The prognostic significance of PD-L1 expression in patients with glioblastoma: A meta-analysis

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Background: Glioblastoma (GBM) is a malignant brain tumor associated with high morbidity and mortality rates with a poor prognosis. In recent years, studies on prognostic markers such as programmed death ligand 1 (PD-L1) have increased; however, their conclusions remain controversial. Here, relevant literature was reviewed and a meta-analysis was performed to clarify the correlation between PD-L1 expression and overall survival (OS) in GBM.

Methods: The non-foundational literature on PD-L1 expression associated with OS in GBM up to February 2022 was searched in the PubMed, Medstr, Cochrane, and Web of Science databases. Literature was rigorously screened according to inclusion and exclusion criteria, the total hazard ratio (HR), and corresponding 95% confidence intervals (CIs).

Results: Calculating the combined HR value and corresponding 95% CI of HR=1.124 (95% CI: 1.047–1.201, P=0.000, I² (I-squared)=48.8%), it was shown that PD-L1 expression was significantly associated with low OS in GBM patients. Although I² = 48.8% < 50%, to make the results more credible, in the cutoff values ≥10% subgroup HR=1.37 (95% CI: 1.07–1.67, P=0.000, I² = 0%), which was also the result found in the first meta-analysis. In contrast, in the cutoff value ≥5% subgroup HR=1.14 (95% CI: 0.98–1.30, P=0.000, I² = 59.8%) and in the cutoff value median PD-L1 expression levels subgroup HR=1.05 (95% CI: 0.92–1.18, P=0.000, I² = 0%), indicating that PD-L1 expression was not associated with low OS in GBM. Furthermore, in four studies, we found no significant correlation between PD-L1 expression and the progression-free survival of GBM (HR=1.14, 95% CI:0.40–1.88, P=0.03, I² = 29.3%).

Conclusion: PD-L1 expression was significantly associated with low OS in GBM patients; however, this result needs to be interpreted with caution and requires a large, multicenter clinical study in patients with similar baseline data for further evaluation.

KEYWORDS
glioma, glioblastoma, PD-L1, CD274, B7-H1, prognostic glioma, a primary
Introduction

Glioma, a primary malignant central nervous system tumor, has high morbidity and mortality rates (1). The higher the pathological grade, the more malignant the tumor and the worse the prognosis; glioblastoma is considered the most malignant central nervous system tumor, with an overall 5-year survival rate of only 9.8% (2). The prognosis is very poor, even with a range of conventional treatments available such as surgical resection combined with postoperative radiotherapy (3). Fortunately, in recent years, treatments including the blockade of immune checkpoints (stimulatory or inhibitory factors that generate immune responses) and chimeric antigen receptor T-cell therapy have offered hope for patients (4, 5). Studies have shown that various malignancies are groundwork in this regard (6); for example, blocking programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoints can modify the prognosis of non-small cell lung cancer (NSCLC), gastric cancer, head and neck squamous cell carcinoma, and melanoma to some extent (7–11). With the successful treatment of melanoma and NSCLC with monoclonal antibodies against PD-1/PD-L1, immunotherapy may become a promising approach for the treatment of glioma (12, 13). Although PD-1/PD-L1 expression has been validated in GBM (14–27), the conclusions are controversial and require further investigation.

In this study, a meta-analysis based on previous studies was conducted to verify the correlation between high/positive PD-L1 expression and overall survival (OS) in GBM. Conclusions differing from previous studies were obtained, demonstrating the need for continued in-depth studies of PD-L1 to predict a prognosis in GBM.

Materials and methods

Study identification and data collection

This meta-analysis was conducted based on the recommendations and criteria developed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (28). By using keywords and free words (“GBM” or “glioblastoma”) and (“PD-L1,” “CD274,” or “B7-H1”) in the PubMed, Metstr (http://fmrs.metstr.com/index.aspx), Cochrane, and Web of Science data searches, all literature up to February 2022 was evaluated manually and screened for usable literature (G and J), and senior reviewers (Z) resolved any disputes therein. Finally, basic data from the included literature were extracted, such as the year of publication, first author, country, sample size, cutoff, material, assay method, staining pattern, presence of 1p/19q codeletion, O6-methylguanine-DNA-methyltransferase (MGMT) methylation status, IDH mutation status, analysis methOS rate and 95% confidence interval (CI), progression-free survival (PFS), and 95% CI. The extraction of results was prioritized under multifactorial analysis and for the literature without a corresponding OS hazard ratio (HR) and 95% CI but with corresponding Kaplan–Meier curves. The interrupted point-taking method of Engauge Digitizer version 12.1 was used to extract the survival rates and transform them into HR and 95% CI.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were followed for article selection. The inclusion criteria were as follows: 1) the study investigated the prognostic value of PD-L1 expression in GBM; 2) literature was from the CGGA- and TCGA-published databases; 3) pathological findings were present confirming GBM in all patients with GBM; and 4) all patients were initially diagnosed with GBM. The exclusion criteria were as follows: 1) identical literature in different databases; 2) literature dealing with GBM recurrence; 3) similar meta-analyses; and 4) reviews, letters, and basic trials.

Quality assessment

Two independent reviewers (G and J) assessed the quality of the included studies using the Newcastle–Ottawa Quality Assessment Scale (NOS) (29), which included three main entries (Table 1, 14–27). According to the relevant literature, an NOS score ≥5 was defined as high quality based on the literature (29).

Statistical analyses

The extracted HR values and 95% CIs were combined and displayed in deep forest plots, and the vertical line passing through one was defined as an invalid line that would suggest that PD-L1 expression does not predict a GBM prognosis. P<0.05 was defined as statistically significant. Furthermore, in the Cochrane Handbook criteria, heterogeneity is expressed by the Higgins I-squared (I2) statistic, and when I2 >50% indicates significant heterogeneity (30), a random-effects model was chosen to represent the final combined results; when it was <50%, a fixed-effects model was chosen. When there was significant heterogeneity, subgroup analysis, sensitivity analysis, and meta-regression were used to identify the sources of heterogeneity. Finally, funnel plots were used to detect the presence of publication bias, and when the funnel plots were asymmetric,
| Author and year | Country     | Index | Patients | Age mean ± SD | KPS | Material | Assay | Staining pattern | presence of 1p/19q codeletion |
|----------------|-------------|-------|----------|---------------|-----|----------|-------|------------------|-----------------------------|
| Yawei Liu 2013 | Denmark     | Protein | GBM      | 58.53±10.13   | NM  | NM       | IFC   | NM               | NM                          |
| Nduom, k 2016  | USA         | Gene   | GBM      | NM            | NM  | TCGA     | NM    | NM               | NM                          |
| Berghoff 2014  | Austria     | Protein | GBM      | 58.81±10.43   | ≥70 | FFPE     | IHC   | Membranous       | NM                          |
| Berghoff cohort 2014 | Austria | Gene   | GBM      | NM            | NM  | TCGA     | Agilent microarray | NM                     | NM                          |
| Zeng, J. 2016  | China       | Protein | GBM      | NM            | NM  | TCGA     | IHC   | Membranous/Cytoplasm | NM                          |
| Jiheun Han 2016 | Korea       | Protein | GBM      | 57.24±12.28   | NM  | TMA      | IHC   | membranous/cytoplasmic | NM                          |
| Kyu 2018       | Korea       | Protein | GBM      | 58.18±12.09   | NM  | TMA/FFPE | IHC   | Membranous/fibrillary | NM                          |
| Arnon 2021     | Denmark     | Protein | GBM      | 64.15±7.08    | NM  | FFPE     | NM    | NM               | NM                          |
| Dieter 2017    | Germany     | Protein | GBM      | NM            | NM  | FFPE     | IHC   | NM               | NM                          |
| Dieter cohort 2017 | Germany | Gene   | GBM      | NM            | NM  | TCGA     | Agilent microarray | NM                     | NM                          |
| Chia-Ing 2018  | Italy       | Protein | GBM      | NM            | ≥70 | ADCTA    | IHC   | patchy/diffuse fibrillary and geographic membraneous | NM                          |
| Chia-Ing cohort 2018 | Italy | Protein | GBM      | NM            | ≥70 | reference | IHC   | patchy/diffuse fibrillary and geographic membraneous | NM                          |
| Zheng 2016     | China       | Gene   | GBM      | NM            | NM  | CGGA     | NM    | NM               | NM                          |
| Zheng cohort 2016 | China   | Gene   | GBM      | NM            | NM  | TCGA     | RNAseq data | NM                     | NM                          |
| Drew Pratt 2018 | USA         | Protein | GBM      | 51.2±12.2     | NM  | TMA      | IHC   | NM               | NM                          |
| Drew Pratt cohort 2018 | USA | Gene   | GBM      | NM            | NM  | TCGA     | NM    | NM               | NM                          |
| Zhiyuan Zhu 2020 | China       | Gene   | GBM      | NM            | NM  | TCGA     | NM    | NM               | NM                          |
| Lingui Su 2020 | China       | Protein | GBM      | NM            | NM  | IHC      | Membranous | NM                     | NM                          |
| Yasuo Takashima 2018 | Japan     | Gene   | GBM      | 59.02±12.74   | NM  | TCGA     | NM    | NM               | NM                          |
| Author and year | MGMT methylation status | IDH mutation status | Cut off | Number | analysis method | OS | PFS | NOS |
|-----------------|------------------------|--------------------|--------|--------|-----------------|----|-----|-----|
| Yawei Liu 2013 | NM                     | NM percentage      | ≥10%   | 17     | NM              | 1.5| 1.05| 2.14| NM | NM | NM | NM | 7 |
| Nduomk 2016     | NM                     | NM percentage      | 0.37   | 152    | MA              | 1.52| 1.03| 2.25| NM | NM | NM | NM | 7 |
| Berghoff 2014   | MGMT                   | NM percentage      | ≥5%    | 117    | MA              | 1.18| 0.75| 1.88| NM | NM | NM | NM | 5 |
| Berghoff cohort | NM                     | NM Median PD-L1 expression levels | 446 | MA | 1.036| 0.87| 1.23| NM | NM | NM | NM | 5 |
| Zeng, J. 2016   | NM                     | NM Percentage      | ≥5%    | 62     | MA              | 1.32| 0.96| 1.82| NM | NM | NM | NM | 5 |
| Jiheun Han 2016 | NM                     | NM Percentage      | ≥5%    | 54     | MA              | 4.958| 1.557| 15.79| NM | NM | NM | NM | 5 |
| Kyu 2017        | NM                     | IDH-1 Percentage   | ≥5%    | 115    | MA              | 1.204| 0.584| 2.485| NM | NM | NM | NM | 6 |
| Arnon 2021      | MGMT                   | IDH wildtype Median PD-L1 expression levels | 163 | MA | 1.05| 0.8| 1.5| NM | NM | NM | NM | 7 |
| Dieter 2017     | NM                     | IDH1/2 wildtype    | NM     | 48     | NM              | 0.973| 0.5| 2.0| NM | NM | NM | NM | 7 |
| Dieter cohort 2017 | NM                   | NM                 | NM     | 467    | NM              | 0.98| 0.85| 1.2| NM | NM | NM | NM | 7 |
| Chia-Ing 2018   | MGMT                   | IDH-1 Percentage   | ≥5%    | 27     | MA              | 0.354| 0.103| 1.219| MA | 0.528| 0.178| 1.563| 7 |
| Chia-Ing cohort 2018 | MGMT             | IDH-1 Percentage   | ≥5%    | 20     | MA              | 0.654| 0.254| 1.685| MA | 1.435| 0.498| 4.137| 7 |
| Zheng 2016      | NM                     | IDH1/2 mutations   | NM     | 127    | NM              | 2.2| 1.49| 3.24| NM | NM | NM | NM | 6 |
| Zheng cohort 2016 | NM                   | IDH mutations      | NM     | 160    | NM              | 1.47| 1.05| 2.05| NM | NM | NM | NM | 6 |
| Drew Pratt 2018 | NM                     | IDH wildtype       | Percentage ≥5% | 125 | NM | 2.45| 1.62| 3.72| NM | NM | NM | NM | 7 |
| Drew Pratt cohort 2018 | NM            | IDH wildtype       | Percentage ≥5% | 488 | NM | 1.19| 1| 1.42| NM | NM | NM | NM | 6 |
| Zhiyuan Zhu 2020 | NM                     | NM                 | NM     | 150    | MA              | 1.291| 1.051| 1.586| NM | NM | NM | NM | 6 |
| Lingrui Su 2020 | NM                     | NM percentage      | ≥10%   | 47     | MA              | 1.31| 1| 1.72| NM | NM | NM | NM | 6 |
| Yasuo Takashima 2018 | NM               | NM Median PD-L1 expression levels | 158 | NM | 1.07| 0.88| 1.29| NM | NM | NM | NM | 6 |

IHC, immunohistochemistry; IFC, immunofluorescence histochemistry; FFPE, formalin-fixed paraffin-embedded; TMA, tissue microarray; TCGA, The Cancer Genome Atlas; UA, univariate analysis; MA, multivariate analysis; HR, hazard ratio; CI, confidence interval; NM, not mentioned; Cut-off: Cut-off criterion for PD-L1 positive; KPS, Karnofsky Performance Score; PFS, progression-free survival; NOS: Selection (0–4 points): Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at start of study, comparability control for important factor (0–2 points); outcome (0–3 points): the assessment of the outcome, was follow-up long enough for outcomes to occur, adequacy of the follow-up of cohorts.
Egger’s linear regression and Begg’s rank were used for further quantitative evaluation. The aforementioned data analyses were performed using Stata 16.0.

Results

Search results

A total of 319 publications were initially identified based on the search strategy. Of these, 305 were subsequently excluded for the following reasons: meta-analysis (n=3); GBM recurrence (5); letters, reviews, and base trials (20); and other (277), of which one was excluded for providing HR and 95% CI but the total number of patients for which HR was calculated was unclear (31); another did not provide HR and CI (32) (Figure 1). In total, 14 papers, containing 19 studies, were finally identified for inclusion (Table 1). The 19 studies included 2,943 patients; 8 studies assessed PD-L1 expression from gene expression, and the remaining 11 assessed PD-L1 expression from protein expression. A total of 10 cases showed PD-L1 expression detected by immunohistochemistry (IHC), and 1 case was detected by the immunofluorescence histochemistry (IFC) method. Of these, PFS values were present in four studies. The cutoff values for the percentage of PD-L1 expression–positive cells varied among the included studies, with eight studies having a cutoff value of ≥5%, five studies did not have a cutoff defined, three studies had a median PD-L1 expression level, two studies had a cutoff value of ≥10%, and one study had a cutoff defined as 0.37. Among the analysis methods, eight studies were multifactorial analyses and the others did not mention the analysis type.

Correlation between overall survival, progression-free survival, and programmed death ligand 1 in GBM

The combined HR and corresponding 95% CI were calculated as HR=1.12 (95% CI: 1.047–1.201, P=0.000, I² = 48.8%), indicating that PD-L1 expression was significantly associated with OS in GBM (Figure 2). Although I² = 48.8% < 50%, to make the results more credible, in the cutoff values ≥10% subgroup HR=1.37 (95% CI: 1.07–1.67, P=0.000, I² = 0%), which was also the result found in the first meta-analysis. In contrast, in the cutoff value ≥5% subgroup HR=1.14 (95% CI: 0.98–1.30, P=0.000, I² = 59.8%) and in the cutoff value median PD-L1 expression levels subgroup HR=1.05 (95% CI: 0.92–1.18, P=0.000, I² = 0%), indicating that PD-L1 expression was not associated with low OS in GBM (Figure 3). Furthermore, in four studies, we found no significant correlation between PD-L1 expression and PFS in GBM (HR=1.14, 95% CI:0.40–1.88, P=0.03, I² = 29.3%) (Figure 4).

Heterogeneity and sensitivity analysis

To further explore the sources of heterogeneity, the included literature data were analyzed using a sensitivity analysis; results showed that single studies were not associated with heterogeneity (Figure 5). Second, a subgroup analysis was performed based on gene and protein expression; results showed that in the gene expression subgroup HR=1.12 (95% CI: 1.03–1.20, P=0.000, I² = 53%) and in the protein expression subgroup HR=1.15 (95% CI: 0.99–1.32, P=0.000, I² = 50.4%), there were no reductions of heterogeneity (Figure 6); Meta-regression was used to test
whether the country, year, age, Karnofsky Performance Score (KPS), MGMT methylation status, IDH mutation status, assay, and method of analysis affected heterogeneity. The results of the meta-regression showed that the inclusion of four variables (eight variables) resulted in a heterogeneity between the studies of Tau 2 = 0, which was 0.0303 less than the previous value of 0.0303 in Figure 2, implying that these factors could be used to explain 48.8% of the heterogeneity between studies (Table 2).

**Publication bias**

Funnel plots were used to assess the presence of publication bias (Appendix A Figures A1); when the funnel plots were asymmetric, Egger and Begg tests were used for quantitative assessment (Appendix: Figures A2, A3). As shown in Table 3, P=0.18 > 0.05, 95% CI: –5.499226–2.712886, indicating the absence of publication bias in the included studies.

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**Figure 2**
Association between PD-L1 expression and OS of GBM patients.

**Figure 3**
Analysis of subgroups with different cutoff values of PD-L1.
Discussion

PD-L1 is expressed by a variety of cell types, including macrophages, T cells, B cells, and a subset of non-hematopoietic cell types such as vascular endothelial cells (33). Aberrant expression is present not only in glioma cell lines but also in other tissue specimens (34–36). To date, little is known about the mechanisms regulating PD-L1 expression, although one study suggested that it is regulated by two basic mechanisms: innate immune resistance–mediated structural expression and acquired immune resistance–mediated inducible expression (37). In tumor cells, interferon gamma (IFN-γ), which responds to an antitumor immune activity, is a major regulator of PD-L1; PD-L1 expression in tumors can also be activated by oncogenic mutations, such as the deletion of phosphatase and tensin homologue in gliomas (38–40).

PD-L1 expression has been observed in cancers such as NSCLC, melanoma, and colorectal cancer (41–43). In addition, PD-L1 expression has been found in gliomas, but
the significance in predicting its expression in glioma patients remains controversial. For example, a study by Knudsen et al. (20) on 163 patients with glioblastoma showed that high median PD-L1 expression levels were not significantly related to prognosis, both under univariate and multifactorial analyses (univariate: HR=0.89, 95% CI: 0.66–1.23, P=0.58; multifactorial: HR=1.05, 95% CI: 0.8–1.5, P=0.8). In contrast, Han et al. (18) performed an immunohistochemical analysis of pathological sections from 54 glioma patients and defined at least 5% of cells detected by membrane staining as PD-L1 positive (without regard to staining intensity); high PD-L1 expression was related to gliomas and OS under multifactorial analysis (HR=4.958, 95% CI:1.557–15.79). Although there have been an increasing number of studies on the role of PD-L1 in predicting glioma prognosis in recent years, the conclusions remain mixed. Even though the index, patients, materials, assay, staining pattern, cutoff date, and analysis methods were the same as Han et al. (18), a study by Lee KS (19) showed that PD-L1 expression did not predict prognosis in glioma patients (HR=1.204,95% CI: 0.584–2.485, P=0.615).

Because of this inconsistency, this study reviewed and analyzed all the published literature on the role of PD-L1 expression in predicting OS in GBM patients. The results

TABLE 2 Meta-regression.

| Variable     | Hr    | Coef. | Std. Err. | t     | P>|t| | [95% Conf. Interval] |
|--------------|-------|-------|-----------|-------|-------|---------------------|
| Country      | -0.463142 | .1435912 | 0.32 | 0.754 | -3662554 | 273627 |
| Year         | -0.0577189 | .2209592 | 0.26 | 0.798 | -5481216 | 4326687 |
| Age          | .0808237 | .1512203 | 0.07 | 0.946 | -2487031 | 2647506 |
| KPS          | -2289972 | 1.450993 | 0.16 | 0.878 | -3.46201 | 3.004016 |
| MGMT         | -1.1435453 | 3.524006 | -0.28 | 0.789 | -1.305298 | 1.018208 |
| IDH          | 0.567062 | 2.178329 | 0.26 | 0.800 | -1.4286556 | 5.420681 |
| Assay        | -0.080288 | 3.354776 | -0.24 | 0.816 | -1.827776 | 0.6672027 |
| Analysis method | 0.074851 | 6.897726 | 0.11 | 0.913 | -1.459424 | 1.614394 |
| _cons        | 3.97794 | 10.0847 | 0.39 | 0.702 | -18.49216 | 26.44804 |

Meta-regression Number of obs = 19; REML estimate of between-study variance tau^2 = 0, % residual variation due to heterogeneity I-squared_res = 0.00%; Proportion of between-study variance explained Adj R-squared = %; Joint test for all covariates Model F.
showed a correlation between PD-L1 expression and low OS in GBM patients. Further subgroup analysis showed that PD-L1 did not correlate with low OS in GBM patients in terms of protein expression, which was inconsistent with the findings of Wang H (44). Through discussion, it was found that the HR values included in this study were multifactorial, whereas the study by Wang et al. was univariate. In addition, this meta-analysis found a statistically significant heterogeneity of 0% (P=0.000) in the subgroup with a PD-L1 cutoff ≥10% for the first time, although further studies are needed to demonstrate this due to the paucity of literature. In the meta-regression, differences in the country, year, age, KPS, MGMT methylation status, IDH mutation status, assay, and method of analysis affected heterogeneity.

Fortunately, even though no immune checkpoint inhibitors have been approved for glioma (24), the efficacy of PD-1/PD-L1 inhibitors has been validated in preclinical glioma models; PD-1/PD-L1 inhibitors have been shown to restore antitumor T-cell activity and improve survival, which provides a theoretical basis for clinical trials (45–50). For example, in a study by Reiss SN (51), pembrolizumab prolonged PFS in some patients despite a low response rate. In addition, Lim (52) confirmed that nivolumab was well tolerated by newly diagnosed GBM patients, the incidence of adverse events was consistent with other reported neurological frequencies, and no deaths due to drug toxicity were reported; however, survival data require further follow-up. Therefore, there is a need to further investigate the relationship between PD-L1 expression and low OS in GBM patients. In addition, it has been shown that PD-L1 mRNA is expressed in all glioma grades and shows grade dependency (25, 53), possibly due to the association of expression with the vascular endothelial growth factor, matrix metalloproteinase 9, and KI-67. Further studies are needed to better understand these relationships.

Although the present study showed a correlation between PD-L1 expression and low OS in GBM patients, there are some limitations. First, although we analyzed the effect of the MGMT methylation status and IDH mutation status on heterogeneity, we could not further analyze the prognosis of PD-L1 expression in the MGMT methylation status or IDH mutation status only because the MGMT methylation status or IDH mutation status is not mentioned in part of the literature. Second, this study was retrospective and, as such, it was not possible to define GBM according to the latest WHO pathological classification (54), and only four studies mentioned PFS values. In addition, the impact of treatment on the prognosis of GBM patients could not be further explored because some treatment options were not mentioned. Finally, despite the low heterogeneity of the present study, PD-L1 in protein expression was not shown to be associated with low OS in GBM patients in the subgroup analysis, and despite the analysis of the reasons for this, further studies are needed to demonstrate the relationship between PD-L1 and the prognosis of GBM patients.

Conclusions

In conclusion, despite the limitations of this study, a correlation was found between PD-L1 expression and poor OS in GBM. Statistically significant heterogeneity was found in the subgroup with a PD-L1 cutoff ≥10% after pooled analysis, providing a theoretical basis for prospective clinical studies. Furthermore, meta-regression analysis demonstrated that the country, year, age, KPS, MGMT methylation status, IDH mutation status, assay, and method of analysis-affected heterogeneity were sources of heterogeneity. After controlling for these, the correlation between PD-L1 expression and low OS in GBM patients will become clearer, and interventions aimed at improving patient prognosis will become more defined.

Author contributions

XG is responsible for article screening, writing and analysis; YZ selects the article direction and guides the article framework; HJ is responsible for article screening and data analysis; XM is responsible for article embellishment and guides article revision, submission and payment of page charges.

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Conflict of interest

The authors declare that the content of this article was composed without any commercial or financial relationship ip and without any conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.925560/full#supplementary-material

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