Check for updates

Metronomic Capecitabine With Cyclophosphamide Regimen in Unresectable or Relapsed Pseudomyxoma Peritonei

Alessandra Raimondi,[1] Salvatore Corallo,[1] Monica Niger,[1] Maria Antista,[1] Giovanni Randon,[1] Federica Morano,[1] Massimo Milione,[2] Shigeki Kusamura,[3] Dario Baratti,[3] Marcello Guaglio,[3] Chiara Cremolini,[4] Federica Marmorino,[4] Maria Di Bartolomeo,[1] Marcello Deraco,[3] Filippo De Braud,[1,5] Filippo Pietrantonio[1,5]

Abstract

No standard treatment for unresectable or recurrent pseudomyxoma peritonei has been defined. Our study showed that metronomic capecitabine with cyclophosphamide is a well tolerated and potentially active regimen in this disease setting. Neutrophil to lymphocyte ratio baseline < 3, compared with ≥ 3, showed a significant association with a prolonged progression-free survival.

Background: No standard treatment for advanced unresectable pseudomyxoma peritonei (PMP) has been defined so far. PMP is traditionally considered chemoresistant but nonrandomized series showed promising results with regimens for gastrointestinal tumors. **Patients and Methods:** We conducted a single-center prospective single-arm trial. Inclusion criteria were histologically confirmed PMP, unresectable or progressive to surgery/previous treatments. Patients received a continuous metronomic regimen with capecitabine (625 mg/m^2 twice per day) with cyclophosphamide (50 mg/d) until progression, unacceptable toxicity, or consent withdrawal. The primary end point was progression-free survival (PFS); secondary end points were disease control rate (DCR), overall survival (OS), and safety. Exploratory analyses were the variation of circulating tumor biomarkers and neutrophil to lymphocyte ratio (NLR). **Results:** Twenty-three consecutive patients were enrolled from April 2015 to October 2017. At a median follow up of 22.4 months, median PFS was 9.5 months and 1-year OS rate was 73.7%. Overall, DCR was 87% and 6 (27%) patients achieved disease control ≥12 months. The safety profile was manageable: 26% of patients reported Grade 3 drug-related adverse events and none Grade 4/5. NLR baseline <3 versus ≥ 3 was associated with prolonged PFS (12.6 vs. 3.4 months; $P = .0001$). **Conclusion:** Metronomic capecitabine with cyclophosphamide is a well tolerated regimen in unresectable/recurrent PMP, and its safety profile favorably compares with previously investigated regimens.

Clinical Colorectal Cancer, Vol. 18, No. 2, e179-90 © 2019 Elsevier Inc. All rights reserved.

Keywords: Capecitabine, Metronomic chemotherapy, Neutrophils-to-lymphocytes ratio, Pseudomyxoma peritonei, Systemic therapy

All of the data and information on materials are available at the Istituto Nazionale dei Tumori di Milano, Fondazione IRCCS, upon specific request.

Funding for this study provided by Italian Association for Cancer Research (AIRC) grant 2016 entitled: Pseudomyxoma peritonei: optimizing treatment by exploring the connections between oncogene mutations and inflammation; Principal Investigator, M. Deraco.

[1]Medical Oncology Department
[2]Pathology Department
[3]Surgery Department, Istituto Nazionale dei Tumori di Milano, Fondazione IRCCS, Milan, Italy
[4]Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[5]Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

Submitted: Feb 20, 2019; Revised: Mar 9, 2019; Accepted: Mar 25, 2019; Epub: Apr 1, 2019

Address for correspondence: Filippo Pietrantonio, MD, Medical Oncology Department, Istituto Nazionale dei Tumori di Milano, Fondazione IRCCS, Via Venezian 1, 20133, Milan, Italy
E-mail contact: filippo.pietrantonio@istitutotumori.mi.it

1533-0028/$ - see frontmatter © 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.clcc.2019.03.002

Introduction

Pseudomyxoma peritonei (PMP) is an extremely rare disease, with an estimated incidence of 1 to 2 per million per year, characterized by mucinous tumor implants throughout the peritoneum and progressive accumulation of mucinous ascites.[1] PMP includes mucinous tumors endowed with a wide morphologic and biologic spectrum of aggressiveness: from indolent neoplasms to cancers with invasive potential.[2] PMP mostly originates from an appendiceal mucinous neoplasm and its main histological features are the presence of abundant mucinous deposits with scattered neoplastic cells whereas lymph node or distant metastases are uncommon.[3] In the fourth edition of the World Health Organization Classification of Tumours of the Digestive System PMP has been classified as low or high grade according to the histological criteria initially defined by Bradley et al,[4] although controversies about its pathologic classification still remain.[5]

The standard treatment of PMP is cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), aiming at extirpating gross and microscopic disease, respectively.[6,7] This approach, compared with historical data of debulking surgery, offers a significant overall survival (OS) benefit, with a 20-year OS rate $> 70\%$.[8,9] Thus, up to 30% of patients will develop tumor recurrences and eventually die because of progressive disease (PD). The major prognostic factors after curative surgery are the completeness of cytoreduction, peritoneal carcinomatosis index (PCI), and pathological grade,[10] even if molecular biomarkers—such as Kirsten rat sarcoma 2 viral oncogene homolog and guanine nucleotide binding protein, alpha stimulating mutations—with prognostic effect have been studied.[11-13]

In the setting of unresectable or relapsed PMP, no consensus has been reached regarding the optimal treatment. Several studies showed the potential benefit for repeated surgery, associated or not with HIPEC, in selected patients, but poor evidence is available about systemic chemotherapy.[14,15] PMP is endowed with a low proliferation rate and a borderline malignant potential, thus being traditionally considered chemoresistant. Moreover, PMP generally shows an indolent natural history, potentially characterized by phases of spontaneous disease stabilization or extremely slow growth. Therefore, the evaluation of the real effect of medical treatments represents a major challenge, and even the definition of the methods and criteria of disease response assessment is still an open question.[16]

Nevertheless, nonrandomized series reported satisfactory outcomes in patients with unresectable or recurrent PMP receiving fluoropyrimidine-based regimens[17,18]: metronomic capecitabine and bevacizumab,[12,19] FOLFOX (oxaliplatin and 5-fluoruracil),[20,21] mitomycin C and capecitabine (Table 1).[12,17,20,22] However, such systemic treatments might be associated with relevant toxicity and/or costs. Metronomic schedules might be preferred, because of their favorable safety profile, as well as antiangiogenic and immunomodulatory properties, hence potentially improving treatment outcomes in these low-proliferating tumors.[23,24]

On the basis of this evidence, we conducted a single-center prospective study of treatment with metronomic capecitabine and cyclophosphamide in patients with unresectable or recurrent PMP.

Patients and Methods

Study Population

Patients affected by histologically confirmed PMP of appendiceal origin were eligible for this study. Inclusion criteria included: age older than 18 years; histologically confirmed PMP; disease relapse after standard CRS and HIPEC not eligible for surgery, or alternatively primary disease judged unresectable by our multidisciplinary team; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, and adequate bone marrow, hepatic, and renal function. Exclusion criteria were: potential repeated surgery in case of treatment response or preplanned surgery after neoadjuvant treatment, even if with debulking intent; clinically significant cardiovascular disease or other uncontrolled comorbidities; history of malignancy in the previous 3 years; women with childbearing potential and men must agree to use adequate contraception from enrollment until at least 3 months after the last study drug administration.

This single-center study was conducted according to the Good Clinical Practices and Declaration of Helsinki and was approved by the local ethics committee (study protocol INT 14/14 v.3). All subjects provided written informed consent before all of the study procedures.

Treatment Administration

The patients enrolled in the protocol received a continuous treatment schedule of oral metronomic chemotherapy with capecitabine 625 mg/m^2 twice per day with cyclophosphamide 50 mg daily. Treatment was continued until PD, consent withdrawal, or unacceptable toxicity.

Study End Points

The primary study end point was progression-free survival (PFS), defined as time from enrollment to investigator-assessed progression or death, whichever occurred first. Secondary end points were: OS, defined as time from enrollment to death or last follow-up for alive patients; disease control rate (DCR) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria[25] (evaluated by a radiologist with particular expertise in the setting of PMP) to define complete response (CR), partial response (PR), stable disease (SD), and PD; duration of disease control, defined as time from the first documented response or SD to PD or death; and treatment safety profile. For disease evaluation, for each patient we reviewed the baseline radiological imaging and the previous radiological scans (whenever available), to assess the disease evolution over time, and disease progression should be documented at 2 consecutive scans per inclusion criteria. Afterward, we identified the most defined and clearly assessable lesions, that we chose as target lesions; however, nonclearly definable lesions were chosen as nontarget lesions. Mucinous ascites was quantified by identifying the major diameter of the localized ascites accumulations and they were considered as nontarget lesions, if deemed significant. Despite the implicit biases of this approach, in absence of specific guidelines on this topic, we classified as disease progression, besides the standard criteria, all of the cases of unequivocal progression of the localized ascites accumulations chosen as nontarget lesions or the evidence of new significant localized or diffused ascites

Table 1 Efficacy of Chemotherapy Regimens in Advanced Pseudomyxoma Peritonei

Regimen	Median PFS, Months	OS	RR, %	DCR, %
Capecitabine With Bevacizumab[12]	8.2	1-Year rate 91%	20	87
5-Fluorouracil- or Capecitabine-Based[17]	7.6	Median value 56 months	24	56
FOLFOX[20]	8.0	Median value 26 months	20	65
Mitomycin C With Capecitabine[22]	NR	1-Year rate 84% 2-Year rate 61%	8	38

Abbreviations: DCR = disease control rate; FOLFOX = oxaliplatin and 5-fluoruracil; OS = overall survival; PFS = progression-free survival; RR = response rate.

accumulations. Moreover, during the treatment, at any disease evaluation, the radiologist compared the new imaging with baseline as well as previous evaluations during the study protocol and the pattern of pretreatment disease evolution was considered, to better interpret the findings.

Exploratory end points were the correlation of circulating markers: carcinoembryonic antigen (CEA), cancer antigen (CA)-19.9 and CA-125 level, and neutrophil to lymphocyte ratio (NLR) with outcomes.

Study Procedures

Baseline evaluations included: medical history and concomitant medications registration; physical examination and vital signs; complete blood count and biochemical profile; electrocardiogram; computed tomography (CT) of chest, abdomen, and pelvis; assessment of circulating tumor markers including CEA, CA-19.9 and CA-125.

During treatment, patients were evaluated with physical examinations, complete blood cell counts and biochemical profiles, circulating tumor markers and assessment of adverse events before each cycle, considered as 4 weeks of continuous treatment. CT scans were performed every 12 weeks during the treatment phase until PD, with the possibility to anticipate the radiological evaluation if clinically appropriate, at the discretion of the investigators. Adverse events and treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0.[26]

Statistical Analysis

Descriptive statistics were used to summarize patients and disease characteristics. The Kaplan–Meier method was used for survival analyses to estimate PFS and OS. The log rank test was used to test for differences between groups and to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Statistical significance threshold was set to a canonical 2-tailed 0.05 value. GraphPad Prism software version 5.02 (GraphPad Software, La Jolla, CA) was used to perform all the statistical analyses.

Results

Patients and Disease Characteristics

A total number of 23 consecutive patients were enrolled from April 2015 to October 2017 (Supplemental Figure 1). Baseline patient and disease characteristics are shown in Table 2. Median age was 62 years (interquartile range, 44-68 years), patients were predominantly male (61%) and with ECOG performance status 0 (70%). All patients but 1 were affected by low-grade PMP, classified according to previously described criteria.[4] Overall, 16/23 patients (70%) had received a previous CRS/HIPEC procedure and intraoperative PCI was superior or equal to 20 in 77% of them.

Treatment Outcome

At a median follow-up of 22.4 months, median PFS was 9.5 months (Figure 1A) and median OS was not reached, although 1-year OS rate was 73.7% (95% CI, 47.3%-88.3%; Figure 1B). Median treatment duration in the overall population was 8.9 months.

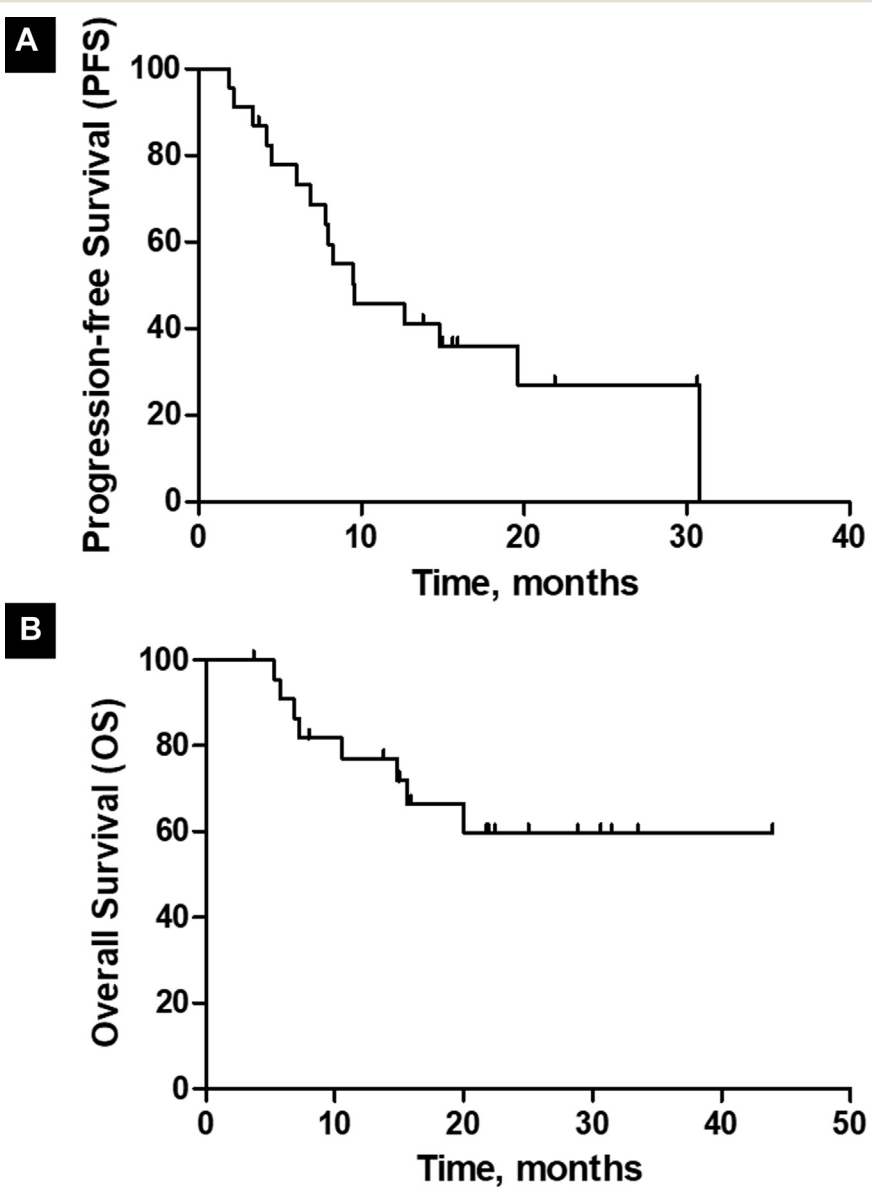
Overall no CR, 1 PR, 19 SD, and 2 PD as best disease response to treatment were observed. In 1 case, best response was not assessed

Table 2 Baseline Patients and Disease Characteristics

Characteristic	Value
Median Age (IQR), Years	62 (44-68)
Sex	
Male	14 (61)
Female	9 (39)
ECOG Performance Status	
0	16 (70)
1	7 (30)
Grade	
Low	22 (96)
High	1 (4)
Previous CRS/HIPEC	
No	7 (30)
Yes	16 (70)
Peritoneal Cancer Index	
Median (range)	27 (9-39)
<20	3 (23)
≥20	10 (77)
Unknown	3
CRS/HIPEC Not Performed	7
Time From CRS/HIPEC to Relapse	
Median (range), months	12.7 (1.8-67.9)
≤12 months	8 (50)
>12 months	8 (50)

Data are presented as n (%) except where otherwise noted.
Abbreviations: CRS = cytoreductive surgery; ECOG = Eastern Cooperative Oncology Group; HIPEC = hyperthermic intraperitoneal chemotherapy; IQR = interquartile range.

Figure 1 Survival Analysis. Progression-Free Survival (A) and Overall Survival (B) Curves in the Overall Study Population

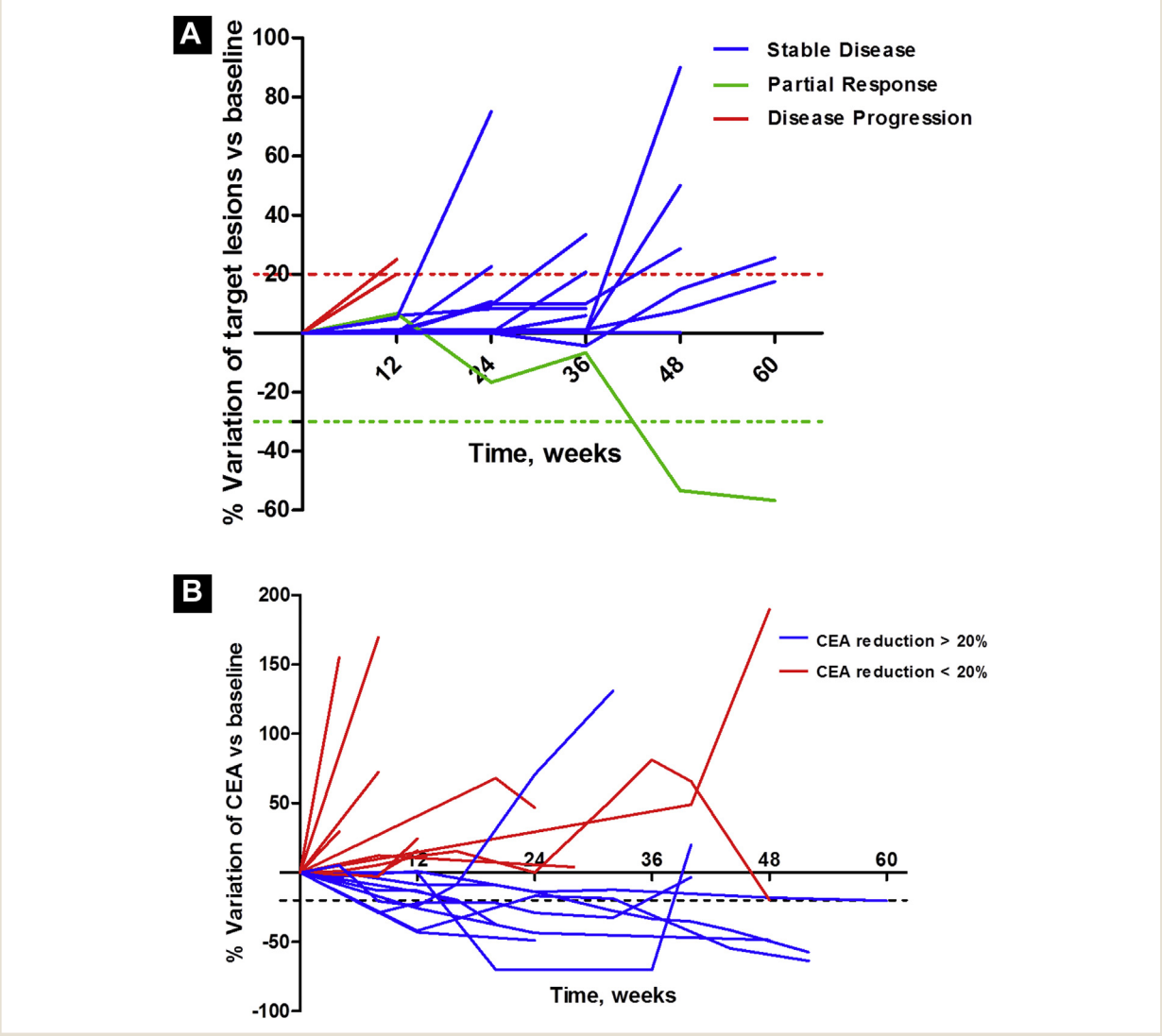


because the patient discontinued treatment before the first radiological evaluation for the occurrence of persistent creatinine increase of Grade 2 not related to the study treatment. In the intention to treat population, overall response rate was 4% and DCR was 87% (Figure 2A). In the 22 patients evaluable for disease response, 6/22 patients (27%) achieved disease control ≥12 months and 3 of 22 (14%) ≥18 months.

Safety Profile

All patients received at least 1 treatment cycle and were evaluable for safety analysis. The safety profile was manageable: 22/23 (96%) patients reported any grade treatment-related adverse events, 6/23 (26%) patients experienced Grade 3 drug-related adverse events, and none Grade 4/5 adverse events. As expected, the main toxicities were respectively, anemia, hand-foot syndrome, fatigue, neutrophil count decreased, diarrhea, nausea, platelet count decreased, and mucositis (Table 3). Overall, 4 of 23 (17%) patients required a capecitabine dose reduction to the first level (75% of the total predicted dose) and 1 patient of 23 (4%) to the second level (50% of the total predicted dose) for the occurrence of adverse events, whereas none received a dose reduction for cyclophosphamide. Overall, 1 patient discontinued treatment for drug-related adverse events, whereas 3 patients discontinued because of medical decision, in consideration of the prolonged disease control and of the persistence of Grade 1/2 treatment-related toxicities.

Figure 2 Response Evaluation Criteria In Solid Tumors and Carcinoembryonic Antigen (CEA) Best Tumor Response and Dynamics. (A) The Percentage Variation versus Baseline of the Sum of the Longest Diameters of Target Lesions During Treatment for Each Patient. In Red, Blue, and Green Are Reported Patients With PD, SD, and PR as Best Response, Respectively. (B) The Percentage Variation versus Baseline of CEA During Treatment for Each Patient Is Illustrated, With Patients Achieving a CEA Reduction Superior or Inferior to 20% in Blue and Red, Respectively



Circulating Biomarkers

A significant tumor marker reduction, considered superior to the cutoff of 20% of the baseline value, was seen in 11/20 (55%) patients for CA-19.9, 4/10 (40%) for CA-125 and 10/20 (50%) for CEA (Figure 2B). CA-19.9 or CA-125 decrease superior or inferior to 20% were not associated with PFS ($P = .53$ and $P = .47$, respectively). However, CEA reduction superior to 20% was nonsignificantly associated with prolonged PFS compared with <20% reduction, 21.7 versus 7.8 months (HR, 0.37 [95% CI, 0.12-1.14]; $P = .08$; Figure 3A) and showed a nonsignificant trend for longer OS, median OS not reached versus 32 months (HR, 0.42 [95% CI, 0.41-8.41]; $P = .42$; Supplemental Figure 2A).

Regarding NLR, median NLR baseline value was 1.7. We chose a baseline NLR cutoff value of 3, on the basis of previous literature data.[26] NLR baseline <3 resulted as statistically significantly associated with a prolonged PFS compared with NLR baseline ≥3, median PFS 12.6 versus 3.4 months (HR, 0.003 [95% CI, 0.0-0.06]; $P = .0001$; Figure 3B) and showed a trend toward an improved OS (HR, 0.18 [95% CI, 0.02-1.84]; $P = .15$; Supplemental Figure 2B).

We tested the potential association between NLR and survival outcome (PFS and OS) in the overall data set of patients affected by advanced unresectable or relapsed PMP treated with a chemotherapeutic fluoropyrimidine-based regimen at our institution in this study and in the 2 previously published trials.[12,20] Overall, 44 patients with available data were included in the analysis. Median baseline NLR value was 2.2. Baseline NLR value < 3 versus ≥3 showed a statistically significant association with improved PFS

Table 3 Treatment-Related Adverse Events in the Overall Study Population

Adverse Event	G1	G2	G3	G4
Anemia	6 (26)	4 (17)	0	0
Hand-Foot Syndrome	4 (17)	1 (4)	3 (13)	0
Fatigue	3 (13)	3 (13)	1 (4)	0
Neutrophil Count Decreased	2 (9)	1 (4)	2 (9)	0
Diarrhea	3 (13)	1 (4)	1 (4)	0
Nausea	3 (13)	1 (4)	0	0
Platelet Count Decreased	1 (4)	0	0	0
Mucositis	1 (4)	0	0	0

Data are presented as n (%).
Abbreviation: G = grade.

(median PFS, 14.8 vs. 3.37 months; HR, 0.06 [95% CI, 0.01-0.26]; $P = .0002$), and showed a trend toward an increased OS (median OS, 47.1 vs. 19.1 months; HR, 0.40 [95% CI, 0.11-1.43]; $P = .16$; Figure 4A and B).

Discussion

The treatment of unresectable or relapsed PMP is still matter of debate and lacks a well established standard of care. In this light, we performed a single-center prospective study on the safety and efficacy of a capecitabine with cyclophosphamide metronomic regimen. The study treatment resulted to be active and endowed with a manageable safety profile in this patient population.

We report a median PFS of 9.5 months and a median OS not reached at the median follow-up of 22.4 months, with a 1-year OS rate of 73.7%. These results are consistent with the available previous literature evidence and they are acceptable compared with formerly investigated treatment options for what concerns PFS, because FOLFOX4 and metronomic capecitabine with bevacizumab regimens obtained a median PFS of approximately 8 months,[12,20] and a pooled analysis including patients treated with fluoropyrimidine-based chemotherapy reported a median PFS of 7.6 months.[17]

Considering tumor response, we appreciated a remarkable rate of prolonged disease control (superior to 12 months in 27% of patients and to 18 months in 14% of cases), although we did not obtain a significant disease shrinkage, except for 1 case. This result was in line with our expectations, because PMP is a tumor endowed with a low proliferation rate and a borderline malignant potential. However, because the natural history of PMP is of slow growth and possible phases of spontaneous disease stabilization or extremely slow growth, we were not able to clearly appreciate the real effect of chemotherapy on the disease natural course. Of note, we included in this study only patients with demonstrated disease progression at 2 consecutive CT scans.[23,24]

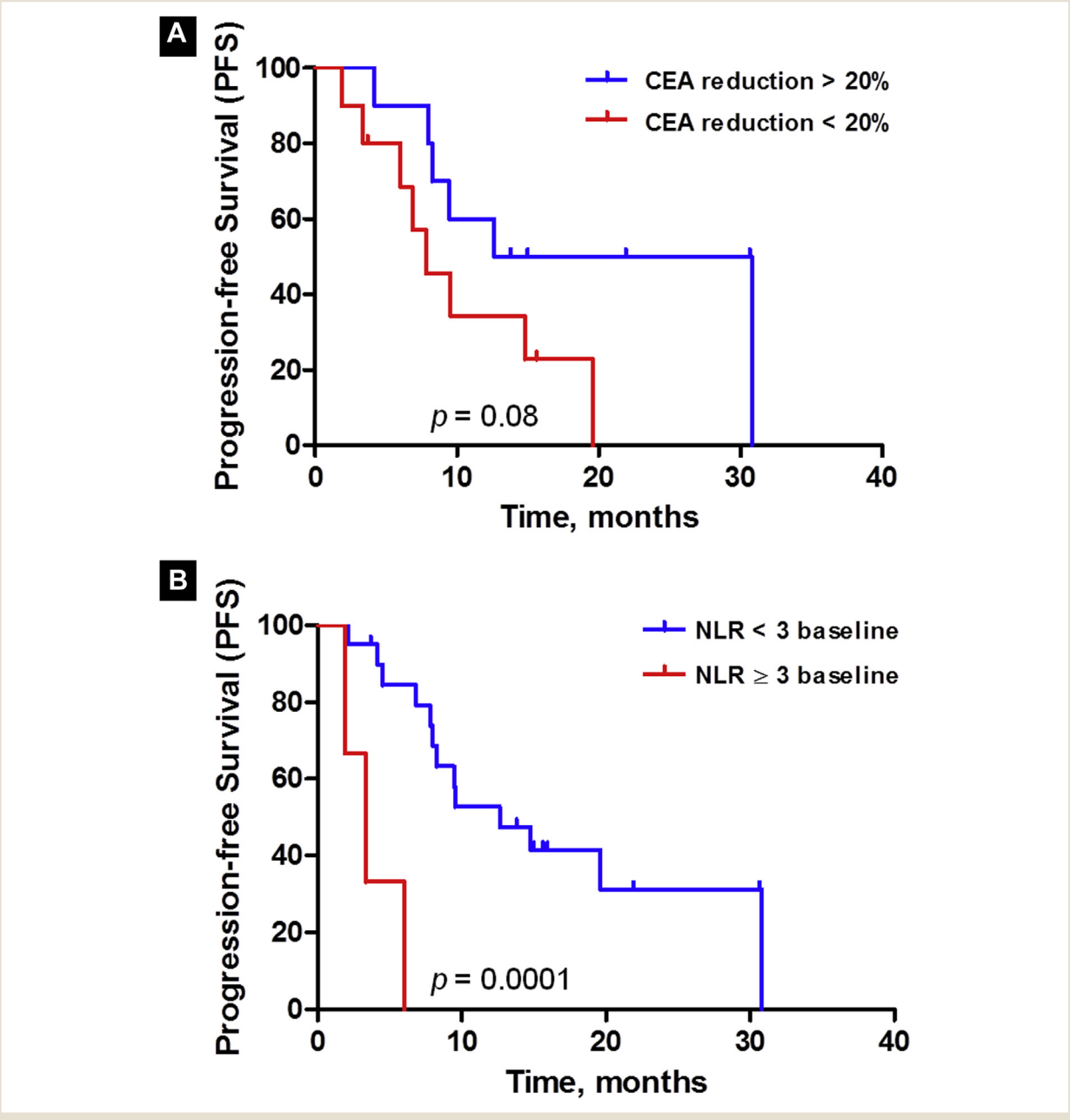
The safety profile was manageable, with most patients experiencing at least 1 any grade adverse event and 26% patients Grade 3 drug-related adverse events, but no Grade 4 adverse events and treatment-related death. The toxicities recorded were mainly cutaneous/mucosal, hematological, and gastrointestinal, being consistent with previous literature data[12,17] and clinical experience, with no unexpected or serious adverse events potentially related to the study treatment. There was only 1 treatment discontinuation because of drug-related adverse events. However, in 3 cases treatment was discontinued because of shared decision-making between clinician and patient, supported by the persistence of Grade 1/2 adverse events besides a prolonged disease control. In fact, PMP is an indolent disease and, in this perspective, treatment holidays seem to be feasible and safe in patients who show a long-term disease stabilization.

Regarding tumor markers, we appreciated a reduction superior to 20% of the baseline value in tumor markers, consistent with literature data.[17,22] Biomarker reduction could be considered a signal of tumor response to treatment even in case of clinical disease stabilization, because of the indolent growth of PMP.

Considering the potential immune modulating property of metronomic chemotherapy, we analyzed the balance between the leukocyte components, belonging to innate and adaptive immunity, namely NLR, showing that NLR baseline value inferior to 3 was significantly associated with a prolonged PFS in the study population and in a larger data set. These results are consistent with previous evidence obtained in other tumor settings, including colorectal cancer, showing an association between elevated pretreatment NLR and worse clinical outcome, although a well established cutoff value has not been defined.[27-30] However, the consistency of this correlation and its potential pathogenetic mechanisms are still unclear. First of all, the role of tumor microenvironment and, specifically, inflammation in cancer development and progression has been pointed out.[31] One possible explanation relies on the association of elevated NLR with systemic inflammation, because neutrophilic reaction is able to suppress the cytolytic activity of effector immune cells and to promote the development of an immunosuppressive and protumorigenic tumor microenvironment. Other hypotheses account for the imbalance of systemic cytokines or the hyperproduction of tumor growth factors and extracellular matrix proteases able to stimulate the tumor microenvironment toward cancer progression.[32] In the setting of PMP, previous studies have shown an association of elevated baseline NLR (using different cutoff values) with poor disease-free survival and OS in patients who undergo CRS/HIPEC.[33-35] However, to our knowledge, this is the first report on the potential prognostic value of NLR in the setting of relapsed/unresectable PMP.

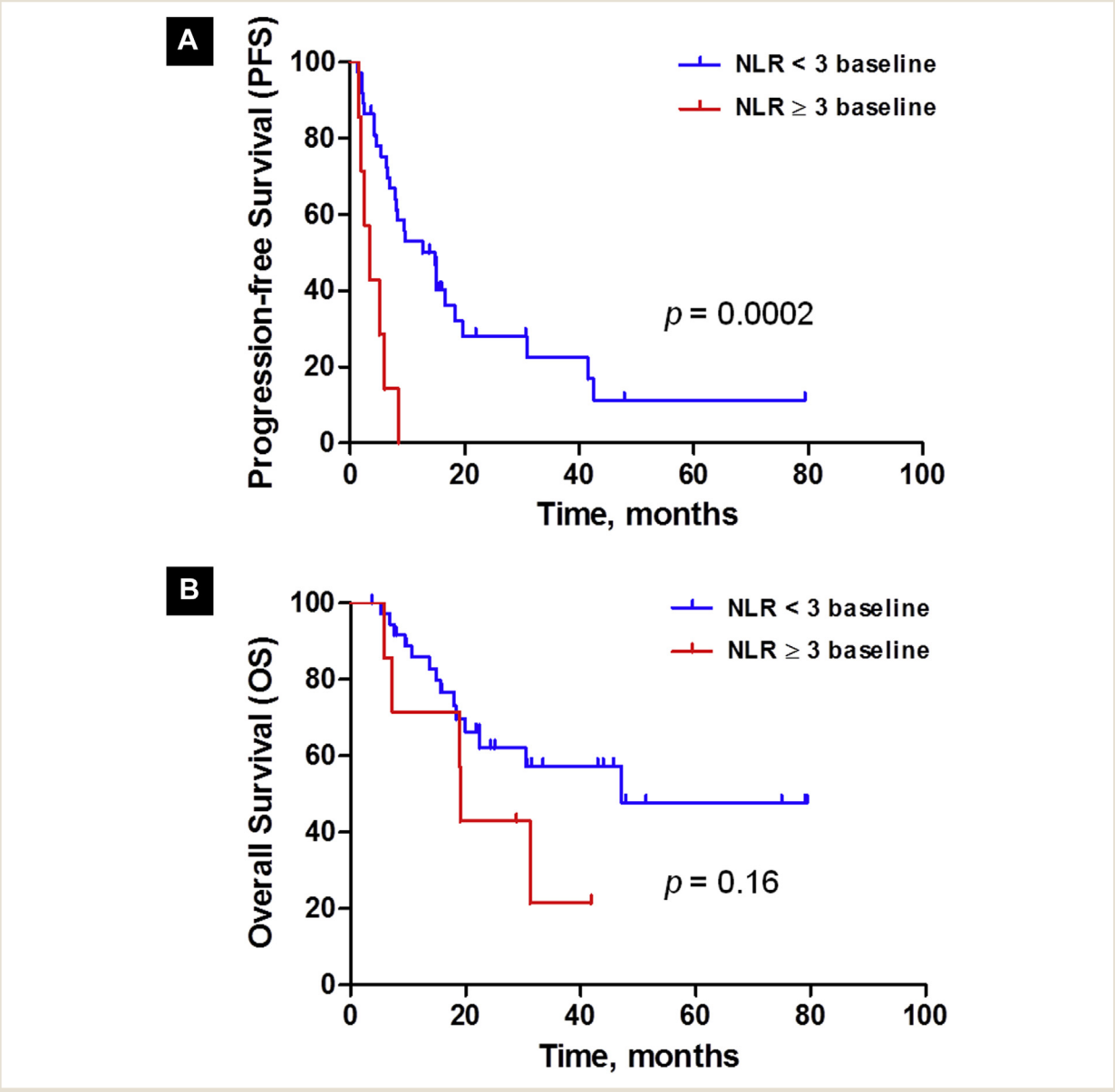
Our study has several limitations. First, the small sample size prevents from achieving solid evidence and could have impaired the statistical significance of the analyses. Anyway, PMP is a rare tumor

Figure 3 Biomarker Association With Progression-Free Survival. Progression-Free Survival Kaplan–Meier Curves According to Biomarkers; (A) Patients Are Stratified for a Reduction During Treatment Superior (in Blue) and Inferior (in Red) to 20% of Carcinoembryonic Antigen (CEA). (B) Patients Are Stratified for Baseline Neutrophil to Lymphocyte Ratio (NLR) Inferior to 3 (in Blue) and Superior or Equal to 3 (in Red)



and its low incidence leads to a high difficulty in collecting a large series of patients, especially in the setting of disease not amenable to surgery. Second, as previously questioned, RECIST version 1.1 criteria do not probably represent the optimal tool to classify the response to treatment of PMP.[16] In this light, studies are ongoing with the aim to identify a novel and more suitable classification, such as the "modified peritoneal RECIST" criteria in the ongoing NCT01946854 trial. However, to date no validated criteria aside from RECIST version 1.1 have been established, thus we chose to use those criteria, although, as previously described, evaluated by a radiologist with particular expertise in this disease setting and according to the specified criteria. Furthermore, for PMP, the clinical evaluation and the increase or reduction of tumor markers are fundamental to evaluate the tumor response to treatment, besides the radiological restaging. Finally, another important bias in this trial is represented by the natural history of PMP itself. In fact, PMP is a slow-growing tumor, and, in some cases, it could be characterized by an indolent clinical course, thus, a chemotherapy-free

Figure 4 Neutrophil to Lymphocyte Ratio (NLR) and Survival Outcome in the Overall Institutional Data Set. (A) Progression-Free Survival and (B) Overall Survival Kaplan–Meier Curves for NLR in the Overall Institutional Data Set of Patients With Advanced Unresectable or Relapsed Pseudomyxoma Peritonei Treated With a Fluoropyrimidine-Based Regimen at our Institution. Patients Are Stratified for Baseline NLR Inferior to 3 (in Blue) and Superior or Equal to 3 (in Red)



control arm could have highlighted the specific action of metronomic treatment in achieving tumor control, aside of a spontaneous disease stabilization in the natural history of the disease. Only few data are available on the possible outcomes of an observation-only management of relapsed PMP,[2] because patients are generally treated either with chemotherapy or, often, with repeated surgical interventions, with curative or palliative/debulking intent.[7,14,36] In this light, as several authors reported, in the current clinical practice, most patients receive an active treatment at the time of first relapse, particularly in case of diffuse tumor deposits, a comparison with a historical no-treatment arm is very difficult.[37] Therefore, clinical trials addressing this specific question are warranted, potentially performed with a randomized design and in a multicenter effort, and the results of the ongoing NCT01946854 study would provide more robust evidence on this issue.

Conclusion

Metronomic capecitabine with cyclophosphamide represents a well tolerated and potentially effective therapeutic option for unresectable or recurrent PMP and it might be considered as an alternative to previously investigated regimens, because of its low toxicity and costs, and to its fully oral administration.

Clinical Practice Points

- Pseudomyxoma peritonei is rare tumor characterized by mucinous peritoneal tumor implants and progressive accumulation of mucinous ascites. The standard treatment of PMP is CRS with HIPEC, which confers a 20-year OS rate >70%.
- In the setting of unresectable or relapsed PMP, no standard treatment has been defined. PMP is endowed with a low proliferation rate and a borderline malignant potential, thus being traditionally considered chemoresistant. Nevertheless, nonrandomized series reported satisfactory outcomes with fluoropyrimidine-based regimens, although not free from relevant toxicity and/or costs.
- We conducted a single-center prospective study on a metronomic capecitabine and cyclophosphamide regimen in the setting of unresectable advanced PMP. This schedule proved to be active, comparing favorably with previous evidence, with a median PFS of 9.5 months, a 1-year OS rate of 73.7% at a median follow-up of 22.4 months, and a DCR of 87% with a prolonged disease control (≥12 months) in 27% of patients. The safety profile was manageable with the occurrence of Grade 3 drug-related adverse events in approximately one-fourth of patients and no evidence of Grade 4/5 side effects.
- Neutrophil-to-lymphocyte ratio baseline < 3 versus ≥ 3 was associated with prolonged PFS (12.6 vs. 3.4 months; $P = .0001$).
- Metronomic capecitabine with cyclophosphamide represents a safe and potentially effective therapeutic option for unresectable or recurrent PMP.

Acknowledgments

We thank all patients enrolled in this study and their families.

Disclosure

Massimo Milione declares honoraria received as speaker and consultant from Novartis Pharma and Ipsen, and institutional financial interest from Roche/Ignyta. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

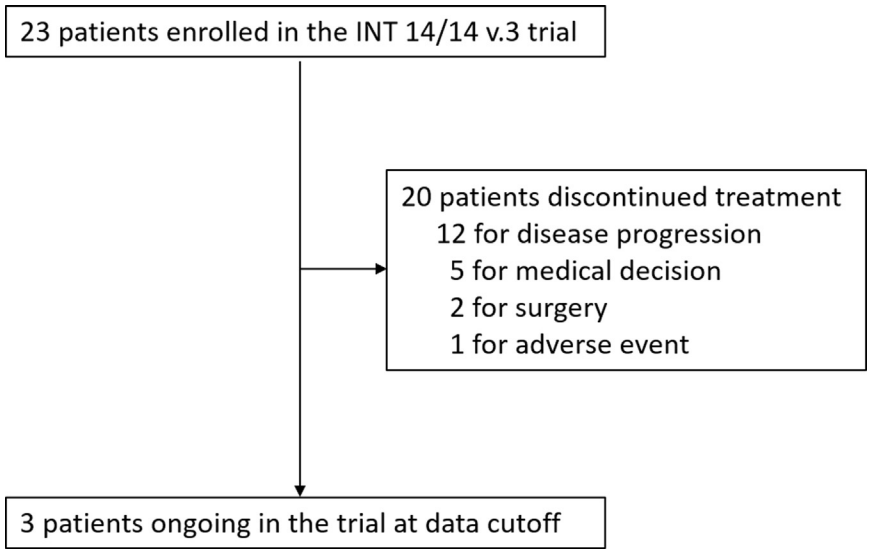
Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.03.002.

References

1. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol* 2008; 34:196-201.
2. Smeenk RM, Bruin SC, van Velthuysen ML, Verwaal VJ. Pseudomyxoma peritonei. *Curr Probl Surg* 2008; 45:527-75.
3. Sugarbaker PH, Ronnett BM, Archer A, et al. Pseudomyxoma peritonei syndrome. *Adv Surg* 1996; 30:233-80.
4. Bradley RF, Stewart JH 4th, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. *Am J Surg Pathol* 2006; 30:551-9.
5. Overman MJ, Fournier K, Hu CY, et al. Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. *Ann Surg* 2013; 257:1072-8.
6. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006; 7:69-76.
7. Elias D, Gilly F, Quenet F, et al. Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. *Eur J Surg Oncol* 2010; 36:456-62.
8. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol* 2012; 30:2449-56.
9. McBride K, McFadden D, Osler T. Improved survival of patients with pseudomyxoma peritonei receiving intraperitoneal chemotherapy with cytoreductive surgery: a systematic review and meta-analysis. *J Surg Res* 2013; 183:246-52.
10. Austin F, Mavanur A, Sathaiah M, et al. Aggressive management of peritoneal carcinomatosis from mucinous appendiceal neoplasms. *Ann Surg Oncol* 2012; 19:1386-93.
11. Baratti D, Kusamura S, Nonaka D, Cabras AD, Laterza B, Deraco M. Pseudomyxoma peritonei: biological features are the dominant prognostic determinants after complete cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg* 2009; 249:243-9.
12. Pietrantonio F, Berenato R, Maggi C, et al. GNAS mutations as prognostic biomarker in patients with relapsed peritoneal pseudomyxoma receiving metronomic capecitabine and bevacizumab: a clinical and translational study. *J Transl Med* 2016; 14:125.
13. Pietrantonio F, Perrone F, Mennitto A, et al. Toward the molecular dissection of peritoneal pseudomyxoma. *Ann Oncol* 2016; 27:2097-103.
14. Delhorme JB, Honore C, Benhaim L, et al. Long-term survival after aggressive treatment of relapsed serosal or distant pseudomyxoma peritonei. *Eur J Surg Oncol* 2017; 43:159-67.
15. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2014; 109:740-5.
16. Overman MJ, Eng C, Raghav K, et al. Challenges of efficacy assessments in pseudomyxoma peritonea. *Oncologist* 2015; 20:e3-4.
17. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. *Cancer* 2010; 116:316-22.
18. Levitz JS, Sugarbaker PH, Lichtman SM, Brun EA. Unusual abdominal tumors, case 1. Pseudomyxoma peritonei: response to capecitabine. *J Clin Oncol* 2004; 22:1518-20.
19. Sun WL, Hutarew G, Gradl J, Gratzl M, Denz H, Fiegl M. Successful anti-angiogenic combination therapy for pseudomyxoma peritonei with bevacizumab and capecitabine. *Cancer Biol Ther* 2009; 8:1459-62.
20. Pietrantonio F, Maggi C, Fanetti G, et al. FOLFOX-4 chemotherapy for patients with unresectable or relapsed peritoneal pseudomyxoma. *Oncologist* 2014; 19:845-50.
21. Sugarbaker PH, Bijelic L, Chang D, Yoo D. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. *J Surg Oncol* 2010; 102:576-81.
22. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. *Br J Cancer* 2008; 99:591-6.
23. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. *Nat Rev Cancer* 2004; 4:423-36.
24. Andre N, Padovani L, Pasquier E. Metronomic scheduling of anticancer treatment: the next generation of multitarget therapy? *Future Oncol* 2011; 7:385-94.
25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-47.
26. NCI CTEP. Common terminology criteria for adverse events (CTCAE) v4.0, Available at: https://evs.nci.nih.gov/ftp1/CTCAE/, 2010.
27. Jeyakumar G, Kim S, Bumma N, et al. Neutrophil lymphocyte ratio and duration of prior anti-angiogenic therapy as biomarkers in metastatic RCC receiving immune checkpoint inhibitor therapy. *J Immunother Cancer* 2017; 5:82.
28. Zheng J, Cai J, Li H, et al. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for hepatocellular carcinoma patients with various treatments: a meta-analysis and systematic review. *Cell Physiol Biochem* 2017; 44:967-81.
29. Tsai PL, Su WJ, Leung WH, Lai CT, Liu CK. Neutrophil-lymphocyte ratio and CEA level as prognostic and predictive factors in colorectal cancer: a systematic review and meta-analysis. *J Cancer Res Ther* 2016; 12:582-9.
30. Guo J, Fang J, Huang X, et al. Prognostic role of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in prostate cancer: a meta-analysis of results from multivariate analysis. *Int J Surg* 2018; 60:216-23.
31. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144:646-74.
32. Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; 106:dju124.
33. Chua TC, Chong CH, Liauw W, Zhao J, Morris DL. Inflammatory markers in blood and serum tumor markers predict survival in patients with epithelial appendiceal neoplasms undergoing surgical cytoreduction and intraperitoneal chemotherapy. *Ann Surg* 2012; 256:342-9.

34. Kusamura S, Baratti D, Hutanu I, et al. The role of baseline inflammatory-based scores and serum tumor markers to risk stratify pseudomyxoma peritonei patients treated with cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol* 2015; 41:1097-105.
35. Rangarajan K, Chandrakumaran K, Dayal S, Mohamed F, Moran BJ, Cecil TD. The pre-operative neutrophil-lymphocyte ratio predicts overall and disease-free survival following cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with pseudomxyoma peritonei of appendiceal origin. *Int J Hyperthermia* 2018; 34:559-63.
36. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg* 1994; 219:112-9.
37. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Progression of pseudomyxoma peritonei after combined modality treatment: management and outcome. *Ann Surg Oncol* 2007; 14:493-9.

Supplemental Figure 1 Consolidated Standards of Reporting Trials Diagram of the Study Protocol INT 14/14 v.3



Supplemental Figure 2 Biomarkers Association With Overall Survival. Overall Survival Kaplan–Meier Curves According to Biomarkers. (A) Patients Are Stratified for a Reduction During Treatment Superior (in Blue) and Inferior (in Red) to 20% of Carcinoembryonic Antigen (CEA). (B) Patients Are Stratified for Baseline Neutrophil to Lymphocyte Ratio (NLR) Inferior to 3 (in Blue) and Superior or Equal to 3 (in Red)