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Research Article

Predictors of Oncologic Outcome in Patients Receiving Phase I Investigational Therapy for Recurrent or Metastatic Cervical Cancer

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ABSTRACT

Introduction: We aimed to identify clinical, pathologic, and treatment factors that are predictive of response and survival in patients with cervical cancer referred to phase I clinical trials. **Methods:** Patients with cervical cancer who received at least one dose of a phase I investigational agent at our institution between 2014 and 2022 were included. The log-rank test was used to analyze differences in progression-free survival (PFS) and overall survival (OS), and multivariable regression analysis was performed. **Results:** We included 65 patients with a median age of 41 years (range, 20–74), 3 prior therapies (range, 1–7), and 67.7% squamous carcinoma. The rate of distant metastasis at trial entry was 84.6%. The most common molecular alterations included PIK3CA (46.5%), PD-L1+ (46.2%), EPH (30.0%), and CREBBP (23.1%); 23.1% had received a prior checkpoint inhibitor. Phase I trials were for immunotherapy (58.5%) or targeted therapy (41.5%). The rate of biomarker matching was 21.5%. For all patients, median PFS was 3.6 months (95% CI, 2.0–5.2) and OS was 9.3 months (95% CI, 7.0–10.6). Factors at study entry associated with worse survival were presence of bone metastasis (PFS 1.6 vs 4.4 months: hazard ratio [HR], 2.8; $p = 0.001$; OS 3.8 vs 10.0 months: HR, 3.9; $p < 0.0001$) and absolute lymphocyte count below 1000/μL (PFS 1.8 vs 5.2 months: HR, 2.9; $p = 0.0004$; OS 7.0 vs 10.6 months: HR, 3.2; $p = 0.0009$). Factors associated only with worse OS were absolute neutrophil count above 4700/μL, hemoglobin below 10.5 g/dL, and smoking status. Grade 3+ treatment-related adverse events were seen in 16.9% of cases. **Conclusion:** Bone metastasis and absolute lymphocyte count below normal range at phase I study entry portend poor survival in patients with recurrent or metastatic cervical cancer.

Keywords: phase I trial prognosis, recurrent cervical cancer, metastatic cervical cancer, lymphopenia

INTRODUCTION

In 2022, an estimated 14,100 women will be diagnosed with cervical cancer, and 4,280 will die of this disease. Although the incidence of cervical cancer in the United States has dramatically decreased over time owing to improved early screening, the relative survival rate has not significantly improved.[1] Discovery and development of effective treatment options for recurrent or metastatic cervical cancer continue to be desperately needed.

Historically, advanced cervical cancer portended dismal prognosis with the 5-year survival rate of less than 5%.[2,3] The advent of personalized cancer therapy revolutionized the treatment of recurrent, persistent, or metastatic cervical cancer, with unprecedented responses. The addition of bevacizumab to chemotherapy improved the response rate to 48% and conferred a 4-month overall survival (OS) advantage (hazard ratio [HR] 0.71).[4] This benefit was particularly pronounced in patients with a high risk of recurrence.[2] As second-line therapy for recurrent cervical cancer, standard chemotherapy has shown poor response with rates 5–14%.[5–10] According to the updated National Comprehensive Cancer Network guidelines,[11] checkpoint inhibitors have emerged as the preferred monotherapy for second-line treatment of PD-L1 positive tumors.[12–14] In fact, pembrolizumab is moving into first-line treatment in this setting with demonstrable survival benefit.[13] Agents including tisotumab vedotin[15] and LN-145[16] have been granted fast-track approval and breakthrough designation, respectively, by the US Food and Drug Administration, based on robust results from early-phase trials. The high patient need combined with the potential for accelerated drug development accentuates the importance of identifying patients who would benefit from early-phase clinical trials.

In an effort to better determine the prognosis of patients in phase I studies, the Royal Marsden Hospital (RMH)[17] and MD Anderson (MDA)[18] scoring systems were developed. The RMH score is calculated using serum albumin level, lactate dehydrogenase (LDH) level, and number of metastatic disease sites, and the MDA score is calculated using these variables plus Eastern Cooperative Oncology Group (ECOG) performance status and presence of gastrointestinal cancer. For both scoring systems, a higher score correlates with worse OS, which has been internally and externally validated. The applicability of these scores to cervical cancer has not been investigated. Moreover, the contribution of molecular markers to response and survival has not been explored.

In the current study, we aimed to identify clinical, pathologic, and treatment factors that were associated with response and survival in patients with cervical cancer who received at least one dose of an investigational agent in a phase I clinical trial, with the ultimate goal of identifying optimal patients for referral. The utility of RMH and MDA scores in this setting was evaluated.

METHODS

All research activity was approved by the Institutional Review Board, retrospective data protocol 2021-0317. Informed consent was waived in accordance with the approved minimal-risk protocol.

We reviewed the records of all patients with cervical cancer referred for a phase I trial in the Department of Investigational Cancer Therapeutics at our institution between January 2014 and January 2022. Most phase I trials are conducted within this department at our institution in a referral-based practice. Eligible patients had cervical cancer irrespective of histologic subtype or stage who ultimately received at least one dose of a phase I investigational agent. Patients who did not receive a trial drug for any reason and those with cancers of unclear origin were excluded.

Clinical and pathologic data were abstracted, including demographics, histopathologic findings, treatment history, common laboratory parameters at trial entry, and next-generation sequencing results. Smoking status was determined from the most recent patient report on record. Trial type, use of combination therapy, treatment response, survival data, and treatment-related adverse events according to Common Terminology Criteria for Adverse Events version 5.0 (US National Cancer Institute) were also collected. Biomarker matching to the trial was assessed from clinician documentation or available biomarker data. In general, microsatellite instability and mismatch repair deficiency status were determined from next-generation sequencing. PD-L1 status was assessed by immunohistochemistry (IHC). The RMH score and MDA score were calculated for each patient. RMH score was calculated by summing the following: LDH normal = 0, LDH above upper limit of normal = 1; albumin $\geq$ 3.5 g/dL = 0, $<$ 3.5 g/dL = 1; site of metastasis $\leq 2 = 0$, $> 2 = 1$. The upper limit of normal value for LDH at our institution is 214 U/L. MDA score was calculated the same way as the RMH score, plus 1 point for ECOG performance status $\geq$ 1. The gastrointestinal tumor type criterion for the MDA score was not applicable.

Descriptive statistics were used to summarize patient characteristics. The chi-square test or Fisher exact test was used to detect differences in categorical variables, and the Wilcoxon rank-sum test or Kruskal-Wallis test was used to detect differences in continuous variables. Per Response Evaluation Criteria in Solid Tumors 1.1, objective response was defined as the sum of the complete response and partial response, and clinical benefit was defined as the sum of the objective response and stable disease. The distributions of progression-free survival (PFS) and OS were estimated using the Kaplan-Meier method. PFS was defined as the time from cycle 1 day 1 of the phase I trial to the time of progression or death, whichever occurred first; OS was defined as the

time from cycle 1 day 1 of the phase I trial to death. Times were censored at last contact for events that had not occurred. The log-rank test was performed to detect differences in survival. Continuous variables were incorporated as a linear variable when possible, and otherwise dichotomized for analysis. When applicable, clinically significant cutoff values were used: platelet count, 300,000/μL; absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) ratio, 1.9; albumin 3.5 g/L; and LDH upper limit of normal.[17–19] In other cases, the median value was used. Covariates identified as significant in the univariate analysis were then analyzed in multivariable regression based on logistic regression or Cox proportional hazards model to identify predictors of response and survival. Statistical analysis was calculated using SAS version 9.4 (SAS Institute). All *p*-values were two-sided, with 0.05 as the cutoff for statistical significance and 95% CIs included.

RESULTS

A total of 65 patients were included in the analysis. Demographic and clinical characteristics are shown in Table 1. At trial entry, the median age was 41 (range, 20–74) years and median body mass index was 23.6 (range, 13.6–57.6) kg/m^2. Patients were predominantly White (63.1%), and 30.8% were current or former smokers. All patients had an ECOG performance status of 0 or 1 (7.7% and 92.3%, respectively). Patients had mostly stage III or IV disease at diagnosis (56.9%). The most common histologic type was squamous cell carcinoma (67.7%); otherwise, 27.7% had adenocarcinoma, 3.0% had neuroendocrine carcinoma, and 1.5% had adenosquamous carcinoma. Patients had a median of three prior lines of therapy (range, 1–7). In addition, 41.5% had prior surgery for therapeutic purposes, and 23.1% had received a prior checkpoint inhibitor. Patients had median treatment-free interval of 6 months after primary therapy (range, 0–191) and median progression-free interval of 5 months immediately prior to trial enrollment (range, 1–32). At the time of referral, 84.6% of the patients had distant metastasis, with median of two sites (range, 0–5).

Forty-nine patients had next-generation molecular sequencing of various coverage. Nine different types of internal and external next-generation sequencing panels were used, which were all Clinical Laboratory Improvement Amendments certified. After adjusting the number tested, the most common alterations included PIK3CA (46.5%), PD-L1 positive (46.2%, by IHC), EPH (30.0%), and CREBBP (23.1%; Table 2). Specific PIK3CA alterations included missense mutation (4/20), amplification (2/20), and not otherwise specified (14/20). Of the 13 patients tested, 6 were PD-L1 positive and 7 were PD-L1 negative. Of the 3 EPH mutations identified, 2 were missense mutations and 1 was not otherwise specified. Of the 6 CREBBP mutations, 2 were truncation, 1 was a

Table 1. Characteristics of patients with cervical cancer at phase I clinical trial entry ($n = 65$)

Variable	Value
Demographics	
Age, median (range), y	41 (20–74)
BMI, median (range), kg/m^2	23.6 (13.6–57.6)
Race and ethnicity, *n* (%)	
White	41 (63.1)
Asian	9 (13.9)
Hispanic	8 (12.3)
Black	6 (9.2)
Other	1 (1.5)
Smoking status, *n* (%)	
Current	5 (7.7)
Former	15 (23.1)
Never	45 (69.2)
Histopathology	
FIGO stage at diagnosis, *n* (%)	
1 or 2	24 (36.9)
3 or 4	37 (56.9)
Histologic type, *n* (%)	
Squamous cell carcinoma	44 (67.7)
Adenocarcinoma	18 (27.7)
Adenosquamous carcinoma	1 (1.5)
Neuroendocrine carcinoma	2 (3.0)
Type of metastasis or recurrence, *n* (%)	
Distant	55 (84.6)
Local	10 (15.4)
Number of distant metastatic sites, median (range)	2 (0–5)
Treatment characteristics	
Lines of prior treatment, median (range)	3 (1–7)
Treatment-free interval after primary therapy, median (range), mo	6 (0–191)
Prior therapeutic surgery, *n* (%)	27 (41.5)
Prior check point inhibitor received, *n* (%)	15 (23.1)
Progression-free interval immediately prior to trial, median (range), mo	5 (1–32)
Type of trial therapy, *n* (%)	
Immunotherapy	38 (58.5)
Targeted therapy	27 (41.5)
Combination trial, *n* (%)	29 (44.6)
Immunotherapy	21 (72.4)
Targeted therapy	7 (24.1)
Radiotherapy	1 (3.4)
Therapy matched to biomarker, *n* (%)	14 (21.5)
Laboratory parameters at trial entry, median (range)	
Hemoglobin, g/dL	10.5 (8.5–14.7)
Platelet count, k/μL	230.0 (101.0–575.0)
ANC, k/μL	4.7 (1.9–14.5)
ALC, k/μL	0.97 (0.06–2.2)
ANC/ALC ratio	4.8 (1.6–58.7)
Platelet/ALC ratio	279.1 (81.5–3133.3)
Albumin, g/L	4.0 (2.7–4.6)
LDH, U/L	370.5 (111.0–624.0)
CRP, mg/L*	31.5 (1.6–916.0)
CA125, U/mL*	39.3 (10.2–2880.0)
CA19-9, U/mL*	35.7 (3.7–843.0)
CEA, ng/mL*	7.5 (0.9–27,977.0)
RMH score	1 (0–3)
MDA score	2 (0–4)

*$n < 25$.

ALC: absolute lymphocyte count; ANC: absolute neutrophil count; BMI: body mass index; CA 125: cancer antigen 125; CEA: carcinoembryonic antigen; CRP: C-reactive protein; FIGO: International Federation of Gynecologic and Obstetrics; LDH: lactate dehydrogenase; MDA: MD Anderson; RMH: Royal Marsden Hospital.

Table 2. Molecular alterations identified by next-generation sequencing in patients with cervical cancer participating in phase I clinical trials

Molecular Marker	Tested, *n*	Altered, *n* (%)
PIK3CA	43	20 (46.5)
PD-L1	13*	6 (46.2)
EPH	10	3 (30.0)
CREBBP	26	6 (23.1)
NF	37	6 (16.2)
FANC	25	4 (16.0)
ARID	26	4 (15.4)
FGF, FGFR	43	6 (14.0)
NFE2L2	37	5 (13.5)
TERT	30	4 (13.3)
BIRC	16	2 (12.5)
ATR	25	3 (12.0)
KRAS	43	5 (11.6)
GNAS	43	5 (11.6)
NOTCH	43	5 (11.6)
TSC	35	4 (11.4)
LRP1B	10	1 (10.0)
FBXW7	43	4 (9.3)
ERBB2	44	4 (9.1)
Microsatellite instability, high	13†	1 (7.7)
Akt	43	3 (7.0)
KIT	43	3 (7.0)
MET	43	3 (7.0)
MMR deficient	44	3 (6.8)
TP53	44	3 (6.8)
PTEN	43	2 (4.7)
TOP	25	0

Markers tested in fewer than 10 patients were excluded. Results are from next-generation sequencing except: *by immunohistochemistry and †including 3 by PCR.

missense mutation, 1 was a deletion, and 2 were not otherwise specified.

The phase I trials were for either immunotherapy (58.5%) or targeted therapy (41.5%); 44.6% were for combination therapy with another agent, most often another immunotherapy (72.4%). Biomarker matching was used for 14 patients (21.5%) overall, and in 40.7% of patients receiving targeted therapy as monotherapy or in combination. Median values of common laboratory parameters at cycle 1 day 1 are shown in Table 1. Tumor markers showed a wide range, limited by low sample size. The median RMH score was 1 (range, 0–3), and the median MDA score was 2 (range, 0–4).

Best responses were partial response (10.8%), stable disease (47.7%), and progressive disease (32.3%); thus, the objective response rate was 10.8% and the clinical benefit rate was 58.5%. Univariate analysis of covariates in relation to objective response and clinical benefit, including biomarker matching, showed largely nonsignificant results (Supplemental Tables S1 and S2, available online). Of note, response rate was not driven by immunotherapy in patients with traditional markers for checkpoint inhibitor response (0 response in 5 patients with high microsatellite instability, mismatch repair deficiency, PD-L1 positive, or tumor mutational burden intermediate or high).

For all patients, median PFS was 3.6 months (95% CI, 2.0–5.2), and median OS was 9.3 months (95% CI, 7.0–10.6), with an OS rate of 69% (95% CI, 56–79%) at 6 months and 31% (95% CI, 19–43%) at 12 months. Median follow-up time was 34 months. Factors at trial entry associated with both worse PFS and worse OS in univariate analysis were greater than two metastatic sites (PFS: HR, 2.6; 95% CI, 1.5–4.6; $p = 0.0013$; OS: HR, 3.0; 95% CI, 1.6–5.8; $p = 0.0007$), presence of liver metastasis (PFS: HR, 2.0; 95% CI, 1.1–3.7; $p = 0.020$; OS: HR, 2.2; 95% CI, 1.1–4.2; $p = 0.020$), presence of bone metastasis (PFS: HR, 2.1; 95% CI, 1.2–3.7; $p = 0.011$; OS: HR, 2.9; 95% CI, 1.6–5.4; $p = 0.0007$), hemoglobin < 10.5 g/dL (PFS: HR, 2.1; 95% CI, 1.2–3.6; $p = 0.0091$; OS: HR, 1.9; 95% CI, 1.1–3.4; $p = 0.026$), and ALC $< 1000/\mu L$ (PFS: HR, 2.2; 95% CI, 1.3–3.8; $p = 0.0046$; OS: HR, 1.9; 95% CI, 1.1–3.4; $p = 0.032$; Table 3). Prior exposure to checkpoint inhibitors was associated with worse PFS (HR, 2.0; 95% CI, 1.0–4.0; $p = 0.036$), but not OS (HR, 2.0; 95% CI, 1.0–4.0; $p = 0.055$). Other factors associated only with worse PFS were presence of brain and distant lymph node metastasis, progression-free interval of less than 3 months immediately prior to trial entry, and low LDH levels. Factors associated only with worse OS were smoking status, other unspecified metastasis, combination trials involving targeted therapy as second agent compared with immunotherapy as second agent, high ANC, and high C-reactive protein levels. Other characteristics, including lines of prior therapy, treatment-free interval after primary therapy, type of trial (primary investigational agent is targeted therapy vs immunotherapy), combination trial compared with monotherapy, and biomarker matching, were not associated with PFS or OS. RMH and MDA scores were also not associated ($p > 0.1$). With regard to biomarkers, BIRC alteration was associated with worse PFS ($n = 16$; HR, 10.2; 95% CI, 1.4–73.7; $p = 0.021$), and NFE2L2 alteration was associated with better PFS ($n = 37$; HR, 0.3; 95% CI, 0.07–0.9; $p = 0.039$). However, these biomarkers were excluded from further analysis owing to the large amount of missing data (missing $n = 49$ for BIRC and 28 for NFE2L2).

In multivariable regression analysis, factors at study entry associated with worse survival were presence of bone metastasis (median PFS 1.6 vs 4.4 months: HR, 2.8; 95% CI, 1.5–5.3; $p = 0.001$; median OS 3.8 vs 10.0 months: HR, 3.9; 95% CI, 2.0–7.6; $p < 0.0001$) and ALC $< 1000/\mu L$ (median PFS 1.8 vs 5.2 months: HR, 2.9; 95% CI, 1.6–5.3; $p = 0.0004$; median OS 7.0 vs 10.6 months: HR, 3.2; 95% CI, 1.6–6.3; $p = 0.0009$; Table 4, Fig. 1). In patients receiving immunotherapy ($n = 38$), ALC $< 1000/\mu L$ continued to be strongly associated with survival (PFS: HR, 4.6; 95% CI, 2.1–10.1; $p = 0.0001$; OS: HR, 8.1; 95% CI, 2.5–26.0; $p = 0.0004$; data not shown). Other factors associated only with worse OS were ANC $> 4700/\mu L$ (HR, 2.2; 95% CI, 1.1–4.2; $p = 0.018$), hemoglobin $<$ 10.5 g/dL (HR, 2.5; 95% CI, 1.3–4.8; $p = 0.0067$), and current or former smoking status (HR, 2.3; 95% CI, 1.2–4.6: $p = 0.013$).

Table 3. Univariate analysis of factors associated with PFS and OS in patients with cervical cancer treated with an investigative agent in a phase I clinical trial ($n = 65$)

Covariate	Reference	PFS HR	*p*-Value	OS HR	*p*-Value
Demographics					
Age ≤ 40 y	> 40	1.2	0.56	0.8	0.55
BMI, per unit increase	-	1.0	0.44	1.0	0.47
White race	All other	0.6	0.086	0.9	0.62
Current or former smoker	Never	1.7	0.070	1.9	*0.039**
Histopathology					
FIGO stage 3 or 4 at diagnosis	Stage 1 or 2 at diagnosis	1.3	0.32	1.5	0.20
Squamous cell carcinoma	Adenocarcinoma	1.4	0.28	1.2	0.57
Distant metastasis or recurrence	Local	1.4	0.37	1.1	0.77
> 2 metastatic sites	≤ 2 sites	2.6	**0.0013***	3.0	**0.0007***
Metastatic sites at trial entry					
Brain	No brain mets	5.9	*0.045**	1.3	0.78
Lung or pleura	No lung or pleural mets	1.3	0.29	1.1	0.63
Liver	No liver mets	2.0	**0.020***	2.2	**0.020***
Peritoneum	No peritoneal mets	1.3	0.39	1.0	0.99
Bone	No bone mets	2.1	**0.011***	2.9	**0.0007***
Soft tissue	No soft tissue mets	1.0	0.91	0.7	0.56
Distant lymph node	No distant lymph node mets	2.0	*0.015**	1.6	0.091
Other	No other type of mets	1.9	0.078	4.2	*0.0008**
Treatment characteristics					
> 2 lines of prior treatment	1–2 lines	1.4	0.25	0.9	0.64
TFI after primary therapy ≥ 6 mo	< 6 mo	1.0	0.88	1.0	0.89
Prior therapeutic surgery	No prior therapeutic surgery	1.1	0.76	0.9	0.66
Prior check point inhibitor	No check point inhibitor	2.0	*0.036**	2.0	0.055
PFI immediately prior to trial ≤ 3 mo	> 3 mo	2.0	*0.028**	1.6	0.17
Targeted therapy trial	Immunotherapy trial	0.9	0.55	0.8	0.52
Combination trial	Monotherapy	1.0	0.89	1.2	0.51
Combination type					
Targeted therapy	Immunotherapy	1.2	0.72	2.7	*0.05**
Radiotherapy	Immunotherapy	1.1	–	3.4	–
Therapy matched to biomarker	Not matched	1.4	0.27	1.2	0.63
Laboratory parameters at trial entry					
Hemoglobin < 10.5 g/dL	≥ 10.5 g/dL	2.1	**0.0091***	1.9	**0.026***
Platelet count < 300 k/μL	≥ 300 k/μL	0.8	0.53	0.7	0.38
ANC < 4.7 k/μL	≥ 4.7 k/μL	0.7	0.26	0.6	*0.048**
ALC < 1.0 k/μL	≥ 1.0 k/μL	2.2	**0.0046***	1.9	**0.032***
ANC/ALC ratio < 1.9	≥ 1.9	1.0	0.96	0.5	0.42
Platelet/ALC ratio < 279	≥ 279	1.5	0.16	0.8	0.45
Albumin < 3.5 g/L	≥ 3.5 g/L	1.1	0.74	1.3	0.49
LDH < 214 U/L	≥ 214 U/L	2.0	*0.036**	2.0	0.06
CRP < 31.5 mg/L	≥ 31.5 mg/L	0.4	0.071	0.2	*0.015**
CA125 < 39.3 U/mL	≥ 39.3 U/mL	0.4	0.097	0.7	0.38
CA19-9 < 35.7 U/mL	≥ 35.7 U/mL	1.1	0.88	0.6	0.61
CEA < 7.5 ng/mL	≥ 7.5 ng/mL	1.3	0.71	3.1	0.10
RMH score < 1	≥ 1	1.8	0.11	1.8	0.14
MDA score < 2	≥ 2	1.8	0.10	1.8	0.13
Altered molecular markers†					
AKT		1.1	0.88	1.5	0.49
ARID		1.1	0.83	1.5	0.47
ATR		2.0	0.26	1.9	0.39
BIRC		10.2	*0.021**	3.6	0.24
CREBBP		2.4	0.09	0.9	0.85
EPH		1.2	0.79	4.9	0.15
ERBB2		1.4	0.48	2.2	0.13
FANC		0.9	0.82	1.2	0.76
FBXW7		1.6	0.34	0.6	0.44
FGF, FGFR		0.9	0.8	0.7	0.57
GNAS		1.1	0.8	0.7	0.42
KIT		0.6	0.3	1.1	0.87
KRAS		0.8	0.65	1.2	0.68
LRP1B		1.8	0.49	0.6	0.65
MET		1.6	0.39	0.4	0.34

Table 3 continues on next page

Table 3. Continued

Covariate	Reference	PFS HR	*p*-Value	OS HR	*p*-Value
Microsatellite instability, high		1.1	0.9	5.0	0.13
MMR deficient		1.7	0.35	2.4	0.15
NF		1.0	0.97	0.8	0.67
NFE2L2		0.3	*0.039**	0.5	0.19
NOTCH		1.1	0.78	1.4	0.55
PD-L1		0.8	0.73	0.8	0.69
PIK3CA		1.2	0.67	0.9	0.67
PTEN		1.9	0.33	1.9	0.35
TERT		1.3	0.64	1.9	0.3
TP53		1.2	0.72	1.1	0.88
TSC		1.7	0.32	1.4	0.56

Factors significantly associated with both PFS and OS are in bold, those associated with only PFS or only OS are in italics.
*$p < 0.05$.
†Markers tested in fewer than 10 patients excluded; TOP mutation excluded owing to 0% alterations observed.
-: not applicable; –: not calculated due to low sample size; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; BMI: body mass index; CA 125: cancer antigen 125; CEA: carcinoembryonic antigen; CRP: C-reactive protein; FIGO: International Federation of Gynecologic and Obstetrics; HR: hazard ratio; LDH: lactate dehydrogenase; MDA: MD Anderson; mets: metastasis; OS: overall survival; PFI: progression-free interval; PFS: progression-free survival; RMH: Royal Marsden Hospital; TFI: treatment-free interval.

In all, 16.9% of patients experienced grade 3 or higher treatment-related adverse events. Common grade 2 or 3 events included anemia ($n = 6$), nausea or vomiting ($n = 5$), fatigue, neuropathy, and infusion reaction (all $n = 3$; Supplemental Table S3). There was one grade 4 event, which was a fever. There was one treatment-related death, due to myositis, in a patient receiving combination immunotherapy.

DISCUSSION

In our population of heavily pretreated patients with recurrent or metastatic cervical cancer referred for phase I clinical trials of targeted or immunotherapy, ALC below normal range and presence of bone metastasis at study entry independently predicted poor PFS and OS. Molecular alterations in PIK3CA, PD-L1, EPH, and CREBBP were common.

Survival and response in patients with recurrent or metastatic cervical cancer undergoing therapy in a phase I clinical trial have not been reported previously. In our analysis, median PFS was 3.6 months and median OS was 9.3 months, similar to that reported for all patients enrolled in phase I clinical trials.[17–19] This is particularly notable given that patients had received a median of 3 lines of prior therapy. Historically, patients receiving second-line or higher single-agent chemotherapy for recurrent cervical cancer have had a median PFS of 2–3 months and OS of 6–8 months.[6–8,10] Our objective response rate of 10.8% and clinical benefit rate of 58.5% were similar to those reported previously for chemotherapy[5–10] and immunotherapy.[20] We observed one treatment-related death, due to myositis, in a patient receiving dual immunotherapy including a checkpoint inhibitor. Myositis has been reported as a rare but severe toxicity of checkpoint inhibitors, and its incidence is on the rise owing to increased use.[21] Otherwise, treatment

Table 4. Multivariable logistic regression model of factors at phase I clinical trial entry associated with PFS and OS in patients with cervical cancer ($n = 65$)

Factor	Median PFS, mo†	HR (95% CI)	*p*-Value	Median OS, mo	HR (95% CI)	*p*-Value
All patients	3.6 (2.0–5.2)	—	—	9.3 (7.0–10.6)	—	—
Bone mets present	1.6 (1.0–2.1)	2.8 (1.5–5.3)	0.0010*	3.8 (1.5–9.1)	3.9 (2.0–7.6)	< 0.0001*
Not present	4.4 (2.4–7.1)			10.0 (7.6–14.7)		
ALC ≤ 1.0 k/μL	1.8 (1.4–2.8)	2.9 (1.6–5.3)	0.0004*	7.0 (3.4–9.3)	3.2 (1.6–6.3)	0.0009*
> 1.0 k/μL	5.2 (2.0–10.6)			10.6 (8.9–14.7)		
ANC > 4.7 k/μL	—	—	NS	6.9 (3.8–10.0)	2.2 (1.1–4.2)	0.018*
≤ 4.7 k/μL				11.2 (8.5–18.2)		
Hemoglobin ≤ 10.5 g/dL	—	—	NS	7.6 (3.5–10.0)	2.5 (1.3–4.8)	0.0067*
> 10.5 g/dL				10.2 (7.1–19.3)		
Smoker (current, former)	—	—	NS	7.1 (3.4–10.2)	2.3 (1.2–4.6)	0.013*
Never smoker				9.9 (7.0–14.7)		

*$p < 0.05$. †Median (range).
—: not applicable. ALC: absolute lymphocyte count; ANC: absolute neutrophil count; HR: hazard ratio; mets: metastasis; NS: not significant; OS: overall survival; PFS: progression-free survival.

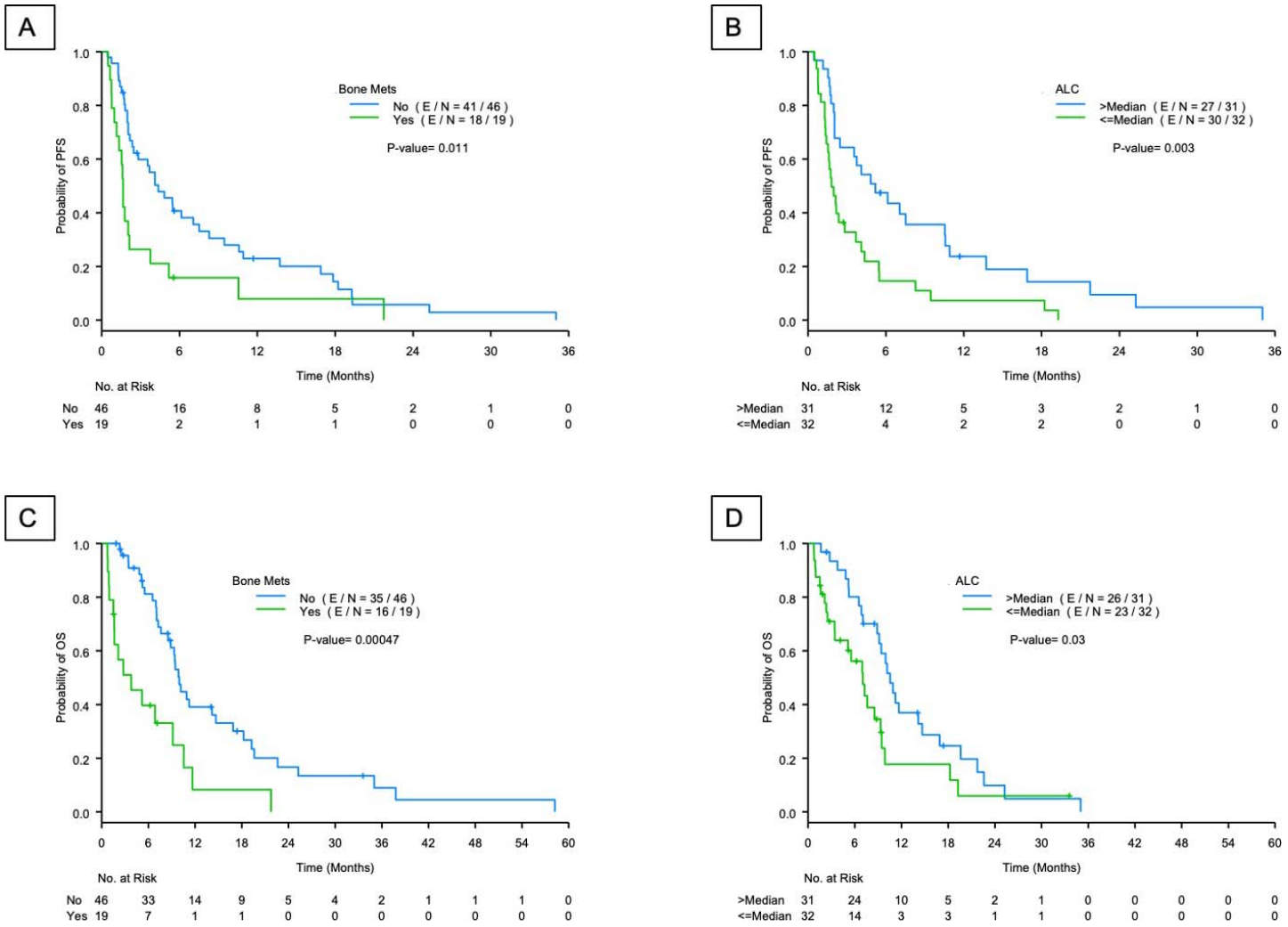

Figure 1. Kaplan-Meier curves showing the effect of bone metastasis and ALC < 1 k/μL on PFS (**A** and **B**) and OS (**C** and **D**) in patients with cervical cancer receiving an investigational agent in a phase I clinical trial. ALC: absolute lymphocyte count; E/N: event/total; mets: metastasis; OS: overall survival; PFS: progression-free survival.

was well tolerated. According to a review of phase I trials submitted to annual meetings of the American Society of Clinical Oncology from 1991 through 2002, targeted or biologic agents had lower treatment-related death rates than cytotoxic agents.[22] Although we cannot generalize a conclusion directly from our data, investigational agents in phase I clinical trials administered to patients with recurrent or metastatic cervical cancer seem to show equivalent efficacy without compromise in safety, compared with historical standard treatments, and thus should be strongly considered. This is particularly true given the relatively young age and generally high-performance status in this patient cohort.

Several inflammatory markers have been proposed to be prognostic in patients with oncologic diseases. Neutrophil to lymphocyte ratio has shown prognostic value in several types of cancer,[23] including cervical cancer.[24] The more recently described platelet to lymphocyte ratio has shown less conclusive association with survival.[25–27] Lymphopenia on its own has been associated with survival in head and neck cancers[28] and in patients receiving immune checkpoint inhibitors,[18] but this is less well described. In our analysis, ALC was associated with prognosis independently, which may be further validated in a larger cohort to provide a convenient clinical marker. This association was particularly strong for patients receiving immunotherapy. Furthermore, our finding that bone metastasis is linked to prognosis is also unique. The incidence of bone metastasis in the current study was 29.2%, which is much higher than the 0.9–1.1% incidence reported in the literature.[29,30] This may relate to patient selection, including multiple lines of prior therapy. Although adenocarcinoma histology has been associated with bone metastasis[31] and constitutes a notably large part of our cohort, the prevalence of adenocarcinoma was not enriched in the subgroup with bone metastasis (26.3%). It is unclear whether the robust association between the

presence of bone metastasis and survival is predictive or prognostic in a phase I clinical trial setting.

Our data did not show prognostic association for RMH and MDA scores, which may be attributable to limitations in sample size. A larger, preferably prospective, study is warranted. Similarly, association between molecular markers and response or survival should be further investigated. Although 75.4% of our patients had next-generation sequencing, the rate of molecular matching was 21.5%. This finding is in accordance with the interim analysis of the NCI-MATCH trial, in which national tumor-based molecular profiling was performed successfully but showed a lag in trial assignment and enrollment for actionable markers.[32] The authors attributed this to exclusions of certain histologic subtypes and mismatch of resources to demand. In our univariate data, exposure to prior checkpoint inhibitors was associated with worse PFS and trended towards worse OS. With the success of the initial wave of personalized cancer therapy, we must continue to develop the next generation of trials with emphasis on patient selection using molecular markers. Innovations are needed to widely implement molecular sequencing and efficiently screen and match patients to trials.

The current study has several limitations. The small sample size constitutes a major limitation of the study, which precludes robust statistical analysis. This is particularly applicable to the largely nonsignificant outcome association with molecular analysis. Subset analyses such as changes in survival over time or stratification by prior therapy were not possible. Less routinely tested laboratory values, as well as the contradictory association of LDH with PFS, were affected by the high number of missing values. Molecular matching was largely inferred from clinical documentation without review of each individual protocol due to lack of availability and is likely underrepresented. Details about the treatment sequence of investigational agents in combinatory trials were unavailable. The retrospective nature of the study makes it hypothesis generating and may aid in future trial design. Despite this, the current study is the first to examine a homogeneous population of patients with recurrent or metastatic cervical cancer receiving phase I investigational agents at a single institution with complete clinical, laboratory, and molecular data available.

CONCLUSION

ALC below normal range and bone metastasis at phase I study entry portend poor PFS and OS in patients with recurrent or metastatic cervical cancer. These parameters may be considered for stratification in future trials. Given the safety and sufficient efficacy of phase I investigational therapies in this population, trial enrollment should be encouraged. Further investigation into molecular alterations and their association with outcome is warranted.

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Supplemental Material

Supplemental materials are available online with the article.

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