



# L1CAM expression in uterine carcinosarcoma is limited to the epithelial component and may be involved in epithelial–mesenchymal transition

MAC Versluis<sup>1</sup> · A Plat<sup>1</sup> · M de Bruyn<sup>1</sup> · X Matias-Guiu<sup>2,3,4</sup> · J Trovic<sup>5,6</sup> · C Krakstad<sup>5,6</sup> · HW Nijman<sup>1</sup> · T Bosse<sup>7</sup> · GH de Bock<sup>8</sup> · H Hollema<sup>9</sup>

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## Abstract

Uterine carcinosarcoma (UCS) has been proposed as a model for epithelial–mesenchymal transition (EMT), a process characterized by a functional change facilitating migration and metastasis in many types of cancer. L1CAM is an adhesion molecule that has been involved in EMT as a marker for mesenchymal phenotype. We examined expression of L1CAM in UCS in a cohort of 90 cases from four different centers. Slides were immunohistochemically stained for L1CAM and scored in four categories (0%, < 10%, 10–50%, and > 50%). A score of more than 10% was considered positive for L1CAM. The median age at presentation was 68.6 years, and half of the patients (53.3%) presented with FIGO stage 1 disease. Membranous L1CAM expression was positive in the epithelial component in 65.4% of cases. Remarkably, expression was negative in the mesenchymal component. In cases where both components were intermingled, expression limited to the epithelial component was confirmed by a double stain for L1CAM and keratin. Expression of L1CAM did not relate to overall or disease-free survival. Our findings suggest L1CAM is either not a marker for the mesenchymal phenotype in EMT, or UCS is not a good model for EMT.

**Keywords** Endometrial neoplasm · Neural cell adhesion molecule L1 · L1CAM · Epithelial–mesenchymal transition · Histology

## Introduction

Uterine carcinosarcoma (UCS) is a rare subtype of endometrial cancer (EC) with a poor prognosis. Approximately 60% of cases present with advanced disease, and recurrence occurs in approximately 50% of patients [1–4]. Accordingly, 5-year survival ranges from 33 to 39%. Histology is peculiar because it contains both an epithelial

as well as a mesenchymal component [1, 5]. Various models have been proposed to explain this feature ranging from collision of two separate and original components to conversion of a common monoclonal neoplasm of epithelial (carcinomatous) origin [5–8]. Currently, most studies support the theory of conversion of an endometrial carcinoma into a cancer consisting of an epithelial and a mesenchymal component.

✉ MAC Versluis  
m.a.c.versluis@umcg.nl

<sup>1</sup> Department of Gynecology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

<sup>2</sup> Department of Pathology and Molecular Genetics/Oncologic Pathology Group, Arnau de Vilanova University Hospital, IRBLleida, University of Lleida, Lleida, Spain

<sup>3</sup> Centro de Investigación Biomédica en Red de Oncología (CIBERONC), Madrid, Spain

<sup>4</sup> Department of Pathology, University Hospital of Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Catalonia, Spain

<sup>5</sup> Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

<sup>6</sup> Department of Clinical Science, Center for Cancer Biomarkers, University of Bergen, Bergen, Norway

<sup>7</sup> Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

<sup>8</sup> Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>9</sup> Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Because UCS contains both an epithelial and mesenchymal component, UCS has been suggested as a model for epithelial–mesenchymal transition (EMT) [5, 9–14]. EMT is a process that is characterized by a functional change in tumor cells that facilitates migration and metastasis [11, 15]. By loss of cell polarity and cell–cell junctions, and by reorganization of their cytoskeleton, tumor cells acquire the ability to migrate. This transformation is thought to be essential to metastasis in gynecologic cancers as well as other tumors [13, 16]. In a study on 76 cases of UCS, Castilla et al. found a different expression of epithelial and mesenchymal markers between the two components. Expression of E-cadherin for example was limited to the epithelial component.

A possible marker for a mesenchymal phenotype is L1 cell adhesion molecule (L1CAM), a transmembrane adhesion molecule important for embryonic development [17]. The extracellular domain interacts with other binding molecules and integrins expressed on either the same or other cells. The cytoplasmic tail mainly interacts with cytoskeletal proteins. Several studies support involvement of L1CAM in EMT [18–21]. Exposure of both endometrial cancer (EC) and breast cancer cell lines to transforming growth factor B1 (TGF-B1), a known inducer of EMT, results in increased expression of L1CAM [19, 21]. Huszar et al. found that increased expression of L1CAM relates to reduced membranous expression of E-cadherin. L1CAM could be a marker for a mesenchymal phenotype of EMT in UCS.

Expression of L1CAM previously described as immunohistochemical staining of more than 10% is absent in normal endometrium [22]. In addition, expression of L1CAM is related to metastasis and poor prognosis in many cancers, including EC [17, 22–28]. In early-stage EC with endometrioid histology, expression of L1CAM is related to unfavorable pathological findings, distant recurrence and poor survival [22, 23]. Correspondingly, in high grade EC and non-endometrioid EC (NEEC), L1CAM expression is related to unfavorable pathological findings such as advanced stage and lymphovascular space invasion (LVSI) as well as distant recurrence but not survival [26–28].

We hypothesize that L1CAM could be involved in EMT in UCS as a marker for the mesenchymal phenotype and may relate to metastasis. Therefore, we aimed to evaluate L1CAM expression in a large cohort of 90 UCS patients assembled in 4 oncologic centers participating in the European Network for Individualized Treatment of Endometrial Cancer (ENITEC) collaboration. Expression was evaluated separately in the epithelial and the mesenchymal component and related to patient and tumor characteristics and survival.

## Methods

### Study population

Four-micrometer formalin-fixed slides were assembled from four separate centers (Haukeland University hospital Bergen, Norway; University hospital Lleida, Spain; Leiden University Medical Center, The Netherlands; and University Medical Center Groningen, the Netherlands). Sufficient material from 88 primary tumors and 10 metastases was available. With an overlap of 8 cases, this added up to a total of 90 cases with UCS diagnosed between 1980 and 2012 to be included in this study. Data concerning age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage as well as patient and tumor characteristics concerning age at diagnosis, histology of both components (homologue or heterologue for the epithelial component), differentiation grade, LVSI, were delivered by each participating center. All material was revised at the University Medical Center Groningen by HH and MV blinded from findings at the primary center. For some cases, clinicopathological information was missing and could not be retrieved from the slides, for example, when information on lymphovascular space involvement was missing. Follow-up data was provided by each center in an anonymized dataset and completed until October 2014. Datasets were combined into a final password-protected database. Patient identity was protected by study-specific patient numbers. Informed consent was obtained according to local protocol in each participating center.

### Histology

Slides, 4- $\mu$ m formalin-fixed paraffin-embedded sections were immunohistochemically stained as described by Bosse et al. [23]. “Briefly, formalin fixed paraffin-embedded (FFPE) tissue blocks were cut into 4  $\mu$ m slides and mounted on Starfrost slides. Antigen retrieval was achieved by microwave oven procedure in 10 mmol/L citrate buffer, pH 6. Sections were incubated overnight with primary monoclonal antibodies against L1CAM (CD171, clone 14.10, SIG-3911, Convance Inc., lot number D13KF03087, Biolegend, San Diego, USA) in a 1:500 dilution. Sections were incubated and stained for 30 min using a secondary antibody (Poly-HRP-GAM/R/R; DPV0110HRP; ImmunoLogic, Duiven, The Netherlands). The slides were counterstained with Mayer’s Haematoxylin, dehydrated and mounted. Omission of the primary antibody was used as a negative control and a highly L1CAM-expressing serous ovarian cancer as an external positive control.”

In eight cases, it was difficult to differentiate between L1CAM expression by the epithelial or mesenchymal components as both components were intermingled. Therefore, these selected cases were double stained for both L1CAM and

**Table 1** Patient and tumor characteristics in 90 cases of uterine carcinosarcoma (UCS). FIGO = International Federation of Gynecology and Obstetrics

	Number	% or IQR
Median age (years)	68.6	62.0–75.5
FIGO stage (2009)		
- I and II	50	55.36
- III and IV	40	44.4
Myometrial invasion		
- Less than 50%	43	53.1
- More than 50%	38	46.9
- Unknown	9	
Lymph node status		
- Negative	36	78.3
- Positive	10	21.7
- Unknown	44	
Lymphovascular space invasion (LVSI)		
- No	24	36.4
- Yes	42	63.6
- Missing	24	
Differentiation grade carcinoma component		
- Grade 2	6	8.3
- Grade 3	63	87.5
- Undifferentiated	3	4.2
- Unknown	18	
Histologic type carcinoma component		
- Endometrioid	27	39.1
- Non-endometrioid	42	60.9
- Unknown	21	
Histologic type sarcoma component		
- Homologue	39	53.4
- Heterologue	34	46.6
- Unknown	17	

cytokeratin-8 as expression of cytokeratin is limited to the epithelial component. Tissue sections were dewaxed in xylene and hydrated in a graded series of alcohol to tap water. Antigen retrieval was performed in 10 mM EDTA pH 8.0 in a microwave at 400 W for 15 min. Endogenous peroxidase was blocked by incubating sections for 30 min in 1% H<sub>2</sub>O<sub>2</sub>. Primary antibody against LICAM (anti-CD171, Biolegend, Sig-3911-1000, San Diego, USA) was applied in a 1:500 dilution and left to incubate overnight at 4 °C. Subsequently, tissue sections were incubated with secondary antibody (RAM-HRP; Dako, Glostrup, Denmark) and tertiary antibody (GAR-HRP; Dako, Glostrup, Denmark), both diluted at 1:100, for 30 min each at room temperature. LICAM staining was visualized with 3,3'-diaminobenzidine. After washing the sections in demineralized water, they were incubated with the antibody against cytokeratin-8 (CAM 5.2, BD Biosciences,

#345779) diluted 1:5 for 1 h at room temperature. Sections were then incubated with secondary antibody (RAMbio; Dako) and tertiary antibody (streptavidin-AP; Dako), both diluted 1:300, for 30 min each at room temperature. Cytokeratin staining was visualized using Fast Blue BB/Naphthol-AS-MX-phosphate (Sigma, F3378) for 30 min at room temperature. Sections were rinsed with demineralized water and mounted with Kaiser's glycerol gelatine (109242; Merck). Omission of the primary antibody was used as a negative control and tonsil tissue as a positive control.

## Evaluation of immunohistochemistry

Evaluation of immunohistochemistry was performed by two independent investigators (MV and AP), blinded for clinical outcome data. Expression of LICAM in either component was scored as the percentage of positive membranous staining and categorized into four groups: 0%, 0–10%, 10–50%, or > 50% as described by Meier et al. [29]. In conformity with previous publications, tumors with more than 10% expression of LICAM were considered positive [23, 29]. There was no disagreement in evaluation of the mesenchymal component. There was disagreement in evaluation of 21 cases of the carcinomatous component mainly on a score of either 3 or 4. Disagreement was resolved by consensus. Location of LICAM staining was scored as expression at the tumor center, tumor margin, or diffusely over the tumor.

## Statistical analysis

All statistical analyses were done by using SPSS (version 23, IBM Statistics, Chicago USA). For analysis, age was dichotomized into 65 and below versus above 65 years as this is an important cutoff in treatment of endometrial cancer. Recurrence was classified as local, pelvic, or distant. Disease-free survival (DFS) was defined as time until any recurrence or death of disease and disease-specific survival (DSS) as time until death of disease. Associations between patient and tumor characteristics were compared using logistic regression analyses. For survival analysis, a relation between LICAM expression and DFS, DSS, or distant recurrence was examined using Cox regression analyses. Patients without evidence of disease were censored at last date of follow-up.

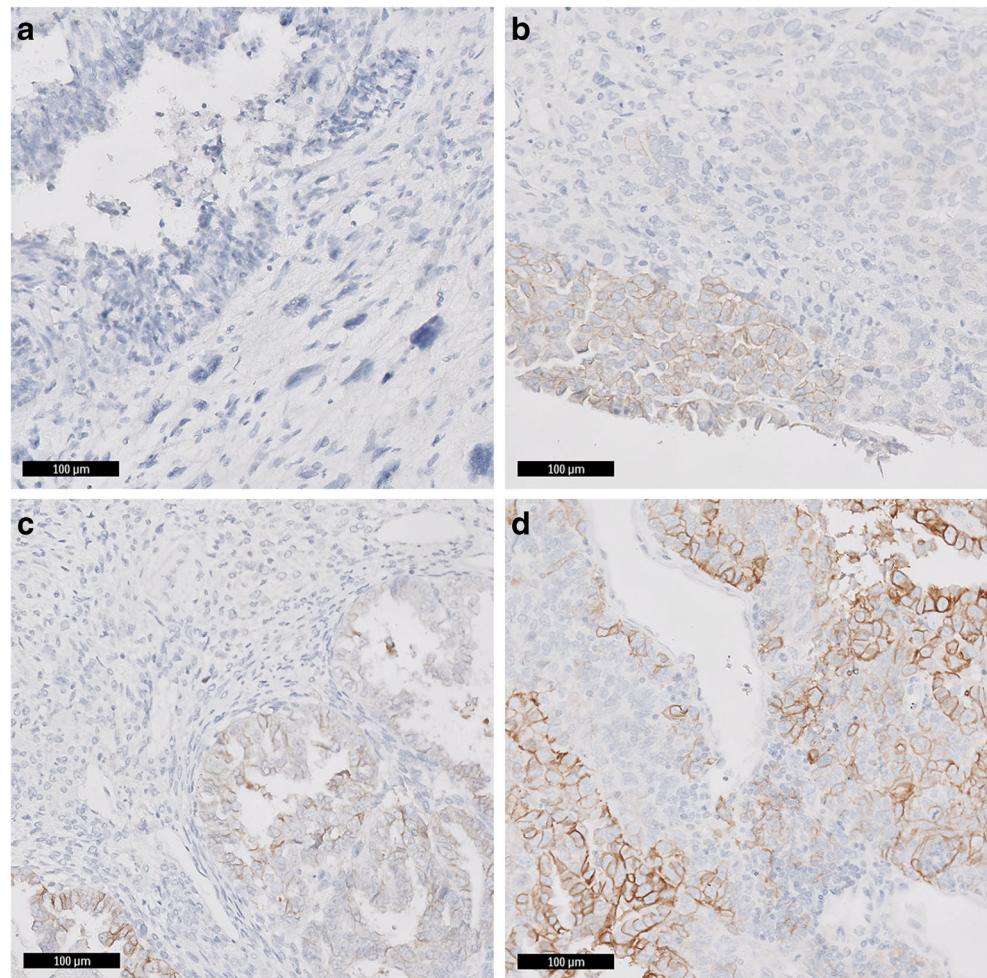
## Results

### Population

Tissue from the primary tumor was available in 88 cases. In 10 cases, metastatic tissue was available. With an overlap of 8 cases (primary as well as metastatic tissue), this added up to a



**Fig. 1** L1CCAM staining in carcinosarcoma. **a** L1CCAM expression scored as 0%. **b** L1CCAM expression scored as less than 10%. **c** L1CCAM expression scored as 10–50%. **d** L1CCAM expression scored as more than 50%. All figures are presented at  $\times 10$  magnification



total of 90 cases to be evaluated. Not all tissue contained both components. The epithelial component was available in 81 cases and the mesenchymal component in 83 cases. Patient and tumor characteristics are shown in Table 1. The median age at diagnosis was 68.6 years (IQR 62.0–75.5). A small majority of cases presented with FIGO stage 1 disease (53.3%), most other cases presented with stage 3a or 3c disease (14.4 vs 12.2%). LVSI was observed in 53.8%, and non-endometrioid histology of the epithelial component was 56.5%.

### Immunohistochemistry

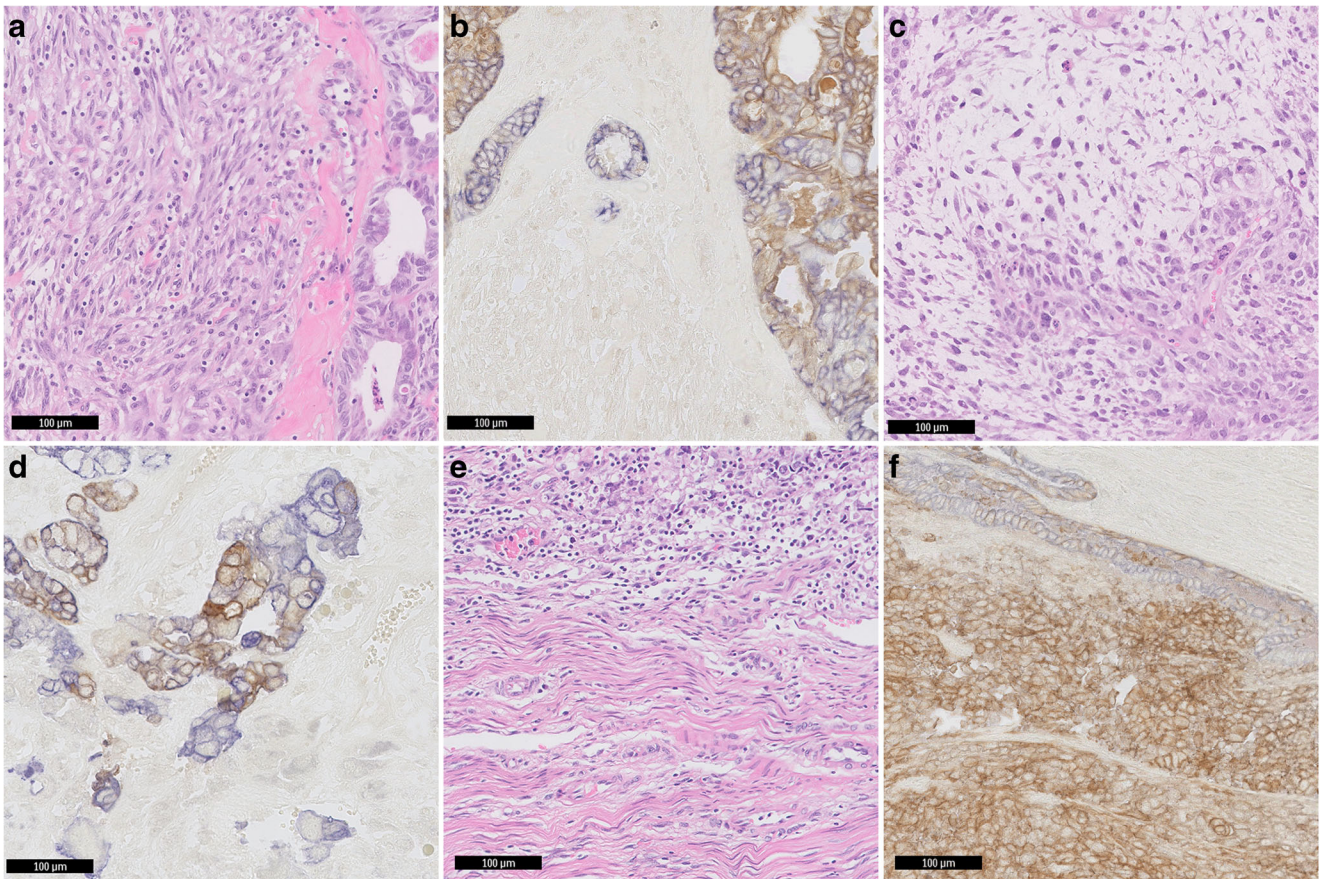
Figure 1 shows examples of L1CCAM expression in both components. Expression was not limited to either the tumor center or margin.

Table 2 shows the results of L1CCAM staining. The epithelial component was L1CCAM positive in a majority of cases (65.4%). Remarkably, the mesenchymal component was determined as negative (<10%) for L1cam in all cases. In 86.7%, no expression was found. In 13.3%, L1CCAM

**Table 2** Expression of L1CCAM in both components in 88 primary UCS tumors and 7 metastatic tumors

	Epithelial component, primary tumor, <i>n</i> (%)	Mesenchymal component, primary tumor, <i>n</i> (%)	Epithelial component, metastasis, <i>n</i> (%)	Mesenchymal component, metastasis, <i>n</i> (%)
0% expression	16 (20.2)	72 (86.7)	1 (12.5)	4 (80)
< 10% expression	11 (15.2)	11 (13.3)	3 (37.5)	1 (20)
10–50% expression	22 (27.8)		4 (50.0)	
> 50% expression	30 (38.0)			
Component not available	9	5	2	5





**Fig. 2** Examples of double stain for L1CAM (brown) and keratin (blue). **a** HE stain of case 8. This case was originally scores as L1CAM expression > 50% in the epithelial component and 0% in the mesenchymal component. **b** Double stain for L1CAM and keratin in case 8. **c** HE stain for case 9. This case was originally scores as L1CAM expression > 50% in the epithelial component and 0% in the mesenchymal component. **d**

Double stain for L1CAM and keratin in case 9. **e** HE stain for case 14. This case was originally scored as L1CAM expression > 50% in the epithelial component and < 10% in the mesenchymal component. **f** Double stain for L1CAM and keratin in case 14. All figures are presented at  $\times 10$  magnification

expression was scored less than 10%. In some of these cases, both components were intermingled and therefore difficult to distinguish. To differentiate between L1CAM expression by either component, a double stain for L1CAM and keratin was performed in eight cases. In all eight cases, L1CAM expression was limited to cells expressing keratin. Figure 2 shows examples of double staining for L1CAM.

### Patient and tumor characteristics in relation to L1CAM expression

Table 3 shows patient and tumor characteristics stratified for L1CAM expression. Logistic regression showed no relation between patient or tumor characteristics and L1CAM expression. L1CAM expression survival in the overall cohort was poor with a median DFS of 2.83 years (95%CI 0.80–4.87) and DSS of 3.30 (1.10–5.50). Known prognostic variables related to DFS in univariate Cox regression analysis: FIGO stage (HR 1.67 95%CI 1.30–2.14), myometrial invasion (HR 1.80

95%CI 0.96–3.34), and differentiation grade (HR 3.81 95%CI 1.13–12.80). LVSI was not a significant predictor for DFS. Findings were similar for DSS. Expression of L1CAM did not relate to either DFS (HR 1.48 95%CI 0.74–3.00) or DSS (HR 1.48 95%CI 0.74–3.00). There was also no relation between L1CAM expression and distant recurrence (HR 1.02 95%CI 0.45–2.30).

### Discussion

L1CAM is frequently expressed in UCS, but expression in UCS is limited to the epithelial component. Expression does not relate to patient characteristics, recurrence, or survival.

Expression of L1CAM in UCS is in accordance with other studies on L1CAM expression in aggressive histologic subtypes of EC such as non-endometrioid EC. These studies describe an L1CAM expression of more than 55% and no relation with survival [22, 23, 27]. We also find a high percentage

**Table 3** Patient and tumor characteristics and L1CAM expression. Data exclude missing values. FIGO = International Federation of Gynecology and Obstetrics

	Epithelial component ( <i>n</i> = 79)		
	L1CAM negative (%)	L1CAM positive (%)	Odds ratio (95% CI)
Age below/above 65			
- 65 and below	12 (44.4)	19 (37.3)	Reference 0.74
- Above 65	15 (55.6)	32 (62.7)	(0.29–1.19)
FIGO stage (2009)			
- I and II	18 (66.7)	28 (53.8)	Reference
- III and IV	9 (33.3)	24 (46.2)	0.58 (0.22–1.54)
Myometrial invasion			
- Less than 50%	14 (53.8)	26 (54.2)	Reference
- More than 50%	12 (46.2)	22 (45.8)	1.01 (0.39–2.64)
Lymph node status			
- Negative	14 (87.5)	21 (72.4)	Reference
- Positive	2 (12.5)	8 (27.6)	0.38 (0.07–2.03)
Lymphovascular space invasion (LVSI)			
- No	13 (58.1)	29 (67.4)	Reference
- Yes	9 (40.9)	14 (32.6)	1.43 (0.50–4.15)
Differentiation grade carcinoma component			
- Grade 2	3 (13.0)	3 (7.0)	Reference
- Grade 3	18 (18.3)	39 (90.7)	2.17 (0.40–11.80)
- Undifferentiated	2 (8.7)	1 (2.3)	0.50 (0.03–8.92)
Histologic type carcinoma component			
- Endometrioid	11 (52.4)	15 (35.7)	Reference
- Non-endometrioid	10 (47.6)	27 (64.3)	0.5 (0.17–1.46)
Histologic type sarcoma component			
- Homologue	12 (50.0)	24 (57.1)	Reference
- Heterologue	12 (50.0)	18 (42.9)	1.33 (0.49–3.65)

of L1CAM positive tumors and no relation between L1CAM expression and survival. A strong relation between expression and survival is therefore unlikely. An explanation for the absence of a relation could be the already poor survival in cohorts of NEEC and the high expression of L1CAM in NEEC as compared to EEC as suggested by van der Putten et al. [27]. Remarkably, L1CAM expression is not expressed in the mesenchymal component. Our working hypothesis was that L1CAM expression could act as a marker for a mesenchymal component in UCS. Several other studies describe increased expression of L1CAM after induction of EMT. In endometrial cancer cell lines, TGF- $\beta$ 1 induces expression of L1CAM and EMT [19, 21]. Exposure to TGF- $\beta$ 1 results in increased expression of L1CAM through upregulation of the EMT transcription factor Slug. In turn, expression of L1CAM relates to cell migration and invasion [21]. TGF- $\beta$ 1-induced L1CAM expression is related to decreased expression of E-cadherin, and E-cadherin expression is limited to the epithelial component in UCS [10, 19]. Considering our findings, L1CAM is

either not a marker for the mesenchymal phenotype in EMT, or UCS is not a good model for EMT.

However, this does not exclude a relevant contribution of L1CAM expression in an early stage of EMT where cancer cells gain motility and invasive properties. This could be by direct function as an adhesion molecule or indirect by acting as a signaling molecule [17, 20]. At a later stage, motility and invasive properties may become less relevant when tumor cells form a secondary tumor.

A strength of this study is a large cohort of 90 UCS cases made possible through an international collaboration. The resulting population covers well the diversity of this type of cancer as can be seen in Table 1. Another strength is the stepwise approach with a double stain for cases where histology proved difficult. A limitation is the retrospective nature of the study.

In conclusion, we describe a large cohort of 90 cases with UCS where the majority of tumors stained positive for L1CAM but where expression is limited to the epithelial



component. L1CAM could be involved in development of UCS and EMT at an early stage but is not a marker for the mesenchymal phenotype. Our study provides further insight into the possible mechanism of EMT and metastasis. Expression of L1CAM did not relate to unfavorable patient and tumor characteristics, recurrence, or survival.

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**Author contributions** All authors have made a substantial contribution to conception and execution of the study including acquisitions of data, processing of material, analysis and interpretation of data, as well as writing of the manuscript. All authors approve of publication.

### Compliance with ethical standards

The experiments reported here were carried out in agreements with the Declaration of Helsinki principles and in agreement with local legislation at each participating center.

**Conflict of interest** The authors declare that they have no conflict of interest.

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