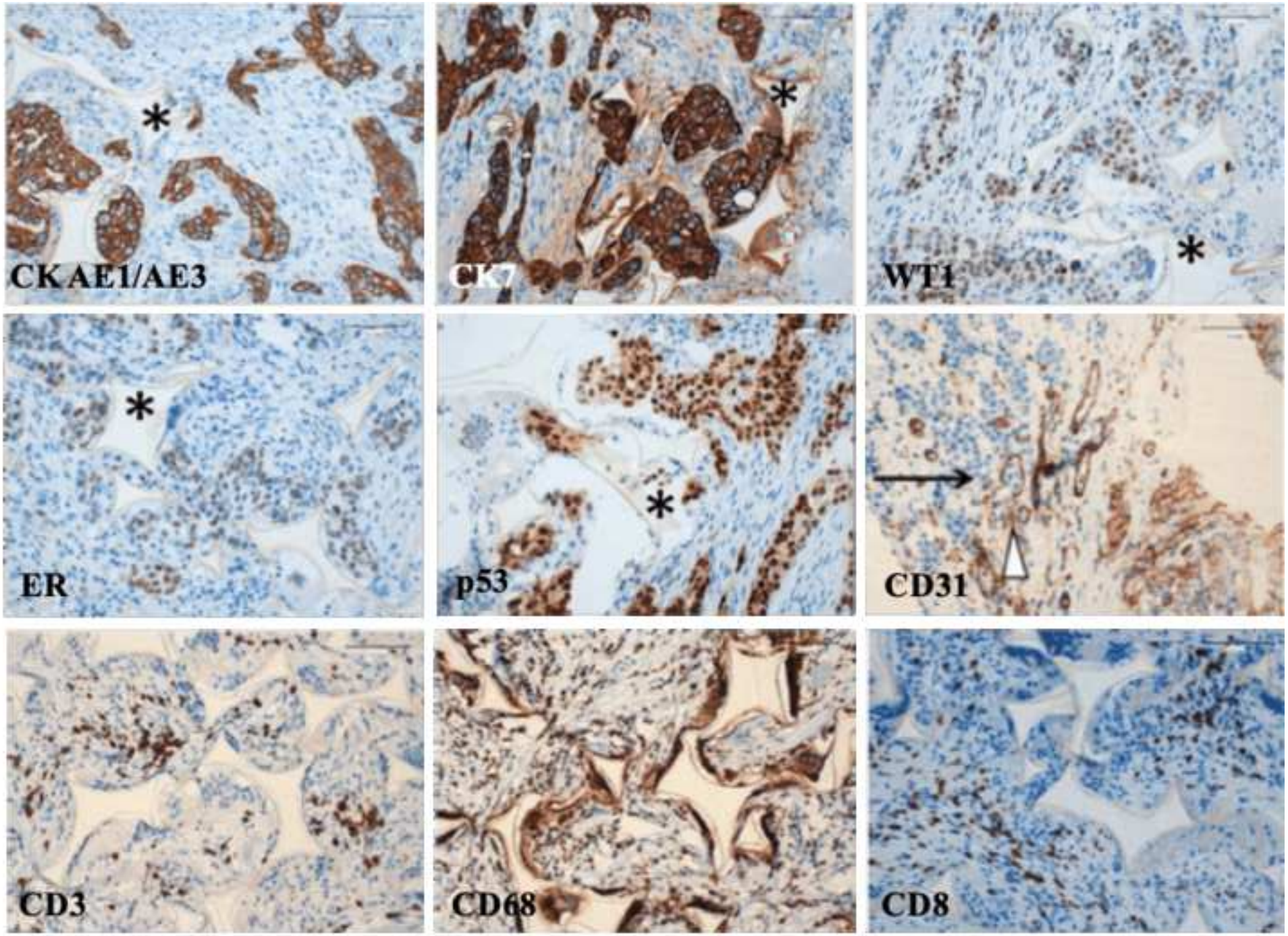
Reason for Planned Device Removal	Treated Patients (n=23; n (%))
Device-related adverse event necessitating device removal	1 (4.3)
Disease progression as defined by objective RECIST 1.1 and CA-125 criteria[21]	15* (65.2)
Final 18-month post-implantation time point	5 (21.7)
Major adverse event not related with the device	1 (4.3)
Devices removed post-mortem	1 (4.3)

*Includes two patients with disease progression whose devices could not be removed due to the presence of significant adherence syndrome throughout abdominal cavity and decline in health resulting from carcinomatosis.

Table 3. Non-Inferiority of freedom from device and procedure-related MAEs at 30 days and 6 Months.

	30 Days (n=23) (Patankar[10] Study Endpoint)	**6 Months (n=23) (M-Trap Study Endpoint)**
No (%)	3 (13.0)	5 (21.7)
95% CI (No)	[2.8% - 33.6%]	[7.5% - 43.7%]
Yes (%)	20 (87.0)	18 (78.3)
95% CI (Yes)	[66.4% - 97.2%]	[56.3% - 92.5%]
Missing	0	0
p-Value	0.0181	0.1309





Supplementary Material

Inclusion & exclusion criteria

Patients were included if they were aged 18 years or older, high-grade serous ovarian carcinoma, ECOG performance status of 0-1 and one of the following: stage IIIC PDS and residual tumor ≤1cm; or stage IIIC or Stage IV disease after neoadjuvant chemotherapy prior IDS and complete resection or residual tumor ≤1cm. The exclusion criteria were life expectancy of <3 months, pregnancy, previous abdominal radiotherapy, significant active concurrent medical illnesses, history of cancer within 5 years and known hypersensitivity to carboplatin or paclitaxel or concurrently using other antineoplastic agents.

Adverse events (AEs) were coded using the Medical Dictionary of Regulatory Activities. The severity of the AEs was graded according to National Cancer Institute Common Terminology Criteria for AEs version 4.0. MAEs include shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation, unplanned reintubation, or adverse events leading to removal of the device, including infection, seroma formation, mesh migration, bowel obstruction, adhesions, and local cancer progression through the abdominal wall at M-Trap. Serious adverse events (SAEs) were defined as an adverse event that meets at last one of the following: fatal, life threatening, requires in-patient hospital admission or prolongation of existing hospital stay or other medically important serious event.

Pathological analysis

Pathology analysis on explanted M-Trap devices was performed at a core laboratory. Each device was fixed in 10% neutral-buffered formalin, and embedded in paraffin. Tissue samples were sectioned (3-5μm) and hematoxylin and eosin stained. Immunohistochemistry (IH) against CD3, CD20 and CD68 was performed to assess the cellular immune response; against CKAE1/AE3, CK7, ER, P53, and WT1 to characterize tumor cells captured by the device semi-

quantitatively and against CD31 and D240 to evaluate the presence of lymphovascular invasion of tumor cells. Antibodies and concentrations listed in following Table.

Immunohistochemistry (IH) against CD3, CD20, CD68, CKAE1/AE3, CK7, ER, P53, WT1, CD31 and D2-40. Antibodies and concentrations.

Antibody	Dilution	Clone	Code	Source
CD3	RTU*	Polyclonal	IR503	Agilent Technologies-DAKO, Santa Clara, United States
CD20	RTU	L26	IR604	Agilent Technologies-DAKO, Santa Clara, United States
CD68	RTU	PG-M1	IR613	Agilent Technologies-DAKO, Santa Clara, United States
CK AE1/AE3	RTU	AE1/AE3	IR053	Agilent Technologies-DAKO, Santa Clara, United States
CK7	RTU	OV-TL12/30	IR619	Agilent Technologies-DAKO, Santa Clara, United States
ER	RTU	EP1	IR084	Agilent Technologies-DAKO, Santa Clara, United States
P53	RTU	DO-7	IR616	Agilent Technologies-DAKO, Santa Clara, United States
WT1	RTU	6F-H2	IR055	Agilent Technologies-DAKO, Santa Clara, United States
CD31	RTU	JC70A	IR610	Agilent Technologies-DAKO, Santa Clara, United States
D2-40	RTU	D2-40	IR072	Agilent Technologies-DAKO, Santa Clara, United States

*RTU: Ready to use.

Table S1. Schedule of study assessments.

Examination/ Assessment	Visit 0 Screening Within 21 days	Visit 1 Procedure (D0)	Visit 2 1M (±1W)	Visit 3 3M* (±2W)	Visit 4 6M* (±2W)	Visit 5 9M (±1M)	Visit 6 12M (±1M)	Visit 7 15M (±1M)	Visit 8 18M (±1M)
Signed Informed Consent	X								
Eligibility criteria check	X	X							
Demographics, medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Biomarker CA-125	X			X	X	X	X	X	X
CT scan	X			X	X	X	X	X	X
Ultrasound		X	X	X	X	X	X	X	X
PCI	X	X							
Cytology/biopsy									X
Pathology (explant)									X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

*The first visit after completion of chemotherapy was considered the baseline visit for assessing disease progression, 3M in IDS and 6M in PDS.
PCI: Peritoneal Carcinomatosis Index.

Table S2. Disease focalization scoring.

Degree of Disease Focalization	Definition
I	Approximately 100% of recurrent disease contained in M-Trap devices
II	Approximately 75% of recurrent disease contained in M-Trap devices
III	Approximately 50% of recurrent disease contained in M-Trap devices
IV	Approximately 25% of recurrent disease contained in M-Trap devices
V	No obvious recurrent disease contained in M-Trap devices

Table S3. Extensive upper abdominal and other surgical procedures.

Extensive Upper Abdominal Procedure	**n (%)**
Diaphragm peritonectomy	17 (73.9)
Splenectomy	8 (34.8)
Full-thickness diaphragm resection	3 (13.0)
Partial hepatectomy	1 (4.3)
Distal pancreatectomy	0
Cholecystectomy	8 (34.8)
Other Surgical Procedure	**n (%)**
Unilateral/bilateral salpingo-oophorectomy	22 (95.7)*
Hysterectomy	20 (86.9)
Omentectomy	23 (100.0)
Large bowel resection	11 (47.8)
Pelvic lymph node dissection	14 (60.9)
Para-aortic lymph node dissection	15 (65.2)
Appendectomy	15 (65.2)
Small bowel resection	4 (17.4)
Ileostomy	2 (8.7)
Colostomy	1 (4.3)
Other surgical procedures	19 (82.6)
Pelvic peritonectomy	9 (39.1)
Celiac trunk lymphadenectomy	5 (21.7)
Others	12 (52.2)

* One of the patients presented with a primary peritoneal tumor.

Table S4. Ease of locating and removing M-Trap devices.

	Location of Device n (%)			
	Right Paracolic (pelvic) Gutter (n=20)	**Left Paracolic (pelvic) Gutter (n=21)**	**Behind Liver Segment 6 in Peritoneal Cavity (n=21)**	**Total (n=62)**
Ease of Location				
Could not be located	0	1 (4.8)	0	1 (1.6)
Some difficulty to locate	4 (20.0)	6 (28.6)	10 (47.6)	20 (32.3)
Easy to locate	16 (80.0)	14 (66.7)	11 (52.4)	41 (66.1)
Ease of Removal				
Could not be removed via laparoscopy*	2 (10.0)	3 (14.3)	4 (19.0)	9 (14.5)
Great difficulty to remove laparoscopically	0	0	2 (9.5)	2 (3.2)
Some difficulty to remove laparoscopically	4 (20.0)	6 (28.6)	10 (47.6)	20 (32.3)
Easy to remove laparoscopically	14 (70.0)	12 (57.1)	5 (23.8)	31 (50.0)
Missing	0	0	0	0

*Includes 4 patients whose all devices could not be removed due to the presence of significant adherence syndrome throughout abdominal cavity (n=3), one of them with decline in health resulting from carcinomatosis, and one patient whose devices were removed during the laparotomy to treat an enterocutaneous fistula (n=1).

Table S5. M-Trap rate of freedom from device- or procedure-related MAEs through 6 months using MAEs expected incidence adjusted for the study population number of extended procedures.

6 Months	Number of Extended Procedures (Patankar Definition[10])				
	0 (n=0)	1 (n=1)	2 (n=8)	3 or more (n=14)	N=23 patients
N Patankar	1352	1214	254	50	2870
N M-Trap	-	1	8	14	23
No (%)	-	0 (0.0)	2 (25.0)	3 (21.4)	4.9%
95% CI (No)	-	[16.7% - 100.0%]	[3.2% - 65.1%]	[4.7% - 50.8%]	[1.6% - 11.1%]
Yes	-	1 (100.0%)	6 (75.0%)	11 (78.6%)	95.1%
95% CI (Yes)	-	[16.7% - 100.0%]	[34.9% - 96.8%]	[49.2% - 95.3%]	[88.9% - 98.4%]
Missing	-	0	0	0	0
p-Value	<0.0001				

Table S6. M-Trap rate of freedom from device- or procedure-related MAEs through 30 days using MAEs expected incidence adjusted for the study population number of extended procedures.

30 Days	Number of Extended Procedures (Patankar Definition[10])				
	0 (n=0)	1 (n=1)	2 (n=8)	3 or more (n=14)	N=23 patients
N Patankar	1352	1214	254	50	2870
N M-Trap	-	1	8	14	23
No (%)	-	0 (0.0)	1 (12.5)	2 (14.3)	2.6%
95% CI (No)	-	[16.7% - 100.0%]	[0.3% - 52.7%]	[1.8% - 42.8%]	[0.5% - 7.9%]
Yes	-	1 (100.0%)	7 (87.5%)	12 (85.7%)	97.4%
95% CI (Yes)	-	[16.7% - 100.0%]	[47.3% - 99.7%]	[57.2% - 98.2%]	[92.1% - 99.5%]
Missing	-	0	0	0	0
p-Value	<0.0001				

Table S7. Serious adverse events. Most SAEs were reported under Infections & Infestations (n=8 in 5 women) and Gastrointestinal SOC (n=7 in 5 women). The most frequently reported SAEs were UTI (n=3 in 2 women), post-operative wound infection (n=2 in 2 women) and intestinal obstruction (n=3 in 2 women).

SOC Name	Patients (N=23)		
	NAE (1)	n (2)	% (3)
ALL	**30**	**11**	**47.8**
INFECTIONS AND INFESTATIONS	**8**	**5**	**21.7**
Urinary tract infection	3	2	8.7
Postoperative wound infection	2	2	8.7
Escherichia sepsis	1	1	4.3
Pneumonia	1	1	4.3
Pyelonephritis acute	1	1	4.3
GASTROINTESTINAL DISORDERS	**7**	**5**	**21.7**
Intestinal obstruction	3	2	8.7
Enterocutaneous fistula	1	1	4.3
Intestinal anastomosis complication	1	1	4.3
Intestinal perforation	1	1	4.3
Pancreatic fistula	1	1	4.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**4**	**3**	**13.0**
Postoperative respiratory failure	2	1	4.3
Postoperative fever	1	1	4.3
Spinal column injury	1	1	4.3
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**4**	**1**	**4.3**
Thrombocytopenia	2	1	4.3
Febrile neutropenia	1	1	4.3
Neutropenia	1	1	4.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**3**	**3**	**13.0**
Pulmonary embolism	2	2	8.7
Bronchoplegia	1	1	4.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**1**	**4.3**
Death	1	1	4.3
INFECTIONS AND INFESTATIONS; INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**1**	**1**	**4.3**
Staphylococcal bacteremia; intervertebral discitis	1	1	4.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS; BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1**	**1**	**4.3**
Procedural hemorrhage; disseminated intravascular coagulation	1	1	4.3
VASCULAR DISORDERS	**1**	**1**	**4.3**
Distributive shock	1	1	4.3

1= Number of SAEs; 2 = Number of Patients with at least one AE; 3 = Corresponding percentage of patients (N/total no. of patients).

Table S8. Histological evidence of tumor cell capture after device explant by device location.

	Right Paracolic (Pelvic) Gutter (N=22)	Left Paracolic (Pelvic) Gutter (N=23)	Behind Liver Segment 6 in Peritoneal Cavity (N=23)	Other (N=0)	Total (N=68)
N	20*	21	21	0	62
No (%)	10 (50.0)	14 (66.7)	12 (57.1)	0 (0.0)	36 (58.1)
90% CI (No)	[NA -69.8%]	[NA -83.2%]	[NA -74.9%]	--	[NA -68.4%]
Yes (%)	10 (50.0)	7 (33.3)	9 (42.9)	0 (0.0)	26 (41.9)
90% CI (Yes)	[30.2% - NA]	[16.8% - NA]	[25.1% - NA]	--	[31.6% - NA]
Missing**	2	2	2	0	6

*One device needed to be removed during surgery, as the site was required for a colostomy.
** Includes two patients with disease progression whose devices could not be removed due to the presence of significant adherence syndrome throughout abdominal cavity and decline in health resulting from carcinomatosis.

Fig. S1. Image of the M-Trap device (left) and a microscopic magnification (right; 150X) showing the biodurable 3D porous polyurethane scaffold. The M-Trap scaffold is a reticulated, polycarbonate polyurethane-urea matrix, coated with Type I collagen, biocompatible and biostable per ISO-10993, available in an oval configuration of 15mm (width) x 50mm (length) x 5mm (thickness).

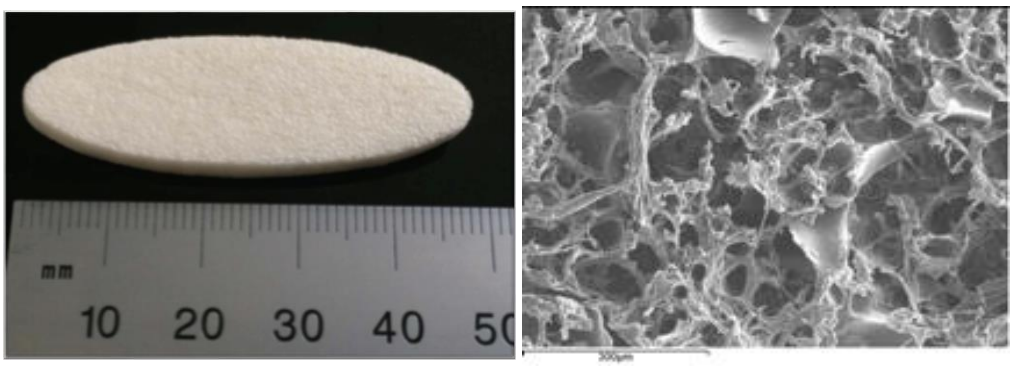


Fig. S2. M-Trap device surgically implanted within the peritoneal cavity, secured using six points of a non-absorbable suture.

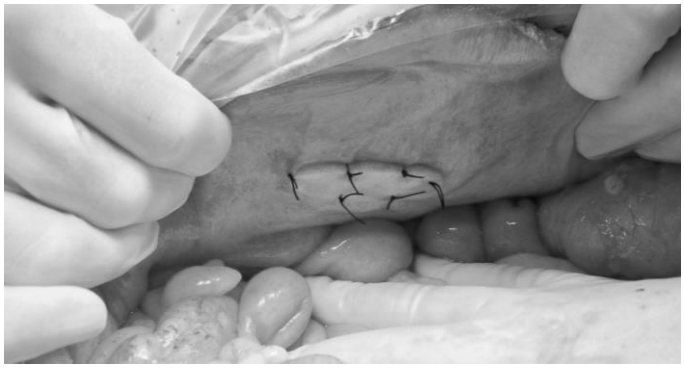
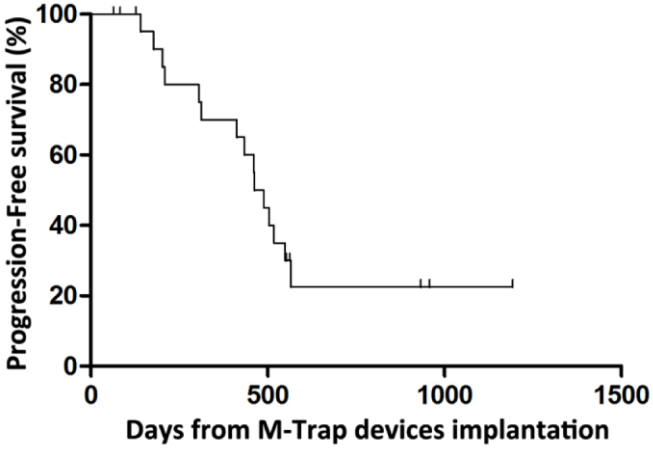


Fig. S3. Kaplan-Meier curve for assessing Progression-Free Survival time after M-Trap devices implantation.



-M-Trap safety&performance clinical trial in high-grade serous advanced ovarian cancer

- M-Trap implantable medical device to capture peritoneal disseminated tumor cells

- Adverse events of complex debulking surgeries conditioned primary safety endpoint

- Devices captured tumour cells but focalization was minimal in recurrent patients