Discovery of a biomarker candidate for surgical stratification in high-grade serous ovarian cancer

Haonan Lu1,2, Paula Cunnea1, Katherine Nixon1, Natasha Rinne1, Eric O. Aboagye1,2 and Christina Fotopoulou1

BACKGROUND: Maximal effort cytoreductive surgery is associated with improved outcomes in advanced high-grade serous ovarian cancer (HGSOC). However, despite complete gross resection (CGR), there is a percentage of patients who will relapse and die early. The aim of this study is to identify potential candidate biomarkers to help personalise surgical radicality.

METHODS: 136 advanced HGSOC cases who underwent CGR were identified from three public transcriptomic datasets. Candidate prognostic biomarkers were discovered in this cohort by Cox regression analysis, and further validated by targeted RNA-sequencing in HGSOC cases from Imperial College Healthcare NHS Trust (n = 59), and a public dataset. Gene set enrichment analysis was performed to understand the biological significance of the candidate biomarker.

RESULTS: We identified ALG5 as a prognostic biomarker for early tumour progression in advanced HGSOC despite CGR (HR = 2.42, 95% CI (1.57–3.75), p < 0.0001). The prognostic value of this new candidate biomarker was additionally confirmed in two independent datasets (HR = 1.60, 95% CI (1.03–2.49), p = 0.0368; HR = 3.08, 95% CI (1.07–8.81), p = 0.0365). Mechanistically, the oxidative phosphorylation was demonstrated as a potential biological pathway of ALG5-high expression in patients with early relapse (p < 0.001).

CONCLUSION: ALG5 has been identified as an independent prognostic biomarker for poor prognosis in advanced HGSOC patients despite CGR. This sets a promising platform for biomarker combinations and further validations towards future personalised surgical care.

It is well accepted that incorporating maximal effort or radical surgery into the initial management of HGSOC significantly contributes to more favourable outcomes for patients, including those with high tumour burden and disseminated disease. Nevertheless, prospective and retrospective data indicate that there is a cohort of patients who will experience early relapse and have less favourable outcome despite complete gross resection (CGR). While there have been many efforts in identifying the patient subgroup that will end up with visible post-operative residual disease, studies focusing on identifying those patients that will have an unfavourable outcome despite CGR are scarce and findings are often influenced by suboptimal or inhomogeneous surgical quality.

The present work attempts to address this unmet need and describes the identification and validation of a transcriptomic biomarker, using multiple HGSOC patient cohorts, that could reliably predict those patients that may not benefit from extensive, multi-visceral cytoreductive techniques, and should therefore have a more tailored approach. Consequently, in the future, we could help personalise surgical treatment for all patients and direct radicality towards those that will benefit most and avoid any unnecessary surgical morbidity in patients without real survival benefit.
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Table 1. Patient characteristics in the TTC and HH cohorts.

| Characteristics | TTC (n = 536) | HH (n = 126) | p-value |
|-----------------|--------------|--------------|---------|
| Age (%)         |              |              |         |
| ≤60             | 270 (50.4)   | 65 (51.6)    | ns      |
| >60             | 208 (38.8)   | 61 (48.4)    |         |
| Unknown         | 58 (10.8)    | –            |         |
| Stage (%)       |              |              |         |
| III             | 479 (89.4)   | 93 (73.8)    | <0.0001 |
| IV              | 57 (10.6)    | 33 (26.2)    |         |
| Post-operative residual disease (%) |          |              |         |
| CGR             | 136 (25.4)   | 82 (65.1)    | <0.0001 |
| Non-CGR         | 400 (74.6)   | 44 (34.9)    |         |
| Follow-up (FU; months) |       |              |         |
| Median          | 46.2         | 46.3         | ns      |
| IQR             | 25.0–75.3    | 17.7–67.9    |         |
| PFS (months)    | 16.0         | 18.4         | <0.0001 |
| IQR             | 10.8–28.2    | 11.7–37.3    |         |
| PFS (months)    |              |              |         |
| CGR             | 21.1         | 23.4         | ns      |
| Non-CGR         | 15           | 13.3         |         |
| OS (months)     | 41.0         | 58.2         | 0.0017  |
| CI              | 37.3–45.3    | 50.1–65.9    |         |
| Relapsed within the FU time (%) |          |              |         |
| No              | 169 (31.5)   | 53 (42.1)    | 0.0317  |
| Yes             | 367 (68.5)   | 73 (57.9)    |         |

METHODS

Public datasets

Four Affymetrix U133 publicly available datasets from patients with high-grade serous ovarian cancer (HGSOC) were downloaded and used in this study: The Cancer Genome Atlas (TCGA), the Tothill (GSE9891) patient cohort, the Charité University Hospital, Berlin, patient cohort (GSE14764) and the UVA-55 cohort (GSE30161). The raw CEL data were downloaded from Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) with accession numbers GSE82191 (TCGA), GSE9891 (Tothill), GSE14764 (Charité) and GSE30161 (UVA-55), respectively. The combined cohorts of TCGA, Tothill and Charité are referred to the TTC cohort and were used as the training dataset for analysis. The UVA-55 cohort was used as a second independent validation dataset. The clinical characteristics of patients in TCC, HH and UVA-55 cohort are summarised in Table 1 and Supplementary Table 1. CGR refers to patients with complete gross resection of tumour burden, non-CGR refers to patients with any remaining residual disease.

Targeted RNA sequencing

RNA was extracted from fresh frozen tumour tissues (n = 85) from the Hammersmith Hospital cohort (HH cohort), including only patients that had primary cytoreductive surgery and CGR, using the protocol described elsewhere in detail. Briefly, each frozen tumour was lysed using a Tissuelyser II (Qiagen, UK) at 15 Hz for 2 min. RNA was then extracted using the RNeasy kit (Qiagen, UK) following the manufacturer’s protocols and quantified using the Bioanalyzer system (Agilent, USA).

To quantify the mRNA expression of ALGS, GPR107 and NUP188 in each tumour sample, total RNA from each individual case was first reverse transcribed into cDNA using ProtoScript® II Reverse Transcriptase (NEB, USA). The cDNAs were then amplified with a pool of indexed primers using TruSeq Targeted RNA Custom Panel Kit (Illumina, USA). The primers were selected using the Illumina DesignStudio. The amplicon sizes in the cleaned PCR product were quality controlled using a TapeStation (Agilent, USA). Next, forty-eight samples were multiplexed in one single MiSeq run, with SR 50 setting which generated 20 million reads per run. The experimental procedures were performed blinded from the study end-point.

TTC and UVA-55 cohort data normalisation

Independent gene expression microarray studies often show significant batch effect. To minimise any batch effect within the combined TTC cohort which originated from three independent studies, frozen robust multi-array analysis (RMA) methodology was first applied to normalise the three microarray datasets (TCGA, Tothill and Charité). The RMA method was chosen as it is particularly robust when combining multiple microarray datasets for analysis. Briefly, RMA function from ‘limma’ package was applied with arguments of background = ‘none’, normalise = ‘quantile’, summarise = ‘robust_weighted_average’ and target = ‘probeset’. Next, the three RMA normalised datasets were combined and batch-adjusted by COMBAT using ‘merge’ function from ‘inSilico-Merging’ package in R.

The UVA-55 dataset (GSE30161) was normalised using the robust multi-array average method from ‘affy’ package in R.

Probe selection for biomarker discovery analysis

Affymetrix microarray platforms contain multiple probes for individual genes, however, filtering should be performed to considered as relapse event. According to the GCIG criteria, response to chemotherapy is being defined on biochemical (i.e. CA125 levels) as well as radiological (i.e. CT /MRI) and clinical level (i.e. ascites, pleura effusion, performance status, etc.). Patients who progressed or relapsed during or within 6 months after platinum-based chemotherapy were classified as platinum refractory/ resistant and those who did not experience a relapse during follow-up or did so at a longer time interval than 6 months after last platinum treatment were defined as platinum sensitive. To note, both the Charité University Hospital and Hammersmith Hospital Imperial College Healthcare NHS centres are certified centres of excellence for ovarian cancer surgery by the European Society of Gynaecologic Oncology (ESGO). The inclusion criteria of the patients in this study were: (1) Advanced (FIGO stage III–IV) HGSOC patients who have undergone primary cytoreductive surgery followed by platinum-based chemotherapy, (2) available tumour samples snap frozen and banked following primary surgery. The exclusion criteria were: (1) Patients with relapsed disease or previous treatment for other cancers; (2) banked samples of the patient with poor tumour tissue quality (e.g. low tumour cellularity and RNA quality). Histological review of tumour samples collected was performed by expert gynaecopathologists based in the West London Gynaec Cancer Centre at Hammersmith hospital, Imperial College Healthcare NHS Trust. This study followed the REMARK criteria for prognostic biomarker discovery. The Table 1 lists the clinicopathological data of the data and samples used.

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remove low-quality probes. To solve this issue, we correlated microarray probes with RNA-sequencing (RNAseq) data using gene names from the TCGA ovarian cancer dataset. Microarray probe: RNAseq pairs with a Pearson coefficient <0.6 were removed. Furthermore, among the multiple probes that target a single gene, the probe that showed the strongest positive Pearson correlation with the corresponding RNAseq data was retained for downstream analysis. As a result, 9207 probes corresponding to unique genes were included in the downstream biomarker discovery analysis.

Survival analysis
To identify potential significant biomarkers of surgical outcome in the TTC cohort, all 9207 probes were correlated with progression-free survival (PFS) as the primary study end-point using Cox proportional hazard regression. The p-values generated were adjusted for multiple testing using the Benjamini & Hochberg procedure. The candidate biomarkers were then tested for their independence by adjusting the Cox model for FIGO stage and age. The C-index as a measure of survival model fitting was calculated using ‘coxph’ function in ‘survival’ package. All the Kaplan–Meier analyses in this study were performed using ‘ggkm’ function from ‘ggkm’ package in R. The cut-off for ALG5-high and ALG5-low was defined by ALG5 expression at upper tertile in TTC, HH and UVA-55 cohorts.

Gene set enrichment analysis
To discover potential biological pathways associated with ALG5 expression, each gene in the TCGA ovarian cancer gene expression microarray dataset was correlated with ALG5 using ‘cor.test’ function in R 3.2.2. The global genes were ranked by the p-values in negative log10 ratio. The ranked gene list (Supplementary Table 2) was then used in the GSEA software (http://software.broadinstitute.org/gsea/index.jsp; Broad Institute), with 1000 permutations, classic enrichment statistic and KEGG as pathway database.

RESULTS
Clinical significance of post-operative residual disease in HGSOC
Clinical outcome data from three independent datasets, the Cancer Genome Atlas (TCGA),13 the Tothill and Charité cohort (TTC) and b Hammersmith cohort (HH). Only HGSOC patients with FIGO stage III–IV are included. P-values from log-rank test are indicated in the bottom left. Hazard ratios (HR) and p-values from Cox proportional hazard regression are indicated on the top left. c Proportion of patients with PFS of <12 months, >12 months and <24 months, and >24 months in the TTC and HH cohort. HGSOC patients with post-operative CGR status and FIGO stage III–IV are included in this analysis.

Discovery and validation of a prognostic biomarker for surgical outcome
The gene expression microarray datasets for patients with CGR in the TTC cohort were combined (Supplementary Fig. 2) and used as the training analysis dataset (n = 136), to identify prognostic biomarkers for patients with less favourable prognosis despite having undergone a CGR (Fig. 2).
Fig. 2 Biomarker discovery workflow. 1 HGSOC patients with FIGO stage III-IV and CGR from TCGA, Tothill and Charité datasets were identified; Affymetrix U133 microarray-based gene expression profile from the TTC cohort were combined and adjusted for batch effect; 2 Unique probes from Affymetrix U133 microarray that had >0.6 Pearson coefficient with corresponding RNA-sequencing data in the TCGA dataset were identified and selected. 3 Continuous Cox proportional hazard regression model was applied for the 9207 probes. Three candidate biomarker genes for PFS with FDR <25% were identified. 4 The three candidate biomarkers were validated in the HH cohort by targeted RNA-sequencing, and then validated in the UVA-55 (GSE30161) cohort by Affymetrix U133 microarray.

Table 2. Summary of Cox proportional hazard regression of ALG5, GPR107, NUP188 in TTC, HH and UVA-55 cohorts.

| Cohort | Gene symbol | Univariate | Multivariable* |
|--------|-------------|------------|----------------|
|        |             | Hazard ratio | 95% CI | p-value | Hazard ratio | 95% CI | p-value |
| TTC    | ALG5 (218203_at) | 2.42 | 1.57–3.75 | \(p < 0.0001\) | 1.90 | 1.10–3.29 | \(0.0209\) |
|        | GPR107 (211979_at) | 0.337 | 0.199–0.574 | \(p < 0.0001\) | 0.361 | 0.190–0.686 | \(0.00185\) |
|        | NUP188 (212691_at) | 0.340 | 0.199–0.581 | \(p < 0.0001\) | 0.260 | 0.126–0.536 | \(0.000263\) |
| HH     | ALG5        | 1.60 | 1.03–2.49 | \(0.0368\) | 1.62 | 1.06–2.49 | \(0.0255\) |
|        | GPR107     | 0.948 | 0.343–2.63 | 0.92 | 0.801 | 0.273–2.36 | 0.687 |
|        | NUP188    | 0.984 | 0.671–1.44 | 0.935 | 0.953 | 0.647–1.41 | 0.810 |
| UVA-55 | ALG5 (218203_at) | 3.08 | 1.07–8.81 | \(0.0365\) | 3.36 | 1.05–10.7 | \(0.0406\) |
|        | GPR107 (211979_at) | 0.451 | 0.117–1.75 | 0.249 | 0.447 | 0.113–1.77 | 0.252 |
|        | NUP188 (212691_at) | 0.398 | 0.11–1.44 | 0.160 | 0.289 | 0.0616–1.36 | 0.116 |

Bold values indicate statistical significance \(p < 0.05\).

*Multivariable analysis adjusted for stage and age. Gene expression, stage and age as continuous variables.

In the TTC cohort, three genes, ALG5, GPR107 and NUP188, were significantly associated with PFS in the Cox proportional hazards regression analysis, using the mRNA expression level of each gene as a continuous variable. The three genes had hazard ratios (HRs) of 1.76 (95% CI: 1.35–2.30; \(p < 0.0001\); range: 7.73–11.3; C-index: 0.623), 0.591 (95% CI: 0.456–0.765; \(p < 0.0001\)) and 0.647 (95% CI: 0.522–0.803; \(p < 0.0001\)), respectively; and these associations were below a false discovery rate (FDR) of 25%. The expression of ALG5, GPR107 and NUP188 failed to retain any association with PFS in the HH cohort (HR \(p = 0.803\); range: 7.73–11.3; C-index: 0.6; Table 2), and UVA-55 cohort (HR = 3.36, 95% CI: 1.05–10.7, \(p = 0.0406\); C-index: 0.692, Table 2). These associations were independent of known clinical prognostic factors, including age and FIGO stage (Supplementary Fig. 4a, b and Supplementary Table 4). In addition, ALG5 expression remains consistent across primary ovarian tumour, omental tissue and peritoneal disease (Supplementary Fig. 4c). GPR107 and NUP188 failed to retain any prognostic significance for PFS in the HH or UVA-55 validation cohorts.

In addition to the Cox regression analysis which used ALG5 expression level as a continuous variable, Kaplan–Meier analysis was also performed to confirm the association of dichotomised ALG5 expression with PFS in each cohort (Fig. 3). The patients with CGR in the ALG5-high subgroup had a median PFS of 15.6 months (TTC), 18.3 months (HH) and 14.5 months (UVA-55) compared to 27.3 months (TTC), 38.8 months (HH) and 32.9 months (UVA-55) in the ALG5-low CGR subgroup.

We further examined the CGR and non-CGR patient subgroups in both HH and UVA-55 cohorts (Supplementary Fig. 5). As expected, CGR HGSOC patients in the ALG5-low subgroup showed a trend of better PFS compared to non-CGR patients (HH: HR = 0.543, 95% CI: 0.271–1.09, \(p = 0.0838\); UVA-55: HR = 0.3, 95% CI: 0.0858–1.05, \(p = 0.0593\)). However, the association between surgical outcome and PFS diminished in the ALG5-high subgroup.
sensitivity, potentially associated with chemotherapy response due to a fucylation pathway, (Fig. 5b and Supplementary Table 2). As a validation, correlations between ALG5 expression is independent of response to platinum-based chemotherapy. We, therefore, tested if there was an association of clinical and surgical outcome in HGSOC patients. We, therefore, propose biomarkers (Supplementary Fig. 6). No relevant correlations were observed, between ALG5 and MYLK3 methylation status or between ALG5 expression and RPV. Moreover, ALG5 remained as an independent prognostic factor even after inclusion of the MYLK3 methylation and RPV in the multivariable Cox regression model (Supplementary Fig. 6). Furthermore, ALG5 expression was not significantly associated with the established general prognostic molecular subtypes biomarkers in HGSOC (Supplementary Fig. 7).

ALG5 expression is associated with oxidative phosphorylation. To better understand the potential biological significance of the variability of ALG5 expression, we identified the biological pathways correlated with ALG5 expression, using pre-ranked gene set enrichment analysis (GSEA). The list of pathways that are significantly associated with ALG5 expression from the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database is shown in Fig. 4a. The oxidative phosphorylation pathway ranks as the most significantly associated pathway (p < 0.001, FDR < 1%) and is also closely linked to the known function of ALG5 (Dolichyl-phosphate beta-glucosyltransferase), which facilitates glucose transfer during N-linked protein glycoylation.22,23 The enrichment plot illustrates the enrichment of oxidative phosphorylation-related genes in the ALG5-correlated gene list: 75.8% of the genes in the oxidative phosphorylation pathway are among the top ALG5-correlated genes (leading edge; Fig. 5b and Supplementary Table 2). As a validation, correlations between ALG5 and two known genes in the oxidative phosphorylation pathway, SUCLA2 or ATP5L, are shown (Fig. 4c, d), again confirming the strong correlation between ALG5 and the oxidative phosphorylation pathway.

ALG5 expression is independent of response to platinum-based chemotherapy. To delineate whether the prognostic value of ALG5 is also potentially associated with chemotherapy response due to a known link between oxidative phosphorylation and platinum sensitivity,24-26 we investigated whether there was any correlation between ALG5 expression and chemotherapy response in the TCGA and HH datasets (Fig. 5a and Supplementary Fig. 8). We could not identify any significant association between ALG5 and chemotherapy response.

DISCUSSION

In the present study, we have identified and independently validated a prognostic biomarker that could help predict progression of HGSOC in patients who have undergone complete gross resection followed by adjuvant chemotherapy. The prognostic value of this novel biomarker, ALG5, appears to be independent from other well-known prognostic factors such as age, FIGO stage and molecular subtypes. By combining with existing prognostic markers, ALG5 could be used as part of clinical pathway to guide treatment options. Hence, ALG5 expression may indicate a distinct biological mechanism reflective of post-operative remission, independent of therapeutic effort.

Cytoreductive surgery for advanced ovarian cancer has experienced a vast evolution over the last decades, reaching from an initial nihilism towards a presumed ‘hopeless’ disease, to the development of ‘ultraradical’ debulking techniques in an effort to reach the ‘holy grail’ of complete tumour resection. However, this increased radicality has not come without a cost. Increased surgical complications, longer theatre times and hospital stays, exhaustion of infrastructural and financial resources have continued to present a challenge, especially for healthcare systems with limited availability and support.27 Most researchers have focused on identifying those patients who cannot have complete gross resection, despite maximal surgical effort, specialised training skills and optimal infrastructural support. However, so far there has been a failure to identify, establish and validate prognostic and predictive biomarkers that could reliably stratify patients to the appropriate surgical pathway towards personalised surgical care. The ultimate goal would be to direct surgical radicality towards those who will benefit most, sparing those patients, who will not gain any benefit, from unnecessary surgical morbidity. We demonstrated across multiple cohorts of HGSOC patients with CGR, that patients with low ALG5 expression have a significantly longer PFS than those with high ALG5. Importantly, we have also shown that in patients with low ALG5 expression, surgical effort does indeed matter, in that those patients with CGR have significantly better survival than patients with residual...
disease of any type. This finding contradicts current arguments towards the value of surgery in advanced ovarian cancer, which claim that it is mainly the tumour biology that dictates survival and also operability and not actual surgical effort.\textsuperscript{6,27} Our data indicate that tumour debulking is an important factor for patient survival and maximal surgical effort can shift the patients towards a more favourable prognosis group.

\textit{ALG5} expression is not associated with known prognostic biomarkers for ovarian cancer including molecular subtypes, \textit{MYLK3} promoter methylation or CT-based biomarker RPV, suggesting \textit{ALG5} may represent a novel biological pathway not affected by CGR. Molecular subtypes were originally derived from transcriptomic data, and the mesenchymal or C1 subtype was shown associated with poor prognosis in HGSOC.\textsuperscript{14} Nevertheless, we did not observe a significant association between molecular subtypes and PFS in the CGR cohorts. Moreover, the prognostic value of \textit{ALG5} was also independent of any interaction or influence on platinum response.

In addition, we demonstrated that \textit{ALG5} expression was significantly associated with a number of biological pathways, including oxidative phosphorylation ($p < 0.001$), which further indicates a prognostic value for \textit{ALG5}. Oxidative phosphorylation, or OXPHOS, is a metabolic process, which generates ATP by transporting electrons across a series of mitochondrial transmembrane protein complexes.\textsuperscript{28} Many cancer types were found to prefer glycolysis instead of OXPHOS to produce ATP, so called ‘Warburg effect’.\textsuperscript{28} Nevertheless, it has been observed that a subset of cancers have an intact mitochondrial metabolism.\textsuperscript{29} Based on this finding, a number of small molecule inhibitors including metformin, arsenic trioxide and CAI (Carboxyamidotriazole) have been used or developed to target the OXPHOS pathway.\textsuperscript{29,30} Studies have also shown that ovarian cancer cells and ovarian cancer stem cells display heterogeneity in their selection of an energy source,\textsuperscript{31–33} and suggest that this flexibility in using either glycolysis or OXPHOS may signal a survival adaptation.\textsuperscript{31} It would therefore be interesting to test whether \textit{ALG5}-high tumours are sensitive to inhibitors of the OXPHOS pathway, as an alternative therapeutic strategy for patients with CGR at early relapse.

A limitation of the present study is the inhomogeneity in surgical techniques and approach, as reflected on the highly disparate total CGR rates between the different cohorts analysed, that may dilute the implementation of our findings in a purely maximal effort surgical setting. Also, further analysis is required to
Fig. 5  ALGS expression may not directly predict primary chemotherapy response. The associations between ALGS mRNA expression and a primary chemotherapy response, b CCNE1 amplification and c BRCA1/2 mutation status in the TCGA dataset. P-values from two-tailed t-test are indicated.

acknowledge whether the identified biomarker could be also predictive of overall survival. As a next step, we propose the prospective validation of ALGS expression in a multi-centre cohort of patients undergoing maximal effort cytoreductive surgery in specialised centres for ovarian cancer surgery with established surgical quality as per objective criteria.18 Furthermore, the combination of gene expression and methylation profiling, and imaging-based approaches may lead to the establishment of a more robust prognostic model.

In summary, we have identified a novel prognostic biomarker that may identify HGSC patients with a more adverse tumour biology, that are less likely to benefit from radical surgical cytoreduction. Prospective validation studies and even a future prospective randomised controlled trial allowing stratification of patients according to their tumour biology profiles are warranted before the safe implementation of any new biomarker into the clinical routine. In the future, this potential biomarker, together with other existing markers or factors, could be combined to generate a score for surgical benefit, allowing stratification of patients to personalised surgical options and alternative treatment pathways.

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AUTHOR CONTRIBUTIONS
C.F. and H.L. conceived and designed this study. K.N. and N.R. collected the clinical annotations. P.C. prepared the tumour samples. H.L. collected the RNA-sequencing data and performed bioinformatics analysis. H.L., P.C., K.N., N.R., E.A. and C.F. contributed to the interpretation of data. H.L., P.C. and C.F. wrote the manuscript. All authors revised the manuscript.

ADDITIONAL INFORMATION
Ethics approval and consent to participate Frozen tumour specimens were provided by the Imperial College Healthcare NHS Trust Tissue Bank after full informed patient consent. The ethical approval was obtained from the Hammersmith and Queen Charlotte’s & Chelsea Research Ethics Committee approval 05/Q0406/17B. The procedures involved human participants were done in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to publish This manuscript does not contain any individual patient data.

Data availability The RNA-sequencing data and clinical annotations are accessible in Mendeley Data with the identifier https://doi.org/10.17632/kw736vpsd.1.

Competing interests The authors declare no competing interests.

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