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Extending the platinum-free interval: The impact of omitting 2nd line platinum chemotherapy in intermediate platinum-sensitive ovarian cancer

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HIGHLIGHTS

- Non-platinum chemo or targeted therapy to prolong PFI in platinum intermediate recurrent ovarian cancer worsens survival.
- This confirms existing prospective data from the MITO-8 study.
- Even with targeted therapies, attempts to artificially prolong the PFI are not likely beneficial.

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ABSTRACT

Objectives: Patients with epithelial ovarian cancer (EOC) recurring between 6 and 12 months after primary platinum chemotherapy have worse prognosis than those recurring in >12 months. Artificially prolonging the platinum-free interval (PFI) with cytotoxic chemotherapy was tested in MITO-8 with poor outcomes. This study aimed to determine the impact of using non-platinum or targeted therapy in 2nd line treatment of EOC patients recurring 6–12 months after completion of primary platinum-based chemotherapy.

Methods: A multi-institutional retrospective review of 177 patients with recurrent EOC and PFI of 6–12 months following primary chemotherapy was performed comparing platinum versus non-platinum chemotherapy or targeted therapy for 2nd line treatment. PFI1 was defined as the date of last chemotherapy to date of recurrence. PFS2/3 were defined as start of 2nd or 3rd line chemotherapy to start of subsequent line.

Results: Of 177 patients, the majority of patients were Caucasian, had serous histology, and underwent primary cytoreductive surgery. Median PFI1 was 8.2 months (95% CI 8–9 months). Second line platinum was omitted in 28% of patients. Bevacizumab was used in 2nd line in 16% of patients; 19% received other targeted therapies. Median PFS2 for platinum chemotherapy was longer than non-platinum (7.1 vs 3 months, $p = 0.0114$). Median PFS2 was significantly longer for platinum vs. targeted therapy (7.1 vs. 3 months $p = 0.0431$). Median OS for platinum in 2nd line vs. no platinum was 43.6 vs. 37.6 months ($p = 0.0174$).

Conclusions: Use of non-platinum chemotherapy and even targeted therapy to prolong PFI in patients with EOC recurring between 6 and 12 months leads to worse survival.

1. Introduction

Current standard of care for upfront treatment of newly diagnosed advanced epithelial ovarian cancer (EOC) includes a combination of cytoreductive surgery and platinum-containing doublet chemotherapy, typically carboplatin and paclitaxel. Despite up to an 80% overall response rate, including a high proportion of complete response to primary platinum-based chemotherapy, the majority of women with EOC experience disease recurrence [1].

Many prognostic indicators must be taken into account when determining expected prognosis and response rate to future lines of therapy in recurrent EOC. These factors include patient ECOG

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performance status, tumor volume and histology, and the platinum-free interval. The time between last platinum chemotherapy and recurrence, known as the platinum-free interval (PFI), represents one of the most important prognostic factors. Traditionally, patients recurring six months or more after last platinum are labeled platinum sensitive, while those recurring <6 months from last platinum are considered platinum resistant. A small study evaluated re-challenging relapsed ovarian cancer patients with the same platinum or crossing over to either cisplatin or carboplatin. The progression-free interval was a significant prognostic factor for response to treatment and survival. 17% who relapsed before 18 months responded, as compared to 53% relapsing after 18 months ($p = 0.006$) [2]. Markman, et al. evaluated response rates to second line platinum chemotherapy in patients with prior platinum exposure. Increasing time from prior platinum correlates with increasing response to subsequent platinum exposure. PFIs between 5 and 12 months demonstrated decreased response rates (27%), as compared to 33% and 59% response rates for patients with PFIs of 13–24 months and >24 months, respectively [3]. Based on this and other data, the time from last platinum therapy to recurrence drives the choice of subsequent line chemotherapy and remains the strongest predictor of response to second line therapy.

Current standard of care regimens for platinum sensitive disease typically include a platinum-containing doublet regimen. Several large trials demonstrate that patients receiving platinum-containing doublets experience response rates of roughly 47–66%. In ICON4/AGO-OVAR 2.2, Parmar, et al. compared single agent platinum therapy versus platinum plus paclitaxel in patients with platinum sensitive recurrent EOC. They demonstrated improvement in median progression free survival (PFS) in the platinum-containing doublet group, with a median PFS of 12 months in the experimental arm versus 9 months in the platinum alone arm ($p = 0.0004$). Additionally, they demonstrated a statistically significant five month improvement in overall survival (OS) in the doublet group of 29 months as compared to 24 months for platinum alone [4]. Pfisterer et al. demonstrated improved PFS and response rate using carboplatin plus gemcitabine as compared to carboplatin alone (8.6 vs. 5.8 months, $p = 0.0031$) [5]. A randomized phase II study (SWOG S0200) comparing single agent carboplatin versus carboplatin with pegylated liposomal doxorubicin revealed improved PFS of 12 versus 8 months and improved OS of 26 versus 18 months ($p = 0.02$), favoring the doublet group [6].

As previously discussed, patients recurring between 5 and 12 months after last platinum demonstrate disappointing response rates to subsequent platinum therapy as compared to those recurring >12 months from last platinum. This group of patients is often termed “platinum intermediate” or partially platinum sensitive. Several studies have examined use of non-platinum chemotherapy, such as topotecan, to extend the PFI with the goal of improving response to future platinum-based therapies. Topotecan was investigated as a method to avoid cross-resistance as well as a way to avoid the cumulative hematologic toxicities of platinum and taxane regimens while preserving platinum sensitivity. Topotecan demonstrates activity in the recurrent setting, both platinum sensitive and resistant/refractory with response rates among the platinum sensitive population ranging from 19% to 32% [7–12].

The MITO group conducted a retrospective review focusing on “partially platinum sensitive” patients and found the use of non-platinum agents to be less effective in this population [13]. Subsequently, MITO-8, a prospective randomized controlled trial, was designed to address the issue of PFI prolongation in this select population of patients. MITO-8 randomized patients with EOC recurring between 6 and 12 months after last platinum treatment to either non-platinum chemotherapy followed by platinum chemotherapy at subsequent recurrence, or the standard arm of platinum-based chemotherapy followed by non-platinum chemotherapy at subsequent recurrence. Non-platinum therapy could include pegylated liposomal doxorubicin, topotecan, or gemcitabine. No OS benefit was noted, and in fact both PFS and quality of life actually worsened in the cohort of patients receiving non-platinum therapy (PFS 12.8 months non-platinum vs. 16.4 months platinum, HR 1.41, 95% CI 1.04 to 19.2, $p = 0.025$) [14].

Given that MITO-8 only assessed single agent cytotoxic therapies and not targeted therapies, we sought to investigate PFI prolongation in patients receiving newer therapies given their frequent use. Therefore, the objective of this study was to determine the impact of using non-platinum based chemotherapy in second line treatment for patients with EOC recurring between 6 and 12 months after completion of primary platinum-based chemotherapy at institutions where targeted therapies are routinely used in this setting.

2. Materials and methods

A retrospective review of 177 patients was performed at two academic institutions which use targeted therapies in the recurrent EOC setting: Stephenson Cancer Center (SCC) at the University of Oklahoma and University of Alabama at Birmingham after Institutional Review Board approval was obtained (study #8440). Eligible patients included those with EOC recurring between 6 and 12 months following primary platinum-based chemotherapy. Comparison was made between those receiving platinum-based chemotherapy in the second line versus those not. Platinum free interval 1 (PFI1) was defined as the date of last dose of first line chemotherapy to the date of first recurrence. Progression free survival 2 and 3 (PFS2, PFS3) were defined as time of start of second or third line chemotherapy to start of subsequent line. Overall survival (OS) was defined as time from the date of diagnosis to the date of all-cause death. If no death occurred, OS was censored at the date of last contact. Data collected included age, race, ECOG performance status, adjuvant or neoadjuvant chemotherapy treatment strategy, response to primary chemotherapy, chemotherapeutic or targeted therapies in subsequent lines, PFI and PFS, OS, response to subsequent chemotherapy, total lines of chemotherapy, and vital status. Targeted therapy was defined as agents other than standard cytotoxic therapy which included biologic agents, antibody-drug conjugates, or targeted therapy.

Data was compiled and analyzed at the lead site (SCC). Descriptive statistics (count, percent, median and range) were used to summarize the categorical and continuous variables. Survival

Table 1
Patient demographics by those receiving platinum-based chemotherapy in the second line versus those not.

N = 177	Platinum in 2nd line n = 131	No platinum in 2nd line n = 46	P-value
Median age at diagnosis, yrs	62	60	0.41
Median PFI1, mos	8.4	7.6	**0.013**
Race (%)			0.41
Caucasian	107 (81.68)	40 (87.0)	
Black	17 (12.98)	2 (4.35)	
Native American	1 (0.76)	2 (4.35)	
Hispanic	3 (2.29)	1 (2.17)	
Unknown	3 (2.29)	1 (2.17)	
Histology			0.80
Serous	109 (83.2)	39 (84.78)	
Endometrioid	1 (0.76)	1 (2.17)	
Mixed	13 (9.92)	1 (2.17)	
Mucinous	1 (0.76)	1 (2.17)	
Unknown	7 (5.34)	4 (8.7)	
Primary debulking surgery (%)	118 (90.1)	41 (89.13)	0.78

Bold values indicates significance at $p < 0.05$.

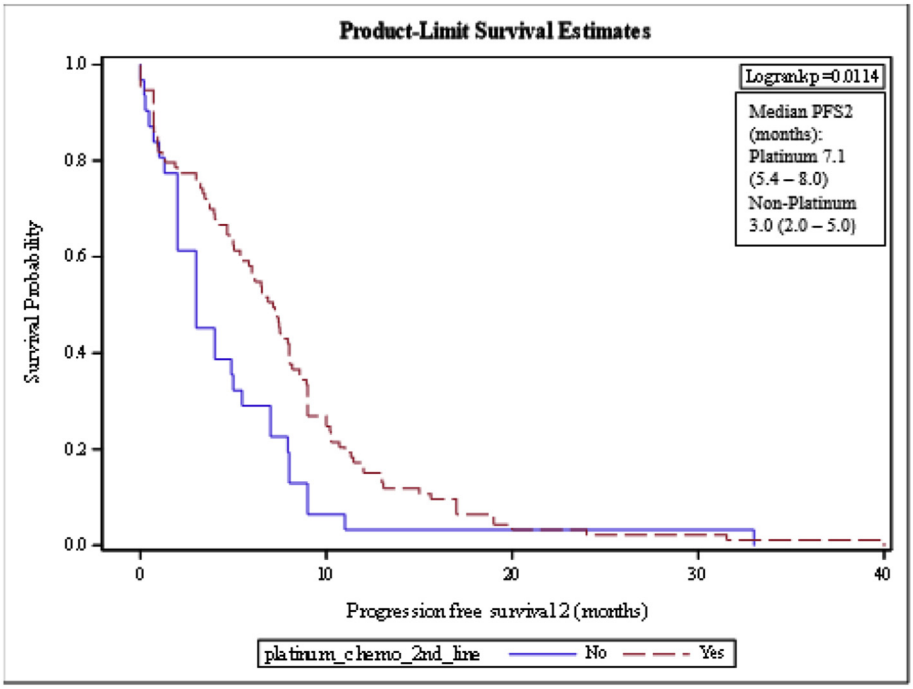

Fig. 1. Median progression-free survival 2 comparing patients receiving platinum-based chemotherapy in the second line versus those not.

times (PFI1, PFS2, PFS3, and OS) were summarized using the Kaplan-Meier method and compared between groups using log-rank tests. Median survival times and associated 95% confidence intervals (CI) were generated from the Kaplan-Meier curves. All tests were two-sided. A p-value of <0.05 defines statistical significance. The SAS software (v9.4) was used for all analyses.

3. Results

Of the 177 women included in the study, the median age at diagnosis was 62 years (range, 38–84 years). The majority of patients were Caucasian (n = 147, 83.1%) as compared to Black (n = 19, 10.7%), Hispanic (n = 4, 2.3%), Native American (n = 3, 1.7%), and Unknown (n = 4, 2.3%). The majority of patients had serous tumors (83.6%) with other histologies including mixed (7.9%), endometrioid (1.1%), mucinous (1.1%), and unknown (6.2%). Additionally, the majority of patients underwent primary debulking surgery (n = 159, 89.8%). Table 1 demonstrates demographics of patients by receipt of platinum in second line chemotherapy.

Median PFI1 for all patients was 8.2 months (95% CI 8–9 months). Median PFI1 was 0.8 months shorter in patients not receiving platinum in the second line (8.4 months platinum vs. 7.6 months no platinum, $p = 0.013$). Second line platinum chemotherapy was omitted in 46 (28%) of patients. Bevacizumab was used

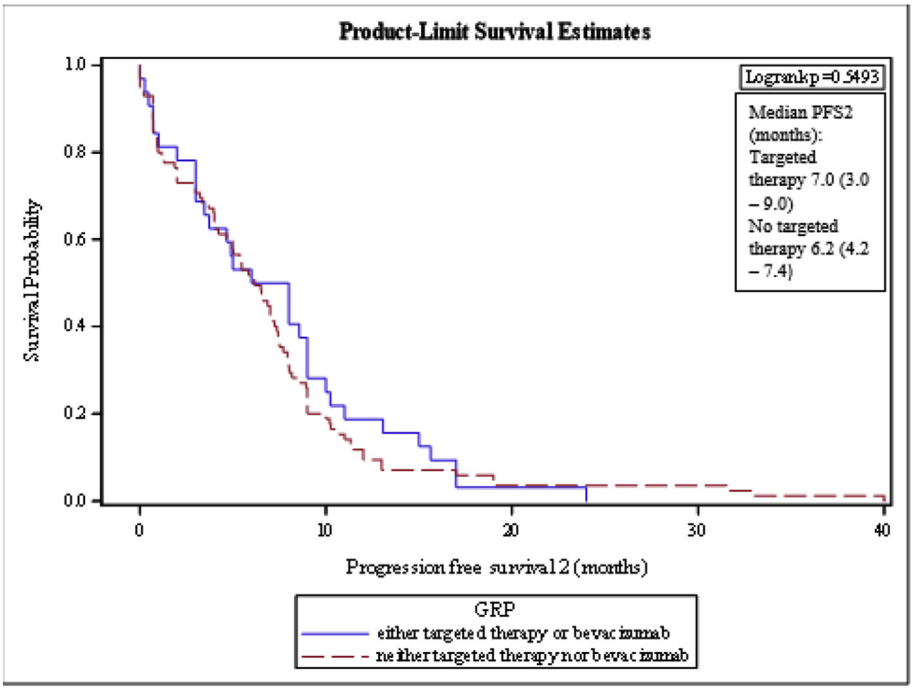

Fig. 2. Median progression-free survival 2 comparing patients receiving targeted therapies versus those not, regardless of platinum status.

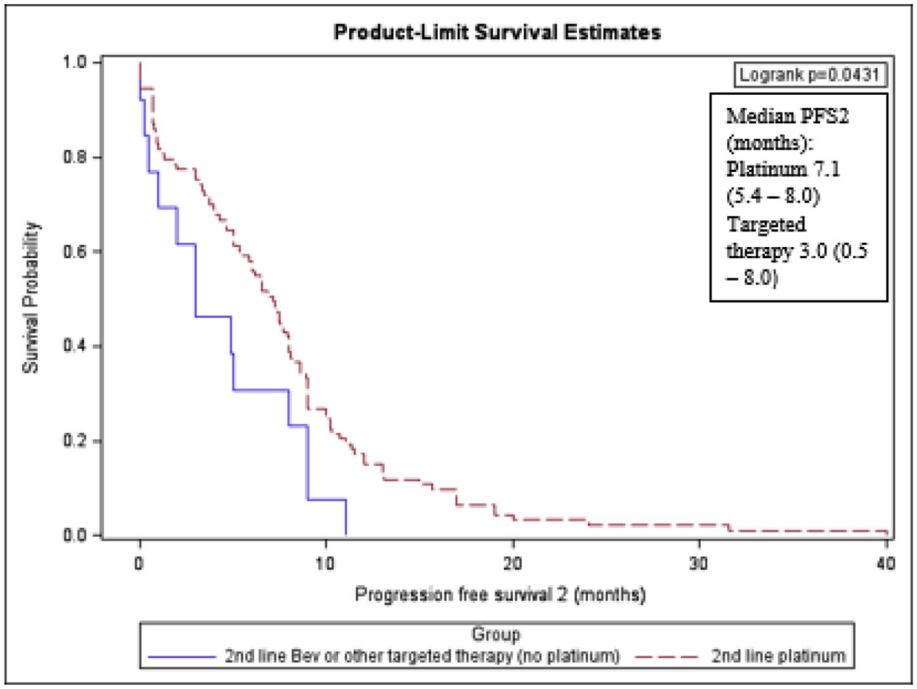

Fig. 3. Median progression-free survival 2 for those receiving platinum in the second line versus those receiving bevacizumab or other targeted therapies without platinum.

in second line therapy in 16% of patients regardless of platinum status, and 19% received other targeted therapies. Of the 25 patients receiving bevacizumab in the second line, 20 received bevacizumab with chemotherapy including maintenance, and 5 patients received bevacizumab alone. 15 patients who received platinum in second line also received targeted therapy/bevacizumab. Median total lines of chemotherapy was 4.0 (range 1.0–11.0). Median PFS2 for the study population as a whole was 6.0 months (95% CI 4.7–7.4 months, n = 125). Median OS for the entire study population was 41.4 months (95% CI 37.6–44.6 months, n = 176). The five year survival rate was 25%.

Median PFS2 for those receiving platinum chemotherapy in the second line was 7.1 months (95% CI 5.4–8.0 months) versus 3.0 months (95% CI 2.0–5.0 months) for those receiving non-platinum ($p = 0.0114$) (Fig. 1). When controlling for PFI1, those receiving non-platinum chemotherapy in the second line experienced shorter PFS2 (HR 1.6, 95% CI 1.1–2.5, $p = 0.019$). There was no difference in median PFS2 for those receiving targeted therapies/bevacizumab (7.0 months, 95% CI 3–9 months) versus those not (6.2 months, 95% CI 4.2–7.4 months), regardless of concurrent receipt of platinum (platinum status) ($p = 0.5493$) (Fig. 2). When comparing median PFS2 for those receiving platinum in the second

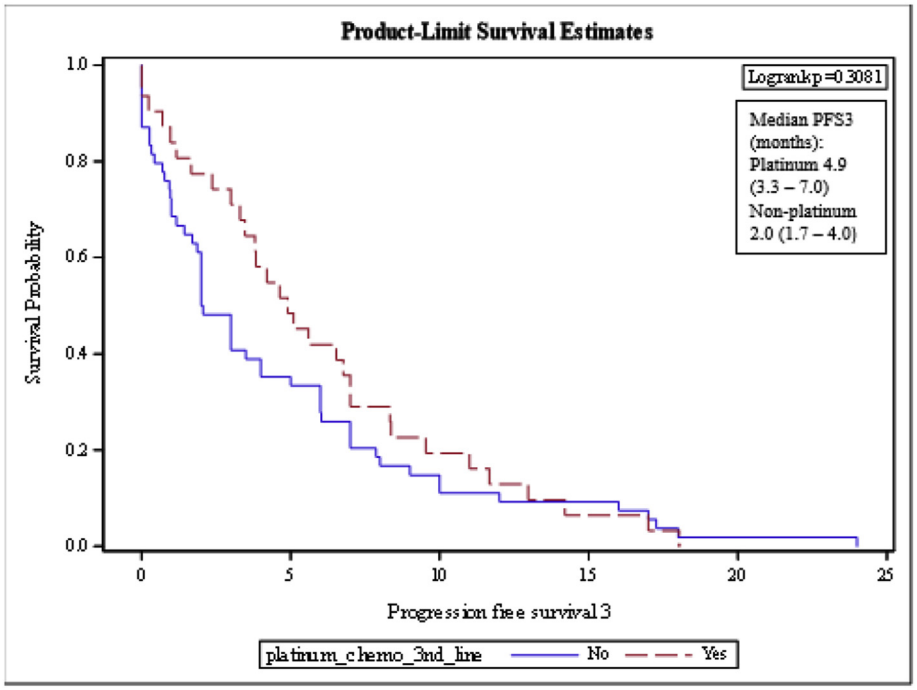

Fig. 4. Median progression-free survival 3 for those receiving platinum in the third line versus those that did not.

line versus those receiving bevacizumab or other targeted therapies without platinum, those receiving platinum experienced a significantly longer PFS2 (7.1 months, 95% CI 5.4–8.0 platinum vs. 3.0 months, 95% CI 0.5–8.0 targeted therapy, $p = 0.0431$) (Fig. 3).

Ten of the total 44 patients who received platinum chemotherapy in the third line did not receive platinum chemotherapy in the second line. PFS3 by third line platinum status was not significant, however suggests a trend towards longer median PFS with platinum (n = 31) versus no platinum (n = 54) (4.9 months vs 2.0 months, $p = 0.3081$) (Fig. 4).

Median OS was 43.6 months for patients receiving platinum in the second line and was significantly longer than those who did not receive platinum during in second line therapy (37.6 months, $p = 0.0174$). This did not change when controlling for PFI1 (HR 1.5, 95% CI 1.0–2.2, $p = 0.042$). Median OS was not significant when comparing those receiving platinum versus targeted therapy in the second line (43.6 months vs. 37.5 months, respectively, $p = 0.098$), however there appears to be a similar trend towards favoring platinum (Fig. 5).

4. Discussion

Despite an excellent upfront response rate to primary platinum-based chemotherapy, the majority of women with advanced EOC will experience a recurrence. The important prognostic marker of the PFI currently dictates choice of therapy in second line and beyond. Additionally, it has been demonstrated that the efficacy of platinum-based therapy is greatest in those with a PFI >12 months

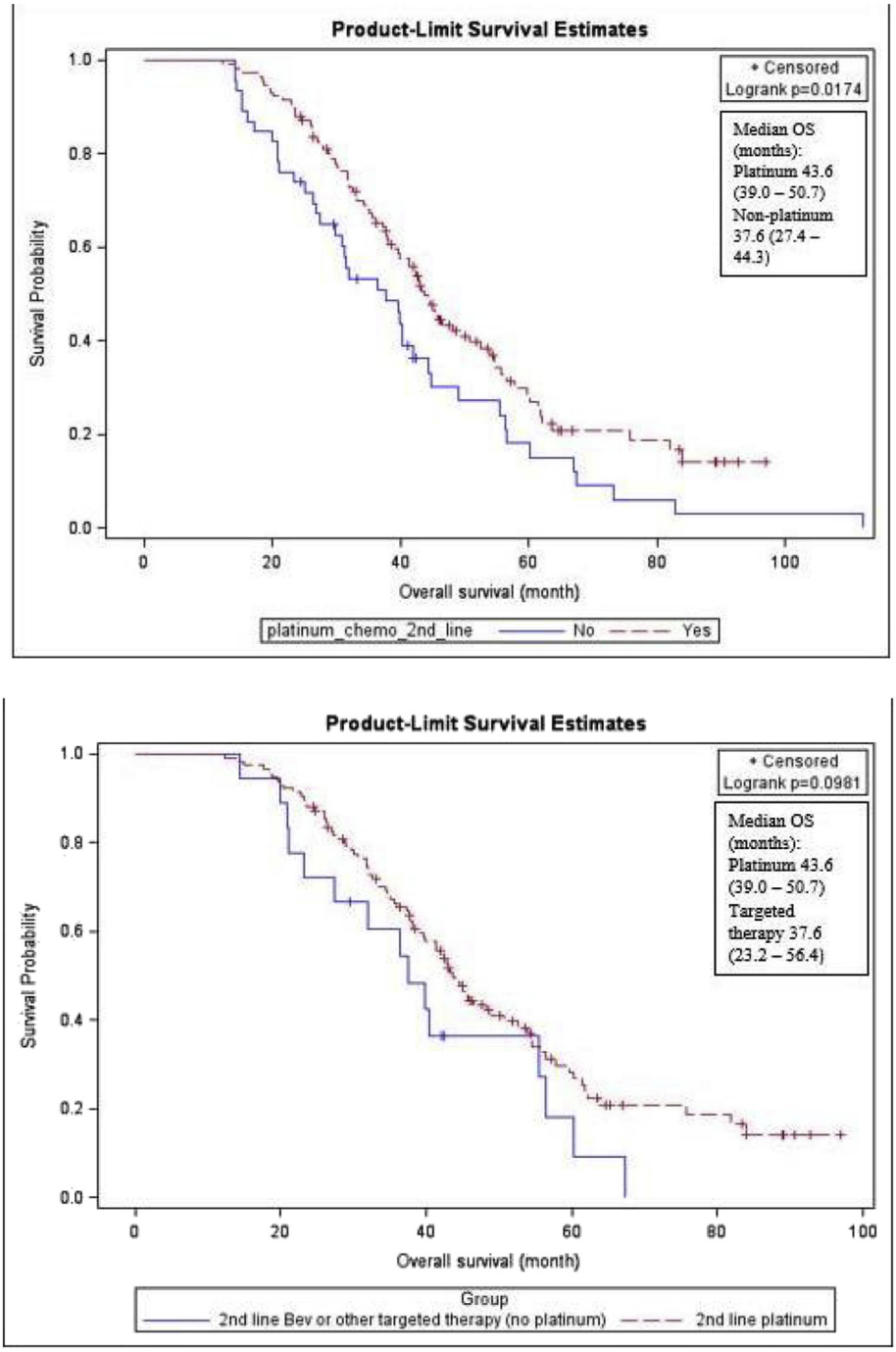

Fig. 5. Median overall survival for patients receiving platinum in the second line as compared to those not and median overall survival when comparing those receiving platinum in second line therapy versus those receiving targeted therapy without platinum.

[3]. Until the MITO-8 study addressed "partial" or "intermediate" platinum sensitivity in women recurring between 6 and 12 months after primary platinum, little data existed to support management of patients in this population.

Our study demonstrates that even when using standard of care or targeted therapies, no benefit is apparent for prolonging PFI in women experiencing recurrence between 6 and 12 months after primary platinum therapy. In fact, attempts at prolonging the PFI with non-platinum therapies appears to lead to worse outcomes in both PFS and OS. This data underscores the importance of platinum as a key agent for women with recurrent EOC and should encourage physicians to include a platinum agent when deciding on treatment regimen for this patient population. The results of this study must be taken in context of the varying agents and clinical trials available to patients diagnosed with ovarian cancer between 1996 and 2014. New agents and targeted therapies continue to be developed which continue to shift treatment paradigms. It is important to highlight, however, that with recent approval of agents such as the anti-angiogenic agent bevacizumab during front-line treatment and for maintenance thereafter and the PARP inhibitor olaparib for upfront maintenance therapy (in patients with *BRCA* mutations), the dichotomous concept of platinum sensitivity may become more of an historic definition. In fact, in light of the use of maintenance therapy, current clinical trials are being designed based upon number of lines of prior therapy rather than platinum sensitive status [15,16]. Additionally, use of these treatments after initial platinum-based chemotherapy may modify the biologic properties of recurrent disease, as pointed out by the MITO-8 investigators [14].

The data from MITO-8 and our study suggests that the biology of platinum resistance plays a critical role in disease outcome. Several pathways have been identified as important in regulating platinum resistance such as the Wnt/Beta Catenin pathway, however the functional relevance is yet to be well understood. In fact, multiple pathways are likely involved [17]. Little progress has been made in identifying therapies with response rates exceeding those of platinum chemotherapy. This highlights the importance of identifying methods of preserving or prolonging platinum sensitivity. Because platinum resistance remains poorly understood, identifying biomarkers for poor response to platinum in the partially platinum sensitive group represents an important goal to better triage patient prognosis and subsequent lines of therapy.

This study is limited by its retrospective nature and the limitations inherent to this design. Furthermore, the study was limited by a relatively small sample size, particularly among comparisons of patients treated with targeted therapies or those receiving platinum in the third line that did not in the second line. Due to large volumes of patients treated on clinical trials, including phase 1 trials, at both institutions it was not possible to specify all targeted agents. Additionally, all patients were treated at two large academic centers which may not be widely generalizable.

In conclusion, this study suggests that the use of non-platinum chemotherapy and even targeted therapies in lieu of platinum-based therapy in an attempt to prolong PFI in patients with epithelial ovarian cancer recurring between 6 and 12 months after primary platinum therapy leads to worse survival. Our results confirm the existing prospective data from MITO-8 [14]. Even with targeted therapies, attempts to prolong the PFI are not likely beneficial. It remains to be seen how this will change in the era of increased use of maintenance therapies.

Author contribution

Dr. Dockery, Dr. Gunderson, and Dr. Moore contributed to development of the research, data collection, analysis of data, and manuscript preparation.

Dr. Ding served as biostatistician for the study and contributed to data analysis and manuscript preparation and approval.

Dr. Rubenstein, Dr. Mashburn, Dr. Burkett, Dr. Davis, Dr. Doo, and Dr. Arend all contributed to data collection and final approval of the manuscript.

Declaration of competing interest

Dr. Dockery, Dr. Rubenstein, Dr. Ding, Dr. Mashburn, Dr. Burkett, Dr. Davis, and Dr. Doo have no conflicts of interest.

Dr. Gunderson serves on advisory boards for Agenus, Clovis, and Cordgenics.

Dr. Arend serves on advisory boards for Clovis, AstraZeneca, Pfizer, Tesaro, and VBL Therapeutics.

Dr. Moore reports relationships with Immunogen, Clovis, Tesaro, Pfizer, Janssen, Aravive, VBL Therapeutics, Onco Med, Samumed, Lilly, and Eisai, unrelated to this research.

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