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Prognostic relevance of *c-MYC* gene amplification and polysomy for chromosome 8 in suboptimally-resected, advanced stage epithelial ovarian cancers: A Gynecologic Oncology Group study☆

Kathleen M. Darcy[a], **William E. Brady**[a], **Jan K. Blancato**[b], **Robert B. Dickson**[b,1], **William J. Hoskins**[c], **William P. McGuire**[d], and **Michael J. Birrer**[e,*]

[a]GOG Statistical and Data Center, Elm and Carlton Street, Buffalo, NY 14263-0001, USA

[b]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC 20007, USA

[c]Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA

[d]Medical Director, Harry and Jeanette Weinberg Cancer Institute, Franklin Square Hospital Center, Baltimore, MD 21237, USA

[e]Massachusetts General Hospital, Yawkey 9072, 55 Fruit Street, Boston, MA 02114, USA

Abstract

Objective—The Gynecologic Oncology Group (GOG) examined the prognostic relevance of *c-MYC* amplification and polysomy 8 in epithelial ovarian cancer (EOC).

Methods—Women with suboptimally-resected, advanced stage EOC who participated in GOG-111, a multicenter randomized phase III trial of cyclophosphamide + cisplatin vs. paclitaxel + cisplatin, and who provided a tumor block through GOG-9404 were eligible. Fluorescence *in situ* hybridization (FISH) with probes for *c-MYC* and the centromere of chromosome 8 (CEP8) was used to examine *c-MYC* amplification (≥2 copies *c-MYC*/CEP8) and polysomy 8 (≥4 CEP8 copies).

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*Corresponding author. Fax: +1 617 724 6898. mbirrer@partners.org (M.J. Birrer).

[1]Deceased.

Conflict of interest statement

The authors declare that there is no conflict of interest with the exception of William Brady who received payment from Merck and Co, Inc. for working as an independent contractor in the past 2 years.

Results—*c-MYC* amplification, defined as ≥2 copies *c-MYC*/CEP8, was observed in 29% (28/97) of EOCs and levels were ranged from 2.0–3.3 copies of *c-MYC*/CEP8. *c-MYC* amplification was not associated with patient age, race, GOG performance status, stage, cell type, grade, measurable disease status following surgery, tumor response or disease status following platinum-based combination chemotherapy. Women with vs. without *c-MYC* amplification did not have an increased risk of disease progression (hazard ratio [HR] = 1.03; 95% confidence interval [CI] = 0.65–1.64; $p = 0.884$) or death (HR = 1.08; 95% CI = 0.68–1.72; $p = 0.745$). *c-MYC* amplification was not an independent prognostic factor for progression-free survival (HR = 1.03, 95% CI = 0.57–1.85; $p = 0.922$) or overall survival (HR = 1.01, 95% CI = 0.56–1.80; $p = 0.982$). Similar insignificant results were obtained for *c-MYC* amplification categorized as ≥1.5 copies *c-MYC*/CEP8. Polysomy 8 was observed in 22 patients without *c-MYC* amplification and 3 with *c-MYC* amplification, and was associated with age and measurable disease status, but not other clinical covariates or outcomes.

Conclusions—*c-MYC* amplification and polysomy 8 have limited predictive or prognostic value in suboptimally-resected, advanced stage EOC treated with platinum-based combination chemotherapy.

Keywords

c-MYC; FISH; Ovarian cancer; Polysomy 8; Gene amplification

Introduction

Ovarian cancer is the leading cause of cancer-related death among the gynecologic malignancies [1]. It is estimated that in the United States 21,850 new cases of ovarian cancer will be diagnosed, 68% of whom will present with advanced disease, and 15,520 women would die from their cancer in 2008 [1]. Currently, surgical staging followed by platinum-based chemotherapy is the standard of care for this disease [2,3]. Even though 70% of women with advanced stage disease respond to first-line platinum-based chemotherapy, five-year survival for women in this setting remains around 30% [1–3]. Researchers continue to study molecular and biochemical defects in epithelial ovarian cancer (EOC) with the hope of identifying biomarkers with prognostic and/or predictive value in this patient setting.

c-MYC is a multifunctional proto-oncogene that exhibits diverse and at times, opposing functions [4–9]. c-MYC protein promotes tumorigenesis by inducing proliferation, inhibiting cells from exiting the cell cycle, stimulating blood vessel formation and cell migration, enhancing genomic instability, and helping tumor cells adapt and thrive in hypoxic environments [4,8,10–13]. In contrast, c-MYC inhibits tumorigenesis by sensitizing cells to apoptosis [14]. *c-MYC* is activated in about 20% of human cancers by several mechanisms including gene amplification, mutation or rearrangement, promoter insertion, transcriptional and post-translational [4–9], and appears to be a feasible target for cancer therapeutics [15–16].

Amplification of *c-MYC* has been described in a variety of human cancers [17–32] including ovarian cancer [33–51]. Investigators have shown an association between *c-MYC* amplification and poor outcome in breast cancer [18–23], prostate cancer [24–27] and

chondrosarcoma [28], but not in non-small cell lung cancer (NSCLC) [29–30], colorectal cancer [31] or esophageal squamous cell carcinoma (SCC) [32]. In EOC, amplifications of *c-MYC* have been shown to be associated with stage [43], cell type [37,51] and/or grade [41,43], or conversely to not be associated with stage [46,51], cell type [43,46], grade [36,37,46,51], progression-free survival (PFS) [45,46], overall survival (OS) [45,46,48,49] and/or response to platinum-based chemotherapy [36].

The Gynecologic Oncology Group (GOG) undertook a study of *c-MYC* amplification in women with suboptimally-resected, advanced stage EOC who participated in a multicenter randomized phase III trial and provided a tumor block for research. Fluorescence *in situ* hybridization (FISH) with probes for *c-MYC* and the centromeric region of chromosome 8 (CEP8) was used to examine *c-MYC* amplification defined as ≥2 copies of *c-MYC*/CEP8 per cell [23,28,21] or ≥1.5 copies *c-MYC*/CEP8 [22,24] and polysomy for chromosome 8 defined as ≥4 copies of CEP8 per cell (as recommended by the manufacturer). Our results will be discussed in context with the other studies of *c-MYC* amplification in invasive EOC and our current understanding of the c-MYC proteins.

Methods

Patients

Women who participated in GOG-111, a phase III treatment protocol, and provided a tumor block through GOG-9404 were eligible for this translational research study. Women on the GOG-111 protocol had to have previously-untreated, histologically-confirmed, surgically-staged EOC with evaluable or measurable stage III disease that was suboptimally-resected (>1 cm residual disease) or stage IV disease, a GOG performance status of 0 to 2, and adequate bone marrow counts, renal function and hepatic function as previously described [52]. Women with a borderline tumor or optimally-resected stage III disease were specifically excluded from GOG-9404. Women were required to provide written informed consent, and participating institutions were required to obtain annual Institutional Review Board approval for GOG-111 and GOG-9404 consistent with federal, state and local requirements.

Platinum-based combination chemotherapy

Women on GOG-111 were randomly allocated to receive either 75 mg/m^2 cisplatin intravenously on day 1 and 750 mg/m^2 cyclophosphamide intravenously on day 1 every 3 weeks for a total of 6 cycles, or a 24-hour continuous intravenous infusion of 135 mg/m^2 paclitaxel on day 1 and 75 mg/m^2 cisplatin intravenously on day 2 every 3 weeks for a total of 6 cycles [52]. Treatment at the time of disease progression was left to the discretion of the treating physician and patient.

Clinical end-points

Women on GOG-111 were followed quarterly for 2 years, semiannually for the next 3 years and then annually until death from the time they went off-treatment due to completion of protocol-specified therapy, toxicity, or disease progression [52]. Progression-free survival (PFS) was calculated as the time in months from enrollment on GOG-111 to disease

progression or death (failure), or to the date of last contact for women who were still alive with no evidence of disease progression (censored). Overall survival (OS) was calculated as the time in months from enrollment on GOG-111 to death (regardless of cause) or to the date of last contact for women who were alive. Tumor response was evaluated after every 2 cycles of treatment in the women with measurable disease. Complete disappearance of all disease was required for a complete response. A partial response required a ≥50% reduction in tumor (product of perpendicular diameters). Progressive disease required a ≥50% increase in the dimensions of any lesion documented within 6 weeks of study entry or the appearance of new lesions within 8 weeks of study entry. Stable disease was defined as any condition not meeting the above categories. Women on GOG-111 who were clinically-free of disease after primary chemotherapy, or who had CA125<100 U/ml and were entered with non-measurable disease were required to undergo a reassessment laparotomy as specified in the protocol. Disease status was assessed following primary chemotherapy and classified as negative when the reassessment laparotomy showed no evidence of disease, or positive when disease progression was documented during treatment or when microscopic or macroscopic evidence of disease was observed during the reassessment laparotomy.

Tumor specimens and fluorescence in situ hybridization

Previously-untreated, primary tumor was excised during cytoreductive surgery, fixed in formalin and then embedded in paraffin. Unstained tissue sections, 5 μm in thickness, were prepared on charged glass slides. Dual-label FISH was used to quantify the number of copies of *c-MYC* and chromosome 8 in unstained slides as previously described [24]. Briefly, unstained sections were baked overnight at 60 °C, deparaffinized, dehydrated, treated for 10 min with 4% (w/v) pepsin at 45 °C, denatured for 10 min at 90 °C, hybridized for 12 to 16 h at 37 °C with a probe cocktail consisting of an alpha satellite probe to chromosome 8 (CEP8) directly labeled with Spectrum Green and a *c-MYC* region probe directly labeled with Spectrum Orange (Vysis Inc., Naperville, IL). The slides were post-washed for 5 min with 2×SSC buffer (0.3 M NaCl and 30 mM sodium citrate tribasic dihyrate, pH 7.0) at 72 °C and counterstained with 4′,6′-diamidino-2-phenyindole (DAPI). Red staining for chromosome 8 and green staining for *c-MYC* were visualized using a Zeiss Axiophot fluorescence microscope (Carl Zeiss MicroImaging, Inc. Thornwood, NY, USA) with appropriate filters and an Applied Imaging Cytovision system (Pittsburgh, PA, USA), and quantified in at least 50 tumor cells per case by one or two technicians (CC and GV; see Acknowledgements) working under the direct supervision of one of the authors (JKB). Average copies of *c-MYC* and CEP8 per case were calculated for the 28% of equivocal cases scored by two reviewers. *c-MYC* amplification is defined as ≥2 copies of *c-MYC*/CEP8 per cell, and unless specifically stated otherwise, this is the definition used. Supportive analyses were done defining *c-MYC* amplification as ≥1.5 copies of *c-MYC*/CEP8 per cell based on studies in breast cancer [22] and prostate cancer [24] showing that low level amplification increased protein expression.

Statistical methods

Biomarker and clinical data were analyzed using SPSS versions 14.0 (SPSS Inc., Chicago, IL) and SAS® version 9.1 software (SAS Institute, Inc. Cary, NC). All tests were two-sided and the level of significance was set at 0.05. Associations between categorical variables were

evaluated using Fisher's Exact Test [53,54]. Estimates of survival probabilities were calculated using the Kaplan–Meier method [55]. Logrank tests [56] were used to test the equality of survival distributions between groups. Cox proportional hazards regression [57] was used to model associations of variables with PFS or OS.

Results

GOG-111 was a randomized phase III trial that enrolled 410 women between April 13, 1990 and March 2, 1992 [52]. Ninety-seven women on GOG-111 were enrolled on the companion protocol, GOG-9404 and provided primary tumor tissue for research. The patient characteristics for the 97 women in this cohort are summarized in Table 1 and are representative of that observed in the entire GOG-111 cohort [52]. At the time of the final analysis, five women were alive with no evidence of disease, four women were alive with disease progression and 88 women died due to disease progression. Median follow-up for the nine women who were still alive at the time of the final analysis was 127 (range 15 to 207) months including three women who were lost to follow up after 15, 24 or 87 months of enrollment.

Twenty-eight (29%) of women had tumors that exhibited *c-MYC* amplification with levels ranging from the lower limit of 2.0 up to 3.3 copies of *c-MYC*/CEP8 per cell. Of the 69 (71%) of women with tumors without *c-MYC* amplification, the ratio of *c-MYC*/CEP8 ranged from 0.42 to 1.98 copies per cell. *c-MYC* amplification was not associated with patient age, race, GOG performance, stage, cell type, grade or measurable disease status following primary surgery (Table 1). There was no difference in the PFS distributions (Fig. 1A, $p = 0.885$) or OS distributions (Fig. 1B, $p = 0.745$) for women with or without *c-MYC* amplification. Unadjusted Cox modeling demonstrated that women with *c-MYC* amplification did not have an increased risk of disease progression (hazard ratio [HR] = 1.03; 95% confidence interval [CI] = 0.65–1.64; $p = 0.884$) or death (HR = 1.08; 95% CI = 0.68–1.72; $p = 0.745$) compared with women without *c-MYC* amplification (Table 2). After adjusting for patient age and stratifying by tumor stage, histologic cell type, tumor grade, measurable disease status, and treatment regimen, *c-MYC* amplification was not an independent prognostic factor for PFS (HR = 1.03, 95% CI = 0.57–1.85; $p = 0.922$) or OS (HR = 1.01, 95% CI = 0.56–1.80; $p = 0.982$) in women with suboptimally-resected, advanced stage EOC (Table 2). *c-MYC* amplification was not associated with tumor response following platinum-based combination chemotherapy or disease status following platinum-based combination chemotherapy (Table 3). *c-MYC* amplification using the ≥1.5 copies of *c-MYC*/CEP8 per cell yielded similar insignificant associations with clinical characteristics, PFS, survival, response, and disease status as reported using the ≥2.0 cut point (Tables 1–3).

Polysomy for chromosome 8, defined as a tumor with ≥4 copies of CEP8 per cell, was observed in 22 women without *c-MYC* amplification and 3 patients with *c-MYC* amplification. Polysomy 8 was not associated with any of the clinical covariates tested except for patient age at enrollment and measurable disease status (Table 1). Although statistically significant, the relationship between polysomy 8 and age category was not consistent: the proportion of women with polysomy 8 increased incrementally by age for

women up to 69 years but none of the women who were ≥70 years old had polysomy 8 (Table 1). The percentage of women with polysomy was statistically significantly higher in women with measurable disease (36%) than in those with non-measurable disease (14%). PFS distributions (Fig. 1C, $p = 0.982$) and OS distributions (Fig. 1D, $p = 0.747$) were very similar for women with vs. without polysomy 8. Unadjusted Cox modeling demonstrated that women with polysomy 8 did not have an increased risk of disease progression (HR = 0.99; 95% CI = 0.62–1.59; $p = 0.982$) or death (HR = 1.08; 95% CI = 0.67–1.74; $p = 0.747$) compared with women without polysomy 8 (Table 2). After adjusting for patient age and stratifying by tumor stage, histologic cell type, tumor grade, measurable disease status, and treatment regimen, polysomy 8 was not an independent prognostic factor for PFS (HR = 1.07, 95% CI = 0.57–2.02; $p = 0.823$) or OS (HR = 1.04, 95% CI = 0.54–1.99; $p = 0.916$) in women with suboptimally-resected, advanced stage EOC (Table 2). Finally, polysomy 8 was not associated with tumor response or disease status following platinum-based combination chemotherapy (Table 3).

Discussion

Our study is unique because it is a multicenter study of *c-MYC* amplification, detected by FISH using probes for *c-MYC* and CEP8, in FFPE primary tumor specimens from women with suboptimally-resected, advanced stage EOC treated with platinum-based combination chemotherapy. The availability of detailed clinical, treatment and follow-up data was a major strength of this study. We not only examined the relationship between *c-MYC* amplification and a full spectrum of clinical covariates but also evaluated the association between *c-MYC* amplification and multiple measures of clinical outcome. Limited FISH data for *c-MYC* amplification is currently available in EOC. Our study examined FFPE primary tumor from women with advanced stage EOC ($N = 97$), adjusted for copy number alterations in chromosome 8, used two different cut points for *c-MYC* amplification (≥2 and ≥1.5 copies of *c-MYC*/CEP8 copies) and demonstrated that *c-MYC* amplification was not associated with tumor stage, cell type, grade, PFS, OS, tumor response or disease status following platinum-based combination chemotherapy. Wang et al. studied mechanically- and enzymatically-dispersed, frozen, early and advanced stage, epithelial and non-epithelial, ovarian cancers, adjusted for copy number alterations in chromosome 8, used ≥1.5 *c-MYC*/CEP8 copies cut point for *c-MYC* amplification, and showed that *c-MYC* amplification was not associated with OS [48]. Dimova et al. studied FFPE tumor from women with invasive, early and advanced stage, epithelial and non-epithelial, ovarian cancers ($N = 280$), did not adjust for copy number alterations in chromosome 8 or have access to any measures of clinical outcome, used >2 copies *c-MYC* cut point for *c-MYC* gain/amplification, and reported that copy number increases in *c-MYC* were associated with histologic subtype but not with tumor grade or stage [51]. The disparity between our study and Dimova et al. with respect to the relationship of *c-MYC* amplification and tumor stage may be attributable at least in part to differences in tumor stages, histologic cell type and the adjustment for chromosome 8 copy number alterations.

Our study demonstrated that *c-MYC* amplification was observed in 29% (28/97) of the women with suboptimally-resected advanced stage EOC. This result is similar to the 25 to 34% levels described in some ovarian cancer studies using Southern/dot/slot blotting

[33,34,36,39,45], polymerase chain reaction (PCR) [46] or comparative genome hybridization (CGH) [44,50], but is higher than the 0 to 17% levels reported in some other studies that also used Southern/dot/slot blotting [35,40,42], PCR [38] or CGH [47], and is lower than the 38 to 55% levels provided in still other studies using Southern/dot/slot blotting [37,41,43], PCR [49], CGH [49], or FISH [48,51]. Differences in the source, type and stage of the tumor specimens, method for detecting gene amplification and the definition for *c-MYC* amplification may offer some explanation for these disparities.

In the 97 EOC studied herein, *c-MYC* amplification was not associated with tumor stage, cell type, grade, PFS, OS, tumor response or disease status after platinum-based combination chemotherapy. These findings are consistent with studies demonstrating that *c-MYC* amplification was not associated with tumor stage [46,51], histologic cell type [43,46], tumor grade [36,37,46,51], progression-free survival (PFS) [45,46], overall survival (OS) [45,46,48,49], and/or response to platinum-based chemotherapy [36] but contradict studies showing that *c-MYC* amplification was associated with tumor stage [43], histologic cell type [37,51] and/or tumor grade [41,43]. The disparities between studies with respect to the relationship of *c-MYC* amplification and tumor characteristics or outcome may be explained at least in part by differences in sample size, surgery, type of chemotherapy, tumor stage, clinical end-points, follow-up, type of tumor specimen, method for detecting *c-MYC* amplification, definition for *c-MYC* amplification and/or adjustment for copy number alterations in chromosome 8 in these studies. The lack of an association between *c-MYC* amplification and OS was also observed in other diseases including NSCLC [29,30], colorectal cancer [31] and esophageal SCC [32]. In contrast, studies in breast cancer [18–23], prostate cancer [24–27] and chondrosarcoma [28] demonstrated a strong association between *c-MYC* amplification and poor outcome.

Wang et al. undertook a chromosome 8 centromere study of ovarian cancer using interphase FISH in mechanically- and enzymatically-dispersed, frozen, invasive ovarian cancers and demonstrated that ≥50% of both *c-MYC* amplified and non-amplified tumors exhibited polysomy 8 [48]. Despite the prevalence of alterations in the centromeric region of chromosome 8 in these 40 ovarian cancers, the presence of polysomy in chromosome 8 did not appear to be correlated with clinical presentation or disease progression [48]. Herein, we utilized a dual color FISH in 97 FFPE EOC and showed that 11% (3/28) of women with *c-MYC* amplified tumors and 32% (22/69) of women with non-amplified tumors exhibited polysomy 8. Despite the differences in the prevalence of polysomy 8 in women with amplified and non-amplified *c-MYC*, we confirmed that polysomy 8 was not associated with OS [48] and went on to demonstrate that polysomy 8 was not associated with PFS, tumor response and disease status following platinum-based combination chemotherapy. Unlike studies in prostate cancer [25,27], hematologic malignancies [58], NSCLC [29–30] or chondrosarcoma [28], polysomy 8 does not appear to have prognostic value in ovarian cancer patients.

c-MYC protein is a well recognized transcription factor with a basic helix–loop–helix leucine zipper motif responsible for sequence-specific DNA binding and protein–protein interactions [59–62] that binds to an estimated 25,000 sites in the human genome and regulates as many as 15% of human genes [63]. c-MYC not only upregulates genes involved

in cell cycle regulation, metabolism, ribosome biogenesis, protein synthesis, mitochondrial function and apoptosis and represses genes involved in cell growth arrest and adhesion [64–67], but influences DNA replication, translation and chromatin structure [68–71]. In humans, the *c-MYC* gene encodes three isoforms: the transcription factors c-MYC-1 and c-MYC-2 as well as c-MYC-S, a dominant-negative inhibitor of c-MYC-1 and c-MYC-2 [72–77]. The level and function of the c-MYC isoforms can be influenced by binding other proteins [78,79] and by phosphorylation, ubiquitinylation and acetylation [80–83].

In conclusion, *c-MYC* amplification and polysomy 8 were not associated with PFS, OS, tumor response or disease status following platinum-based combination chemotherapy and have limited prognostic value in suboptimally-resected, advanced stage EOC. These results, however, do not rule out the potential that *c-MYC* has prognostic value when evaluated in a panel of biomarkers that exert epistatic interactions or in women with a borderline tumor or optimally-resected stage III EOC. In addition, the c-MYC isoforms which exhibit diverse and at times opposing functions, and the factors that affect their level and function have yet to be fully evaluated in EOC and may have prognostic value in this disease setting.

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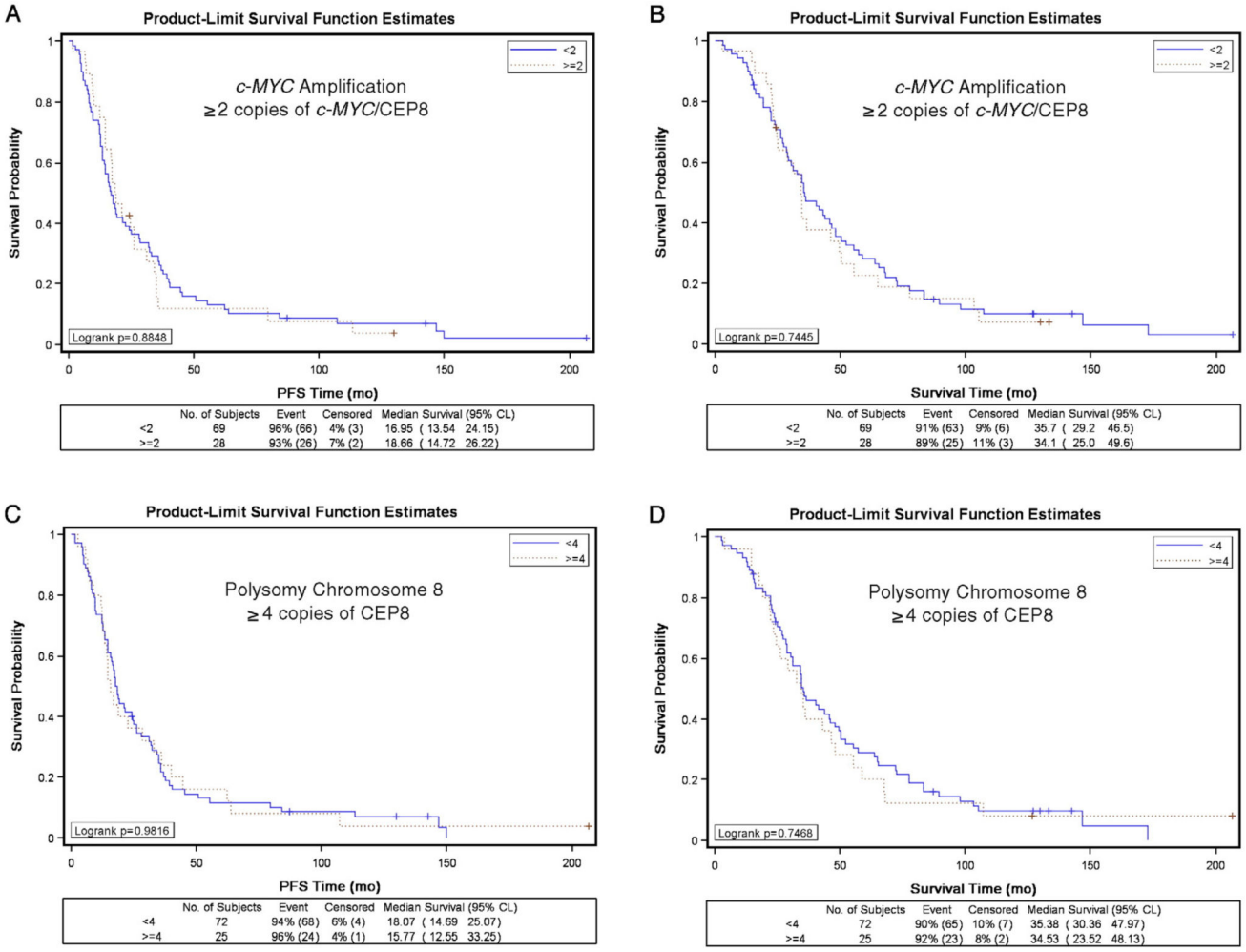

Fig. 1.

Kaplan–Meier estimate of progression-free survival (A, C) and overall survival (B, D) for women without *c-MYC* amplification (A, B: <2 copies of *c-MYC*/CEP8 per cell), with *c-MYC* amplification (A, B: ≥2 copies of *c-MYC*/CEP8 per cell), without polysomy 8 (C, D: <4 copies of CEP8 per cell) or with polysomy 8 (C, D: ≥4 copies of CEP per cell).

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Table 1

Association between clinical characteristics and *c-MYC* amplification or polysomy for chromosome 8.

	Total Cases	***c-MYC* amplification**[a]			***c-MYC* amplification**[b]			**Polysomy for chromosome 8**[c]		
		≥ 2 *c-MYC*/CEP8 copies			**≥ 1.5 *c-MYC*/CEP8 copies**			**≥ 4 CEP8 copies**		
		No	**Yes**	***P****	**No**	**Yes**	***P****	**No**	**Yes**	***p****
Patient age in years				0.479			0.382			**<0.001**
<50	30	20 (66.7)	10 (33.3)		10 (33.3)	20 (66.7)		27 (90.0)	3 (10.0)	
50–59	26	17 (65.4)	9 (34.6)		10 (38.5)	16 (61.5)		19 (73.1)	7 (26.9)	
60–69	28	23 (82.1)	5 (17.9)		15 (53.6)	13 (46.4)		13 (46.4)	15 (53.6)	
≥ 70	13	9 (69.2)	4 (30.8)		4 (30.8)	9 (69.2)		13 (100.0)	0 (0.0)	
Race				0.430			0.489			0.860
Caucasian	86	59 (68.6)	27 (31.4)		36 (41.9)	50 (58.1)		64 (74.4)	22 (25.6)	
African American	6	5 (83.3)	1 (16.7)		1 (16.7)	5 (83.3)		4 (66.7)	2 (33.3)	
Other[d]	5	5 (100.0)	0 (0.0)		2 (40.0)	3 (60.0)		4 (80.0)	1 (20.0)	
GOG performance status				1.000			0.321			0.775
Asymptomatic[score 0/1]	77	55 (71.4)	22 (28.6)		33 (42.9)	44 (57.1)		58 (75.3)	19 (24.7)	
Symptomatic[score 2]	20	14 (70.0)	6 (30.0)		6 (30.0)	14 (70.0)		14 (70.0)	6 (30.0)	
Tumor stage				0.646			0.287			0.633
Stage III	60	44 (73.3)	16 (26.7)		27 (45.0)	33 (55.0)		43 (71.7)	17 (28.3)	
Stage IV	37	25 (67.6)	12 (32.4)		12 (32.4)	25 (67.6)		29 (78.4)	8 (21.6)	
Histologic cell type				0.179			0.051			0.234
Serous	72	53 (73.6)	19 (26.4)		29 (40.3)	43 (59.7)		51 (70.8)	21 (29.2)	
Endometrioid	9	8 (88.9)	1 (11.1)		7 (77.8)	2 (22.2)		9 (100.0)	0 (0.0)	
Clear cell	2	1 (50.0)	1 (50.0)		0 (0.0)	2 (100.0)		2 (100.0)	0 (0.0)	
Mucinous	3	1 (33.3)	2 (66.7)		1 (33.3)	2 (66.7)		3 (100.0)	0 (0.0)	
Other cell types	11	6 (54.5)	5 (45.5)		2 (18.2)	9 (81.8)		7 (63.6)	4 (36.4)	
Tumor grade				0.453			0.386			0.652
1[well differentiated]	6	3 (50.0)	3 (50.0)		2 (33.3)	4 (66.7)		5 (83.3)	1 (16.7)	
2[moderately differentiated]	44	31 (70.5)	13 (29.5)		21 (47.7)	23 (52.3)		34 (77.3)	10 (22.7)	
3[poorly differentiated/not graded]	47	35 (74.5)	12 (25.5)		16 (34.0)	31 (66.0)		33 (70.2)	14 (29.8)	

	Total Cases	*c-MYC* amplification[a]			*c-MYC* amplification[b]			Polysomy for chromosome 8[c]		
		≥ 2 *c-MYC*/CEP8 copies			≥ 1.5 *c-MYC*/CEP8 copies			≥ 4 CEP8 copies		
		No	Yes	*p**	No	Yes	*p**	No	Yes	*p**
Measurable disease				1.000			0.837			**0.019**
Non-measurable	44	31 (70.5)	13 (29.5)		17 (38.6)	27 (61.4)		38 (86.4)	6 (13.6)	
Measurable	53	38 (71.7)	15 (28.3)		22 (41.5)	31 (58.5)		34 (64.2)	19 (35.8)	
Treatment				1.000			1.000			1.000
Cyclophos + cisplatin	52	37 (71.2)	15 (28.8)		21 (40.4)	31 (59.6)		39 (75.0)	13 (25.0)	
Paclitaxel + cisplatin	45	32 (71.1)	13 (28.9)		18 (40.0)	27 (60.0)		33 (73.3)	12 (26.7)	
Total	97	69 (71.1)	28 (28.9)		39 (40.2)	58 (59.8)		72 (74.2)	25 (25.8)	

[a] *c-MYC* amplification was categorized as 'No' when tumors had <2 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥ 2 copies of *c-MYC*/CEP8 per cell. Results presented as cases with row percentages in parentheses.

[b] *c-MYC* amplification was categorized as 'No' when tumors had < 1.5 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥ 1.5 copies of *c-MYC*/CEP8 per cell. Results presented as cases with row percentages in parentheses.

[c] Polysomy for chromosome 8 was categorized as 'No' when tumors had < 4 copies of CEP8 per cell or 'Yes' when tumors had ≥ 4 copies of CEP8 per cell. Results presented as cases with row percentages in parentheses.

[d] Other includes two Asians, one American Indian, and two with an unspecified race.

* *p*-value based on Fisher's Exact Test.

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Table 2

Associations between *c-MYC* amplification or polysomy for chromosome 8 and progression-free survival or overall survival.

	Progression-free survival[a]						Overall survival[a]					
	Unadjusted model			Adjusted model[b]			Unadjusted model			Adjusted model[b]		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
c-MYC amplification[c]												
≥ 2 *c-MYC*/CEP8 copies												
No	1.00			1.00			1.00			1.00		
Yes	1.03	0.65–1.64	0.884	1.03	0.57–1.85	0.922	1.08	0.68–1.72	0.745	1.01	0.56–1.80	0.982
c-MYC amplification[d]												
≥ 1.5 *c-MYC*/CEP8 copies												
No	1.00			1.00			1.00			1.00		
Yes	1.37	0.89–2.10	0.151	1.06	0.63–1.77	0.837	1.14	0.74–1.76	0.555	1.03	0.60–1.75	0.920
Polysomy for chromosome 8[e]												
≥ 4 CEP8 copies												
No	1.00			1.00			1.00			1.00		
Yes	0.99	0.62–1.59	0.982	1.07	0.57–2.02	0.823	1.08	0.67–1.74	0.747	1.04	0.54–1.99	0.916

Estimated hazard ratio (HR), 95% confidence interval (95% CI).

[a] Cox regression analysis for modeling the relative risk of disease progression or death; *p*-values are based on the Wald test.

[b] Models were adjusted for patient age at enrollment in years, and stratified by tumor stage (III vs. IV), histologic subtype (clear cell or mucinous vs. other histologic subtypes), tumor grade (well differentiated vs. moderately differentiated vs. poorly differentiated), measurable disease status (non-measurable vs. measurable), and treatment regimen (cyclophosphamide + cisplatin vs. paclitaxel + cisplatin).

[c] *c-MYC* amplification was categorized as 'No' when tumors had <2 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥2 copies of *c-MYC*/CEP8 per cell.

[d] *c-MYC* amplification was categorized as 'No' when tumors had <1.5 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥1.5 copies of *c-MYC*/CEP8 per cell.

[e] Polysomy for chromosome 8 was categorized as 'No' when tumors had <4 copies of CEP8 per cell or 'Yes' when tumors had ≥4 copies of CEP8 per cell.

Table 3

Association between *c-MYC* amplification or polysomy for chromosome 8 and clinical response or disease status after completion of first-line treatment.

	Clinical response				Disease status			
	No response	Response[a]		*p*-value*	No evidence of disease	Positive for disease[b]		*p*-value*
c-MYC amplification[c]								
≥2 *c-MYC*/CEP8 copies								
No	7 (18.4%)	31 (81.6%)	22 CR	1.000	14 (22.2%)	49 (77.8%)	34 + RL	1.000
			9 PR				15 + DP	
Yes	3 (20.0%)	12 (80.0%)	5 CR		6 (24.0%)	19 (76.0%)	14 + RL	
			7 PR				5 + DP	
c-MYC amplification[d]								
≥ 1.5 *c-MYC*/CEP8 copies								
No	3 (13.6%)	19 (86.4%)	15 CR	0.494	10 (28.6%)	25 (71.4%)	18 + RL	0.310
			4 PR				7 + DP	
Yes	7 (22.6%)	24 (77.4%)	12 CR		10 (18.9%)	43 (81.1%)	30 + RL	
			12 PR				13 + DP	
Polysomy for chromosome 8[e]4 CEP8 copies								
≥ 4 CEP8 copies								
No	8 (23.5%)	26 (76.5%)	17 CR	0.299	15 (22.7%)	51 (77.3%)	37 + RL	1.000
			9 PR				14 + DP	
Yes	2 (10.5%)	17 (89.5%)	10 CR		5 (22.7%)	17 (77.3%)	11 + RL	
			7 PR				6 + DP	

[a] Response includes a complete response (CR) or a partial response (PR).

[b] Positive for disease includes those with microscopic or gross disease at reassessment laparotomy (+ RL) or with clinical evidence of disease progression documented during first-line treatment (+ DP).

[c] *c-MYC* amplification was categorized as 'No' when tumors had <2 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥2 copies of *c-MYC*/CEP8 per cell.

[d] *c-MYC* amplification was categorized as 'No' when tumors had <1.5 copies of *c-MYC*/CEP8 per cell or 'Yes' when tumors had ≥1.5 copies of *c-MYC*/CEP8 per cell.

[e] Polysomy for chromosome 8 was categorized as 'No' when tumors had <4 copies of CEP8 per cell or 'Yes' when tumors had ≥4 copies of CEP8 per cell.

* Fisher's Exact Test.