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Evaluation of tumorous LCP1 and ADPGK as predictive biomarker for immune-related adverse events in bone and soft tissue sarcomas treated with anti-PD-1 and anti-PD-L1 antibodies

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Abstract

Immune checkpoint inhibitor (ICI) have been utilized in bone and soft tissues sarcoma patients under multiple circumstances in combination with surgeries and chemotherapy. Regretfully, immune-related adverse events (irAE) increases as the usage of ICI increases. Since a large portion of bone and soft tissues sarcoma patients gain long survival times after successful removal of the tumors which makes clinicians to avoid regimens that causes adverse events, especially lifetime irAE. Hence, predicting the development of irAE are of special significance for utilizing ICI in bone and soft tissues sarcoma patients. We have retrospectively stained tumorous LCP1 and ADPGK, two biomarkers previously reported to predict ICI induced irAE, with surgical removed, formalin-fixed and parrffin-embedded samples in a cohort of 50 bone and soft tissues sarcoma patients. We observed that the most common irAE in bone and soft tissues sarcoma patients received ICI is hyperglycemia and high grade irAE happens predominately in patients over 30 years old. Immunochemistry revealed that both LCP1 and ADPGK were elevated in tumorous tissues of patients developed irAE and bivariate-model of LCP1 and ADPGK severs as a better biomarker in comparison to LCP1 or ADPGK alone in the entire cohort. In osteosarcoma, LCP1 alone exhibited an outstanding predication value with an AUC of 0.9244 (*P* value of 0.0013 and a 95% CI of 0.8178 to 1.000). LCP1 and ADPGK bivariate-model serves as a promising biomarker for predicting ICI induced irAE in bone and soft tissues sarcoma patients while LCP1 alone works better in bone malignancy especially in osteosarcoma.

Keywords Immunotherapy, irAE, Sarcoma, Biomarker, ICI

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Background

Bone and soft tissue sarcomas are considered as rare cancers and the estimated new cases of bone and soft-tissue cancer is 17,560 in United States alone in 2024 [1]. Despite the relative infrequency, bone and soft tissue sarcomas accounts for approximately 12% of all pediatric malignancies [2]. A retrospective study analyzing the prevalence, incidence, mortality and survival rate of bone and soft tissue sarcomas showed that the prevalence of bone and soft-tissue are similar in population younger than 20 years old and those older than 65 years old, both of which are higher in population aged between 20–64 [3]. Five-year survival rates of bone and soft-tissue cancer in children and adolescents (age birth-19) are 68% and 65% respectively [4]. Nonetheless, the standard management for bone and soft-tissue sarcomas received limited efficacy especially for soft tissue sarcomas [5] calling for novel drugs and strategies for bone and soft-tissue sarcomas.

Immune checkpoint inhibitors (ICI) have reformed the way we treat cancers including sarcomas, even though low tumor mutational burden and immunosuppressive tumor microenvironment are two key characteristics of sarcomas [6, 7]. A phase II clinical trial of Pembrolizumab (PD-1 monoclonal antibody) revealed promising efficacy in undifferentiated pleomorphic sarcoma patients and liposarcoma patients but limited efficacy in bone sarcomas [8]. Combining Nivolumab and Ipilimumab improved the partial response rate from 5 and 7% respectively to 16% in multiple sarcoma subtypes [9]. Another phase II clinical trial showed that combined therapy with durvalumab and tremelimumab for various types of advanced or metastatic sarcomas patients reached a progression-free survival rate of 49% at 12 weeks [10]. Eribulin plus Pembrolizumab strategy reached 36.8% progression-free survival rate for leiomyosarcoma, 69.6% progression-free survival rate for liposarcomas and 52.6% progression-free survival rate for other metastatic soft-tissue sarcomas in the cohort at 12 weeks [11]. Anti-PD-1 antibody and anti-PD-L1 antibody have also been shown promising roles for combined treatment of bone and soft tissue sarcoma [12–14]. However, ICI gives rise to a whole body overactivation of immune system which inevitable triggers immune-related adverse events (irAEs) and current opinions believes that factors as germline genetics are risks of irAE occurrence [15]. Severe adverse events (Grade 3–5) are sometimes lethal to the patients while even minor adverse events intervene the therapy and influence the overall prognosis [16]. Since about 70% of bone and soft tissue sarcoma patients gains a long survival time after successful removal of the tumors and a considerable number of bone and soft tissue sarcoma patients are children and adolescents, it is critical to choose a precise regimen for each patient and avoiding irAE sometimes are more important when multiple regimens resulted in similar results.

Substantial efforts have been made to identify biomarkers that predicts the occurrence of irAE [17, 18]. Current clinical examines included autoantibodies, blood cell counts and ratios, serum proteins and cytokines have all been analyzed and multiple promising biomarkers regarding genetic variations, leucocyte antigen genotypes, small RNAs and microbiome have been identified in new cohorts [17, 18]. Evaluating the tumorous LCP1 and ADPGK expression level was proposed effective in predicting the occurrence of irAE in pan-cancers [19], yet no validation of this method was reported.

We retrospectively analyzed the demographics and clinical characteristics of 56 bone and soft-tissue cancer patients that underwent anti-PD-1 antibody or anti-PD-L1 antibody treatments and examined tumorous LCP1 and ADPGK expression of surgically removed tumor samples to summarize the occurrence, type and severity of irAE and evaluated the performance of tumorous LCP1 and ADPGK in predicting the occurrence of irAE.

Methods

Patient cohort

Bone and soft tissue sarcomas patients assessed and surgically treated and subsequently treated with anti-PD-1 antibody or anti-PD-L1 antibody after standard regimen in Beijing Jishuitan Hospital from Jun-2018 to Jan-2024 were included. Chemotherapy and ICI regimens were performed according to CSCO guideline 2018 and CSCO guideline 2024. Regimen prior to ICI includes: 1) six cycles of ifosfamide (IFO) – methotrexate (MTX)—cisplatin (DDP) + Adriamycin (ADR), 2) two to five cycles of ADR + IFO, 3) A/I (doxorubicin/ifosfamide) regimen, 4) VAC/IE (vincristine sulfate, Adriamycin, and cyclophosphamide, followed by ifosfamide and etoposide phosphate) regimen, 5) three cycles of ADR, 6) no prior chemotherapy. ICI treatments were triggered when: 1) ineffective chemotherapy; 2) unsuitable for chemotherapy; 3) highly expressed PD-L1 in tumor cells. Patients under eighteen years old and their parents signed written informed consent before ICI treatments. Demographics and clinical information were collected by chart review. Patients without surgical formalin-fixed and parrffin-embedded (FFPE) samples were excluded. irAE were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Evaluation of tumorous LCP1 and ADPGK expression

Pre-PD-(L)1-treatment FFPE tumor samples were firstly evaluated by two pathologists to: 1) confirm the malignancy and subtype of bone and soft

tissue sarcomas; 2) confirm over 50% of the sample are tumorous tissues and less than 20% of the sample are necrotic. Immunohistochemistry was performed with standard protocols and slides were stained with primary antibodies against LCP1 (1:500 LiangJue Technology, LJ-mAB-0002) and ADPGK (1:500, 1:500 LiangJue Technology, LJ-mAB-0001). Secondary antibody and DAB development system were purchased from Servicebio (G1301-100ML, G1212-200 T). Hematoxylin were counterstained and whole slides were scanned with an PANNORAMIC 1000 system (3DHISTECH, Hungary) and CaseViewer2.4 (3DHISTECH, Hungary) were used for image output. Images with 600dpi were quantified using the Aperio ImageScope software v14.3 with Positive Pixel Count v9 (PPCv9) algorithm according to previously reported method [19].

Statistical analysis

At least seven regions of each samples were analyzed and averaged as the final positivity of either LCP1 or ADPGK. The bivariate model of LCP1 positivity and ADPGK positivity were analyzed with logistic regression of LCP1 and ADPGK positivity [19]. Student's t test was used when compare two groups of positivity. P Value less than 0.05 was considered statistically significant. 95% confidence interval and Wilson/Brown method were used for ROC calculation.

Results

General demographics and clinical characteristics

Of 50 bone and soft tissue sarcoma patients enrolled, 12(24%) patients developed irAEs including three (15.7%) female patients and 9 (29%) male patients (Table 1 and Fig. 1A). The average age of patients with irAEs was 32.5 while the average age of all bone and soft tissue sarcoma patients was 38.96 (Table 1), but there is no statistical difference between the ages of patients with or without irAE (P value = 0.1708). Seven out of 24 osteosarcoma patients developed irAEs. Among the 50 bone and soft tissue sarcoma patients, 23 were treated with anti-PD-L1 antibody and three (13.0%) of them developed irAEs while 9 (33.3%) of the rest 27 patients received anti-PD-1 antibody developed irAEs (Table 1). The youngest patient developed irAE was 10 years old while the oldest was 66 years old (Table 2 and Fig. 1A). Four patients developed grade 3 irAEs including pancreatitis, hepatitis and whole-body rashes and only one of them was an adolescent aged 16 (Table 2 and Fig. 1A). We noticed that most adolescents experienced low grade irAEs, predominantly hyperglycemia (Table 2 and Fig. 1A).

Table 1 Demographics and clinical characteristics

	non-irAE	irAE	Total
No. of patients			
All	38	12	50
Female	16	3	19
Male	22	9	31
Average age (years old)			
All	41.2	32.5	38.96
Female	46.25	42.66	45.68
Male	37.5	29.4	32.43
Diagnosis (No. of patients)			
Bone malignancy	28	9	37
Soft tissue tumor	10	3	13
Immune checkpoint inhibitor			
Anti-PD-1 antibody	20	3	23
Anti-PD-L1 antibody	18	9	27

The table shows the basic demographics and clinical characteristics of the cohort

Tumorous LCP1-ADPGK bivariate model predicts the occurrence of irAEs

To test the significance of the LCP1-ADPGK bivariate model which was reported to predict the occurrence of irAEs [19], we stained the LCP1 and ADPGK with immunohistochemistry in samples acquired from surgeries. We observed a relatively stronger expression of both LCP1 and ADPGK in the cytoplasm of specimen from patients with irAE in comparison to those without irAE (Figs. 1B and 2). Hence, we quantified the positivity as previously reported [19]. As excepted, we did not observe any differences of LCP1 positivity, ADPGK positivity as well as bivariate model positivity between patients of different sex (Fig. 3A) or patients receiving different ICI (Fig. 3B). Besides, baseline alkaline phosphatase (AKP) and lactate dehydrogenase (LDH) did not differentiate patients who would develop irAE or not (Fig. 3C and D).

Notably, LCP1 positivity (P value = 0.0006), but not ADPGK positivity (P value = 0.1460) and the geometric mean of LCP1 and ADPGK positivity (P value = 0.0032) were all significantly higher in patients with irAEs in comparison those without irAEs (Fig. 4A). A bivariate model was generated with a logistic regression of LCP1 and ADPGK positivity. The area under the receiver-operating characteristic curve (AUC) of the bivariate model to predict irAE was 0.8057 with a P value of 0.0011 and a 95% confidence interval (CI) of 0.6783 to 0.9330 (Fig. 4B). For osteosarcoma alone, only LCP1 positivity (P value < 0.0001) and the geometric mean of LCP1 and ADPGK positivity (P value = 0.0010) were significantly higher in patients with irAEs in comparison those without irAEs (Fig. 4C) suggesting a negative role of ADPGK

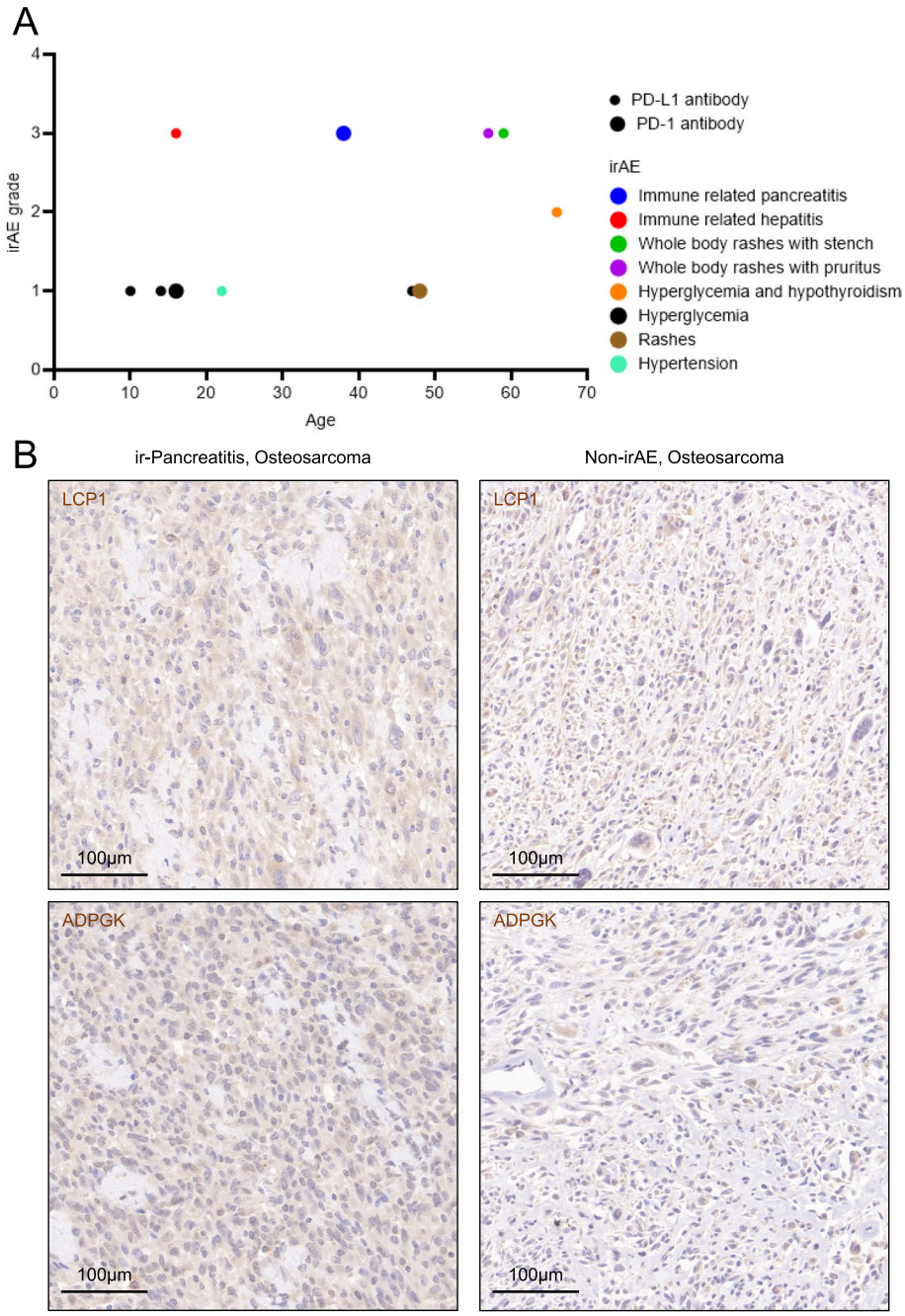

Fig. 1 Overview of irAE types and grades and representative immunohistochemistry of LCP1 and ADPGK. **A** Overview of irAE types and grades. **B** Representative immunohistochemistry of LCP1 and ADPGK in sample with or without irAE

positivity in predicting the occurrence of irAEs in osteosarcoma patients receiving ICI. However, LCP1 positivity alone exhibited an outstanding predictive value since the AUC of LCP1 positivity to predict irAE reached 0.9244 with a *P* value of 0.0013 and a 95% CI of 0.8178 to 1.000 (Fig. 4D) in this limited sample size. As for bone malignancy, only LCP1 positivity (*P* value = 0.0004) was significantly higher in patients with irAEs in comparison those without irAEs (Fig. 4E) and neither LCP1 nor ADPGK positivity differentiate patients with or without irAEs (Fig. 4F). LCP1 positivity was promising in predicting irAE in all bone malignancy since the AUC reached 0.8175 with a *P* value of 0.0046 and a 95% CI of 0.6300 to 1.000 (Fig. 4D).

Table 2 irAE type and grade

Age group	Tumor Subtypes	Prior-regimen	irAE	Grade
Adult	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Immune related pancreatitis	3
Adolescent	Small cell osteosarcoma	VAC/IE	Immune related hepatitis	3
Adult	Pleomorphic sarcoma	A/I 3 cycles	Whole-body rashes with stench	3
Adult	Chondromatosis	A/I 3 cycles	Whole-body rashes with pruritus	3
Adult	Liposarcoma of bone	IFO-ADR2 2 cycles	Hyperglycemia and hypothyroidism	2
Adult	Mesenchymal chondrosarcoma	A/I 3 cycles	Hyperglycemia	1
Adult	Osteosarcoma	No prior-regimen	Rashes	1
Adolescent	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Rashes	1
Adolescent	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Hyperglycemia	1
Adult	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Hypertension	1
Adolescent	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Hyperglycemia	1
Adolescent	Osteosarcoma	IFO-MTX-DDP + ADR 6 cycles	Hyperglycemia	1

The table shows the age group, tumor subtypes, prior-regimen, irAE type and grade of the patients in the cohort that developed irAE

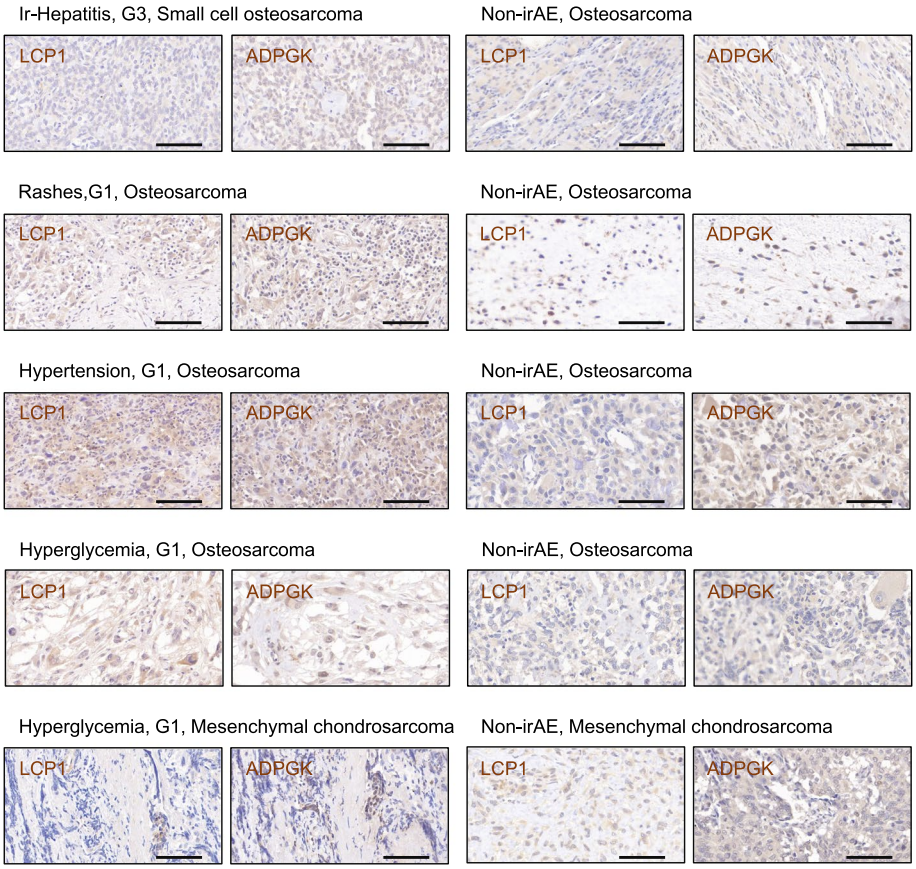

Fig. 2 Immunohistochemistry of LCP1 and ADPGK in patients with or without irAE

Discussion

Sarcomas have always been merciless threats to children and adolescents yet immunotherapies provided the clinicians additional methods to save those young lives. However, irAE resulted from ICI severely affects the life quality of bone and soft tissue sarcoma underwent successful surgical removal of the tumors. Development of lifetime irAE, especially in children and adolescents actually violates the original intention of bone and soft tissue sarcoma treatments.

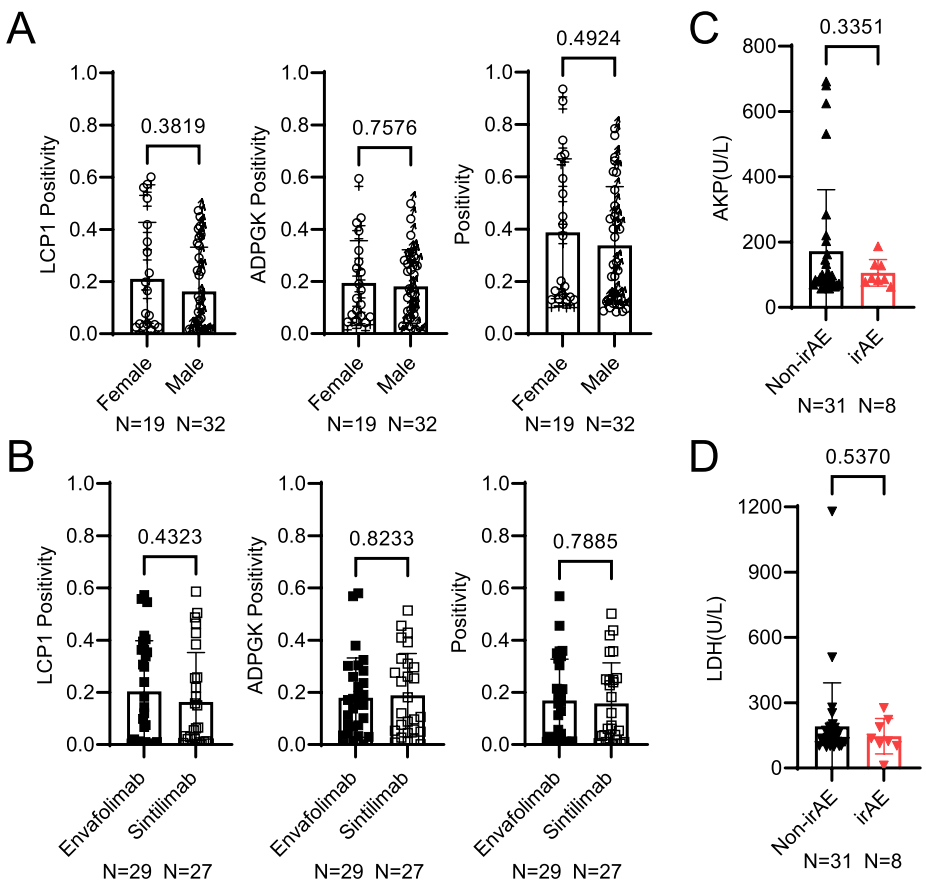

Fig. 3 LCP1 positivity, ADPGK positivity and Bivariate-model positivity grouped by sex and ICI. **A** LCP1 positivity, ADPGK positivity and Bivariate-model positivity grouped by sex. **B** LCP1 positivity, ADPGK positivity and Bivariate-model positivity grouped by ICI. **C** AKP level in patients with or without irAE. **D** LDH level in patients with or without irAE

In this bone and soft tissues sarcoma cohort, 12 out of 50 (24%) patients experienced at least one adverse effect after receiving PD-1 or PD-L1 antibodies and 4 (8%) patients including oen adolescent developed grade 3 irAEs. Identification of the patients that might develop irAE is valuable for both clinicians and patients. An alert in advance will facilitate the clinicians to customize the regimen and prepare the patients psychologically. In this bone and soft tissues sarcoma cohort, the bivariate model achieved high predication value with an AUC of 0.8057 while in osteosarcoma, LCP1 alone exhibited an outstanding predication value with an AUC of 0.9244. These results suggested a promising role of LCP1 alone and the bivariate model in predicating the potential irAE after receiving PD-1 or PD-L1 antibodies in bone and soft tissues sarcoma patients expending the toolbox of the clinicians in customizing the regimen against bone and soft tissues sarcoma.

With limited number of cases, we noticed that anti-PD-1 antibody were more likely to induce irAEs in comparison to anti-PD-L1 antibody and anti-PD-1 antibody were more likely to induce higher grade irAEs, yet no systematic analysis has been performed to compare the two therapies in terms of adverse effects. Our theory suggests that the irAE is patient dependent which is determinable by the tumorous expression levels of LCP1 and ADPGK rather than the therapy received. A larger cohort shall be established to have further evidences on the difference of irAE induced by different ICI. Luckily, we did not observe any of irAE over grade 4 for both ICIs even though the number of cases is limited. Since most irAEs were minor and controllable, it is promising for further utilization of ICIs in bone and soft tissue sarcomas. However, managements of the irAEs are especially important in regard to the treatment of children and adolescents. Hence, developing an accurate and convenient method to predict irAE occurrence and customize treatment regimen are of special significance.

Meanwhile, a limitation of this work is that the study was design retrospectively which might raise concerns about the judgements of the irAE. Yet, retrospectively analysis was largely employed in identifying

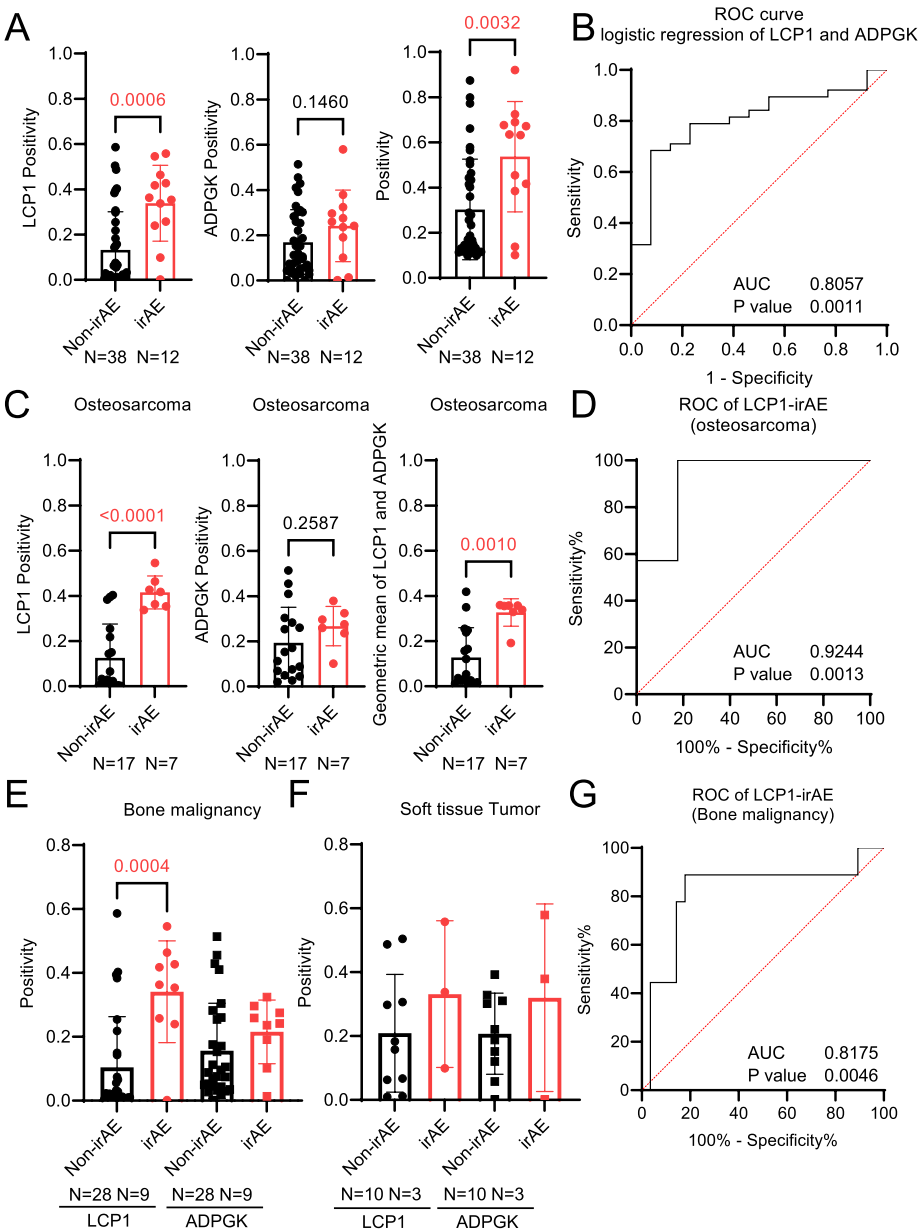

Fig. 4 LCP1 positivity, ADPGK positivity and Bivariate-model positivity grouped by irAE. **A** LCP1 positivity, ADPGK positivity and Bivariate-model positivity in patients with or without irAE. **B** Receiver-operating characteristic curve of the bivariate model to predict irAE. Negative predictive power is 60.00% while positive predictive power is 82.93%. **C** LCP1 positivity, ADPGK positivity and Bivariate-model positivity in osteosarcoma patients with or without irAE. **D** Receiver-operating characteristic curve of the LCP1 positivity to predict irAE in osteosarcoma patients. When sensitivity is 100% and specificity is 82.35% reaches the maximal Youden index. **E** LCP1 positivity and ADPGK positivity in all bone malignancy patients with or without irAE. **F** LCP1 positivity and ADPGK positivity in soft tissue tumor patients with or without irAE. **G** Receiver-operating characteristic curve of the LCP1 positivity to predict irAE in all bone malignancy patients. When sensitivity is 88.89% and specificity is 82.14% reaches the maximal Youden index

biomarkers that predicts irAE [20–23] since high grade irAEs were critical for the clinicians and the diagnosis and treatment of the irAEs were usually properly recorded. In our study, the irAE was recorded by the clinician participated in this work independently and all adverse events were re-evaluated again according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 based on the clinical

records and telephone follow-up during the revision the manuscript. To further validate the models, we are now working on a prospective and larger cohort.

The LCP1 and ADPGK model for irAE predicting was initially proposed from a multi-omics analysis and a 28 patients' cohort (predominantly lung cancer) was utilized as a validation cohort [19]. Here, we provided an external validation of this model in sarcomas which further suggested a possible utilization of this model in the future. However, a larger prospective cohort is in need to further confirm the possibility of clinical application. A most recent study showed in a late-stage non-small cell lung cancer with KARS G12C mutation cohort that combined LCP1 and ADPGK expression is predictive biomarker for irAE with a AUC = 0.808 [24]. Taken together, the LCP1 and ADPGK model might serve as a pan-cancer method in predicting ICI induced irAE.

LCP1 was required for TCR-mediated cytokine production and T cell proliferation [25]. More importantly, LCP1 deficient mice developed less symptoms in autoimmune encephalomyelitis models [25]. A recent identified causal mutation in LCP1 revealed that in human hematopoietic cells, LCP1 deficiency resulted in immune deficiency and hematologic cytopenia [26]. Additionally, downregulation of LCP1 in monocyte-derived macrophages reduces neuroinflammation and attenuates lymphopenia [27]. ADPGK was previously found that ADPGK is activated by TCR and further facilitated T cell activation through glucose metabolism and ROS generation [28, 29]. Interestingly, ADPGK was designed as a neo- epitope to induced CD8 + T cell responses [30–32]. All these data suggested a pro-inflammation role of LCP1 and ADPGK in immune system. In the current cohort, staining of LCP1 and ADPGK showed acceptable effectiveness in predicting the occurrence of irAEs especially for LCP1 in predicting the occurrence of irAEs in osteosarcoma. The bivariate model improves the efficacy, yet it does not necessarily mean that the efficacy of the bivariate model must be better than that of an independent gene in a specific cancer type. In this cohort, LCP1 exhibited a higher prediction value in osteosarcoma. However, due to the limitation of cases, the models require larger retrospective cohorts and prospective cohorts for further validations. Moreover, the variations between immunohistochemistry makes it difficult as a quantitative method. Hence a massive number of samples and high-quality data are required to establish a clinical-applicable model.

Nonetheless, our data provided in-depth validation of the tumorous LCP1-ADPGK bivariate model which is prospectively a functional method to predicts the occurrence of irAEs in bone and soft-tissue sarcomas.

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Authors' contributions
Q.Z. and C.W. conceptualization; Q.Z., Z.W. and C.W. data curation; C.W. data collection and analysis; Q.Z., Y.D. and C.W. methodology; Y.D. and XQ.Z. pathology; C.W. writing; C.W. funding acquisition; and Q.Z. and C.W. project administration.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Beijing Jishuitan Hospital with the approval ID number of K2022164-00. All patients were informed and signed on consents and all experiments were conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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