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MET amplification correlates with poor prognosis and immunotherapy response as a subtype of melanoma: a multicenter retrospective study

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Abstract

Background Mesenchymal epithelial transition factor (MET) variant is an independent prognostic factor for worse prognosis in patients with lung cancer or gastroesophageal adenocarcinoma. MET gene variants can be regarded as a subtype of melanoma but there is a lack of studies regarding the frequency of MET genetic alterations and the efficacy of immunotherapy in melanoma patients. The purpose of this study is to explore potential therapeutic strategies for melanoma subtypes with MET alterations.

Methods A total of 1751 malignant melanomas were analyzed to illustrate the landscape of MET mutations. We collected 55 melanoma cases from multicenter for a retrospective cohort from 2010 to 2023. We analyzed the impact of MET amplification on the efficacy of immunotherapy in the retrospective cohort after propensity score matching (PSM) and a pancancer cohort. CIBERSORT was used to evaluate the immune infiltration.

Results There were no instances of MET 14 exon skipping, and only instances of MET amplification were found in the 1751 melanomas and our retrospective cohort. Cox proportional hazards model analysis showed that MET amplification ($P=0.006$) was significantly associated with poorer overall survival (OS) in patients who received immunotherapy as the first-line treatment. Compared with patients with MET amplification, patients in the negative control (NC) group had a significantly better OS ($P=0.022$) after PSM. Analysis of 1661 pancancer cases with the MSK-IMPACT assay showed that patients receiving immunotherapy in the MET amplification group had a trend toward worse OS than those without MET amplification ($P=0.025$).

Conclusions This database analysis showed that the main type of MET mutation is amplification in malignant melanoma. MET-amplified solid tumors might be considered for targeted therapy, as MET amplification can be regarded as a risk factor affecting the prognosis of patients with tumors treated with immunotherapy.

Keywords Melanoma, MET amplification, Immunotherapy

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Background

Melanoma accounts for 1.7% of new cases of tumors and 0.6% of tumor mortality worldwide [1]. In contrast to Western people with lighter skin who mainly develop cutaneous melanoma (CM) as a result of sunlight exposure, populations from Asia and Africa mainly suffer from acral and mucosal melanomas (MMs). Early-stage melanoma can be treated effectively with surgical resection [2]. Additional treatment options include antagonists of various immune checkpoints and adoptive T-cell therapy, but these generate an antitumor response in only a fraction of patients with advanced melanoma [3, 4]. Although clinical trials of PD-1 blockade therapy have demonstrated efficacy in the treatment of advanced-stage melanoma, approximately two-thirds of patients with melanoma progress after immune checkpoint inhibitor (ICI) therapy, and half of them ultimately die from the disease [5]. A large whole-genome sequencing (WGS) analysis comparing cutaneous and mucosal subtypes revealed that mucosal melanomas have a lower point mutation burden [6]. Over 50% and nearly 28% of CMs have BRAF mutations and NRAS mutations, respectively, making these mutations typical features of CMs, while only 6%–16.4% and 15.8%–17.9% of MM cases have BRAF mutations and NRAS mutations, respectively [7, 8]. Approximately 20% of melanoma patients are intrinsically insensitive to targeted therapy despite having a mutated BRAF gene [9, 10]. Moreover, drug resistance usually inevitably occurs within 6–12 months [11]. The five-year OS rate of MMs ranges from 22 to 34%, depending on the primary site [12]. Thus, it is vital to explore other reliable predictive biomarkers to treat refractory disease.

The proto-oncogene MET, located in the 7q31 locus, encodes mesenchymal–epithelial transition factor (c-Met), which is a transmembrane tyrosine kinase receptor with a molecular weight of 190 kDa [13]. c-Met participates in processes including angiogenesis, cell growth, cell migration and cell differentiation [14]. MET alterations, including base substitutions, insertions or deletions at splice sites or in intronic noncoding regions immediately adjacent to splice acceptor sites, and perhaps whole exon deletions, can result in exon 14 skipping [15, 16]. Exon 14 encodes the MET juxtamembrane domain, which recruits casitas B-lineage lymphoma proto-oncogene (c-CBL) via phosphorylation [14, 17]. CBL then targets MET for ubiquitin-mediated degradation to negatively regulate receptor stability and activity [18]. Aberrant c-Met activity is associated with aggressive cancer phenotypes, metastatic dissemination, and poor disease prognosis in human cancers, including lung, kidney, stomach, and liver cancers and melanoma [19, 20]. C-met has emerged as an appealing target in the development of anticancer therapeutics. MET exon 14 skipping mutations occur in 3 to 4% of patients with non-small cell lung cancer (NSCLC). MET exon 14 alterations occur at lower frequencies in other cancers, including gastric cancers and neuroblastomas [15]. Several kinds of MET receptor inhibitors have shown activity in NSCLC patients with MET exon 14 mutations or MET amplification, such as tepotinib and capmatinib, which show higher efficacy in patients who have not been treated previously [21, 22]. Accumulating studies suggest that MET exon 14 mutation is an independent prognostic factor for poorer survival in patients with NSCLC [23].

Systematic retrospective data collected from Fujian Cancer Hospital and Peking University Cancer Hospital were used to investigate whether immunotherapy is suitable for patients with MET genetic alterations. The results were verified with The Cancer Genome Atlas (TCGA) and Memorial Sloan Kettering Cancer Center (MSKCC) data. Based on the results of several studies related to the frequency of MET genetic alterations and MET-targeted therapy in melanoma, our study aimed to explore the MET gene landscape to uncover effective potential therapeutic strategies for melanoma patients with MET alterations.

Materials and methods

Workflow for the multicenter retrospective cohort study

We collected 21 melanoma cases with MET amplification from Peking University Cancer Hospital, 7 melanoma cases with MET amplification and 27 wild-type cases without BRAF, NRAS, KRAS, KIT and MET alterations from Fujian Cancer Hospital from April 2010 to January 2023 to form a systematic retrospective data cohort (Supplementary Material 2). Patients without BRAF, NRAS, KRAS, KIT and MET alterations were regarded as wild type and placed into the negative control (NC) group. The patients with MET amplified tumors without BRAF, NRAS, KRAS, or KIT alterations like those in the NC group. Data collected included demographics and clinical features, including diagnosis and treatment details. The results of gene testing, including MET copy number and the mutation status of other driver genes, were also incorporated into the analysis.

Chinese cases from the Geneplus cohort

The Geneplus cohort in this study encompassed 873 patients with melanoma enrolled from 1 September 2015 to 28 December 2022 who were subjected to target capture next-generation sequencing (NGS) of 1021 cancer-related genes in tumor DNA and paired germline DNA as part of clinical care (Supplementary Material 1). DNA was extracted from all samples

using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Valencia, CA), QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA) and DNeasy Blood Kit (Qiagen, Valencia, CA). DNA concentrations were quantified using a Qubit fluorometer (Invitrogen, Carlsbad, CA, USA). The length of cell-free DNA (cfDNA) fragments was assessed using the Agilent 2100 BioAnalyzer (Agilent Technologies, Santa Clara, CA, USA). Sequencing libraries were prepared as previously reported using the NEB DNA Library Preparation Kit (NEB, MA, USA). Libraries were hybridized to custom-designed biotinylated oligonucleotide probes (Roche NimbleGen, Madison, WI, USA) targeting 59 or 1021 genes (~1.4 Mbp genomic regions of 1021 cancer-related genes or ~230 Kbp genomic regions of 59 genes). Genome analysis was performed at the Geneplus Beijing laboratory accredited by the American Society of Pathologists using a Gene + Seq 2000 instrument or Illumina Nextseq CN 500 instrument [24–26]. After processing the raw sequencing data, the remaining reads were aligned to the hg19 human genome using the Burrows-Wheel Aligner (BWA, version 0.7.12-r1039) program. Subsequently, duplicate reads were identified using Picard's Mark Duplicates tool, and local realignment and quality recalibration were performed using the Gene Analysis Toolkit (GATK, version 3.4–46-gbc02625). Single nucleotide variants (SNVs) and copy number variants (CNVs) were identified using the MuTect2 algorithm (version 1.14) and Contra algorithm (version 2.08), respectively [27].

Data from the TCGA and MSKCC databases

cBioPortal for Cancer Genomics (http://cbioportal.org) was originally developed at MSKCC. This public database integrates data from 213 tumor genome studies to date, including large tumor research projects such as TCGA and International Cancer Genome Consortium (ICGC), covering data from 69,223 samples, and cBioPortal can be used to perform a variety of analyses. The primary functions of cBioPortal are mutation analyses and visualization. Thirty-two TCGA studies are included in cBioPortal, covering 522 melanoma patients. Genetic variant and clinical subtype data of these patients were available for analysis.

Data from the MSK-IMPACT clinical sequencing study, which included 350 melanoma patients, are also included in cBioPortal. From cBioPortal, the variant and clinical subtype data of these patients were obtained. Genomic and survival data from 1661 tumor-normal pairs and targeted sequencing data from 10,000 clinical cases from the MSK-IMPACT cohort and cBioPortal were matched, and 1109 cases were ultimately used to assess the association between MET amplification and OS in patients treated with immunotherapy.

Copy number calculation and definition of MET amplification

In plasma, copy number alterations of MET with a copy number ratio of 1.25 or higher were considered potential amplification. For tissue samples, the tumor cell content should be at least 20% of the tumor tissues, which serves as the quality control standard for NGS testing. We calculated the minimal copy number ratio threshold for MET amplification using the following formula: $[20\% * 5 + (1-20\%) * 2]/2 = 1.3$. Samples that did not meet the above criteria for MET amplification calculation were defined as MET no amplification group cases.

Tumor purity and infiltrating immune cell estimation

The skin cutaneous melanoma (TCGA, PanCancer Atlas) cohort contained 448 samples from 442 melanoma patients. Gene expression data of these samples were downloaded, and based on these data, CIBERSORTx (Newman AM, Liu CL, Green MR et al.) was used to infer gene expression profiles and to estimate the abundances of immune cell types in the mixed cell population. Then, the differences between MET-amplified samples and non-MET-amplified samples were analyzed.

Identification of co-occurring genomic alterations and mutually exclusive mutations

Differentially mutated genes were identified using Venn diagram tools. Fisher's exact test was used to analyze the exclusivity and cooccurrence of mutations. The analysis was performed with the R statistical programming language (version 4.1.3).

Propensity score matching (PSM)

A 1:1 ratio of PSM was used to balance the baseline characteristics of melanoma patients from Peking University Cancer Hospital and Fujian Cancer Hospital using nearest neighbor matching with a caliper width of 0.05 standard deviations of the logit of the propensity scores. The analysis was performed with the R statistical programming language (version 4.1.3).

Statistical analysis

Patient data were visualized in Kaplan–Meier curves using an iterative algorithm and then pooled to generate survival curves. A Cox regression model was used to estimate the effect of prognostic factors and calculate the hazard ratios (HRs) for OS time. Categorical

variables were analyzed using the χ2 test or Fisher's exact test, as appropriate, and continuous variables were analyzed using Student's t test. A p value < 0.05 was considered statistically significant for all analyses. All statistical tests were two-sided. The analyses were performed with the R statistical programming language (version 4.1.3).

Results

Genomic alterations of MET in melanoma

We analyzed MET molecular data from 873 melanomas from the Geneplus Institute database, which is not publicly available and is drawn from multiple treatment centers throughout China (Supplementary Material 1). There were large differences in the composition of melanoma subtypes in Geneplus Institute database and other databases with Western populations. Except for samples with unknown primary site and data deletion, ALM and MM were the predominant melanoma subtypes in Geneplus cohort of Chinese populations. The Geneplus cohort was dominated by MM (24.74%) and ALM (21.53%) (Fig. 1a). For comparison, we collected 878 melanomas from TCGA (n = 528) and the MSKCC database (n = 350), which are both representative of Western populations. The main subtype of melanoma in the TCGA (83.71%) and MSKCC (54.29%) databases was CM (Fig. 1b -1c) but ALM and MM were extremely rare.

Surprisingly, we discovered that there were no MET 14 exon skipping instances in the genomic data described above. The major genomic alteration of the MET gene was amplification. Of the Chinese melanoma patients whose tumor tissues were subjected to targeted sequencing with a 1021-gene pane, 5.73% (50/873) had MET amplification (Fig. 1d). The incidences of MET amplification were 1.14% (6/528) in the TCGA cohort and 1.72% (5/350) in the MSKCC cohort (Fig. 1d). We hypothesize that the differences in proportions of melanoma subtypes between Western and Chinese populations caused the higher incidence of MET amplification in the Chinese cohort. Only 0.57% (2/350) of MM patients and 0.29%(1/350) of CM patients had MET amplification in the MSKCC database, and 1.14% (6/528) of CM patients in the TCGA database had MET amplification (Fig. 1d). Of the 5.73% (50/873) of patients with MET amplification in the Chinese cohort, 0.57% (5/873) had CM, 1.72% (15/873) had MM, and 1.37% (12/873) had ALM (Fig. 1d).

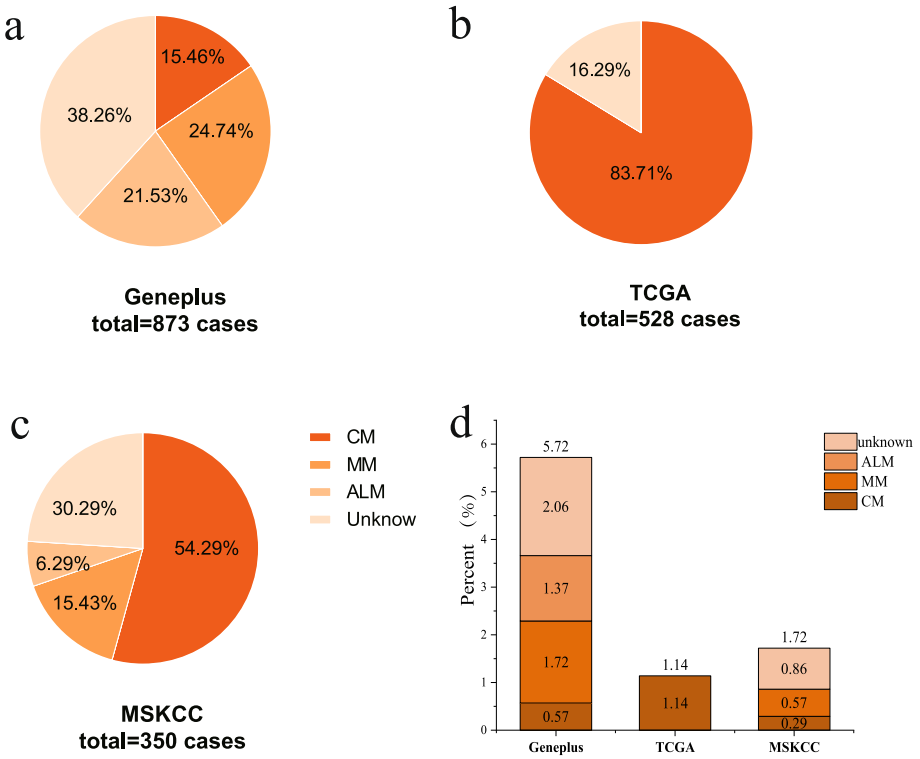

Fig. 1 Melanoma subtype statistics of Geneplus institute (**a**), TCGA (**b**) and MSKCC (**c**) and MET amplification rate in varied subtype of melanoma in each cohort (**d**)

Co-occurring genomic alterations and mutually exclusive mutations in MET and other oncogenic drivers of melanoma

The genes that have been found to be significantly differentially mutated in MM patients are NRAS, BRAF, NF1, and KIT [1]. Previous research suggests that CMs can be divided into four different genetic melanoma subtypes. Based on this categorization, the cases were classified as follows: more than 50% were BRAF-mutant melanomas, 25% were NRAS, KRAS, or HRAS-mutant melanomas, 15% were NF1-mutant melanomas, and 10% were triple-wild-type melanomas [28]. Disease progression is often associated with driver gene alterations, so we evaluated genetic heterogeneity by assessing BRAF, RAS, NF1 and KIT comutation with MET amplification to identify specific gene alterations that coexist with MET amplification in three cohorts mentioned above. Our results revealed that BRAF comutation with MET amplification was present in 1.83% (16/873) of the Geneplus cohort (Fig. 2a), 0.76% (4/528) of the TCGA cohort (Fig. 2b) and 0.57% (2/350) of the MSKCC cohort (Fig. 2c). Approximately 1.37% (12/873) of patients in the Geneplus cohort (Fig. 2a) and 0.29% (1/350) of patients in the MSKCC cohort (Fig. 2c) harbored RAS coalteration with MET amplification, but no patients in the TCGA database did. NF1 comutation with MET amplification was present in approximately 0.46% (6/873) of the Geneplus cohort (Fig. 2a) and 0.19% (1/528) of the TCGA cohort (Fig. 2b). We found rare comutations of KIT in only 0.8% (7/873) of the Geneplus cohort (Fig. 2a), while there were no KIT comutations in the TCGA or MSKCC cohort. The identified co-occurring genomic alterations and mutually exclusive mutations of MET and other driver genes are shown in the heatmap. Comutation of MET and KRAS was significant ($P<0.05$) in the Geneplus cohort (Fig. 2d), and comutation of MET and NF1 was significant ($P<0.05$) in the TCGA (Fig. 2e) and MSKCC (Fig. 2f) cohorts.

Retrospective analysis of 55 melanoma cases from multiple centers with PSM

In total, we collected 28 cases of MET-aberrant melanoma and 27 cases for the NC group from multiple treatment centers to analyze the landscape of MET abnormalities in melanoma (Supplementary Material 2). We found that there were no MET exon 14 mutations in melanoma cases, all of which had MET amplifications. The average copy number of MET was 8.64 (range 3.8 to 19.6). Additional demographic and clinical characteristics of 28 melanoma patients with MET amplification and 27 NC patients are summarized in Table 1. There was no significant difference in OS between the different melanoma subtypes in the retrospective cohort ($p=0.727$), but mucosal melanoma showed a trend towards poorer OS (Supplementary Material 5).

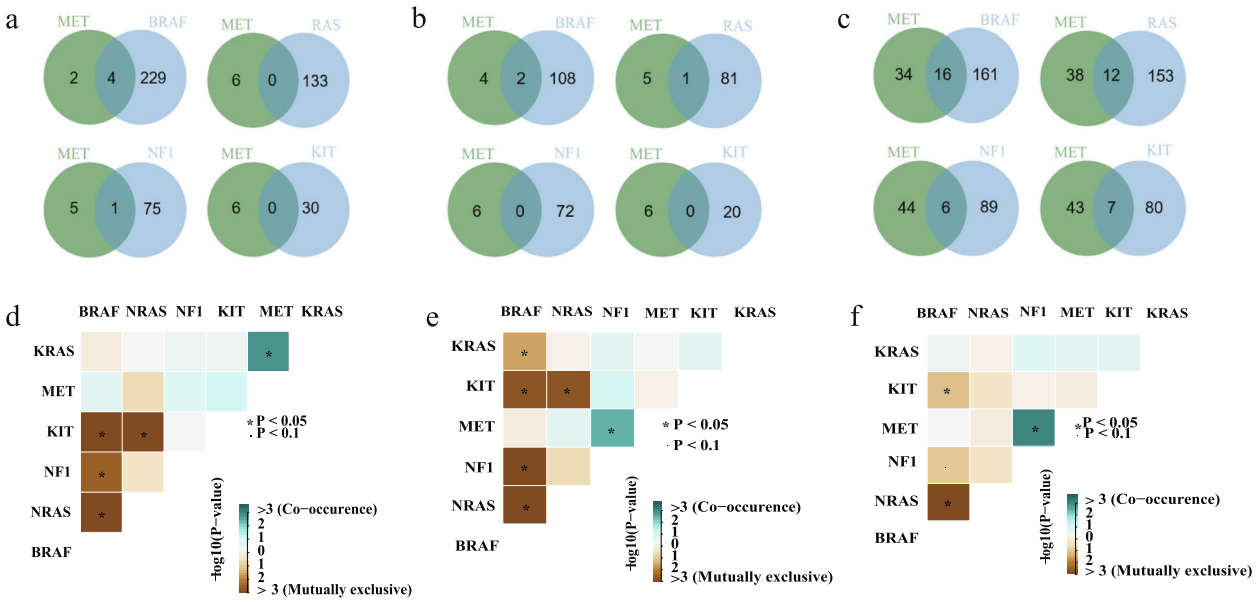

Fig. 2 Co-occurring genomic alterations and mutually exclusive mutations with mutation of MET and other oncogenic drivers of melanomas. The Venn diagram shows the number of genomic alterations in melanoma cases in the Geneplus Institute (**a**), TCGA (**b**) and MSKCC (**c**) cohorts. Fisher's exact test was used to analyze the exclusivity and cooccurrence of mutations in the Geneplus Institute (**d**), TCGA (**e**) and MSKCC (**f**) cohorts. Green indicates co-occurring mutations, while brown indicates mutually exclusive mutations ($P<0.05$, *; $P<0.1$, ·)

Table 1 Summary of characteristics of melanoma cases from multicenter

	MET amplification group($n=28$)	Negative control group($n=27$)
MET copy numbers, mean(range)	8.64 (3.8–19.6)	—
Gender		
Male	10	10
Female	18	17
Age(years)		
<60	13	16
≥60	15	11
Stage		
I-II	3	0
III-IV	25	27
Subtype		
CM	8	11
ALM	18	10
MM	2	6
Immunotherapy		
YES	21	27
NO	7	0

Abbreviations CM Cutaneous melanoma, *ALM* Acral lentiginous melanoma, *MM* Mucosal melanoma

Table 2 Summary of characteristics of melanoma patients receiving immunotherapy from multicenter

	MET amplification group ($n=21$)		Negative control group ($n=27$)	
	NO	%	NO	%
Gender				$P=0.537$
Male	6	28.57	10	37.04
Female	15	71.43	17	62.96
Age(years)				$P=0.422$
<60	10	47.62	16	59.26
≥60	11	52.38	11	40.74
Subtype				$P=0.002$
CM	6	28.57	11	40.74
ALM	1	4.76	10	37.04
MM	14	66.66	6	22.22

Abbreviations NO Numbers, *CM* Cutaneous melanoma, *ALM* Acral lentiginous melanoma, *MM* Mucosal melanoma

Among the 28 patients with MET amplification, 21 patients (75%) had received immunotherapy. To clarify the impact of MET amplification in melanoma on immunotherapy, we further analyzed the data of patients who had received immunotherapy as the first-line treatment (Table 2). A total of 48 patients with melanoma received immunotherapy as the first-line treatment plan, and all had clinical stage IV disease. The results of the univariate analysis to identify prognostic factors associated with the OS of melanoma patients are shown in Table 3. The Cox proportional hazards model analysis revealed that MET amplification ($P=0.006$, HR = 16.59, 95% CI = 2.16–127.7) was significantly associated with a poorer OS rate (Fig. 3a). The results also indicated that subtype ($P=0.601$, HR = 1.17, 95% CI = 0.65–2.12), age ($P=0.534$, HR = 1.40, 95% CI = 0.49–4.00), and sex ($P=0.328$, HR = 1.90, 95% CI = 0.53–6.88) were not prognostic predictors for the effect of immunotherapy. Compared with patients with MET amplification, patients in the NC group had a significantly better OS ($P<0.001$) (Fig. 3a).

Table 3 Univariate analysis of melanoma patients receiving immunotherapy from multicenter

Variables	Univariate analysis	
	P	HR (95% CI)
MET		
amplification		Ref
no amplification	0.007	16.59(2.15,127.67)
Gender		
Male		Ref
Female	0.328	1.90(0.53,6.88)
Age(years)		
<60		Ref
≥60	0.534	1.40(0.49,4.00)
Subtype		
CM		Ref
ALM		Ref
MM	0.601	1.17(0.65,2.12)

Abbreviations HR Hazard ratio, *CI* Confidence interval, *CM* Cutaneous melanoma, *ALM* Acral lentiginous melanoma, *MM* Mucosal melanoma

Because there was a significant difference in the melanoma subtype composition between the MET amplification group and the NC group ($P=0.002$) (Table 2), PSM was used to balance the baseline characteristics between the two groups. After matching at a 1:1 ratio based on propensity scores, 14 pairs were produced. There were no significant differences in sex ($P=1$), age ($P=0.408$) or subtype ($P=0.921$) between the groups after PSM (Table 4). In the Kaplan–Meier analysis, melanoma patients with MET amplification had a poorer OS rate ($P=0.022$) (Fig. 3b). Different analyses confirmed that MET amplification is an adverse prognostic factor for patients with melanoma treated with immunotherapy.

In the 28 melanoma patients with MET amplification, one patient had poor immunotherapy efficacy (evaluated as having PD after several different immunotherapy regimens) with a relapse-free survival (RFS) of 5 months. We

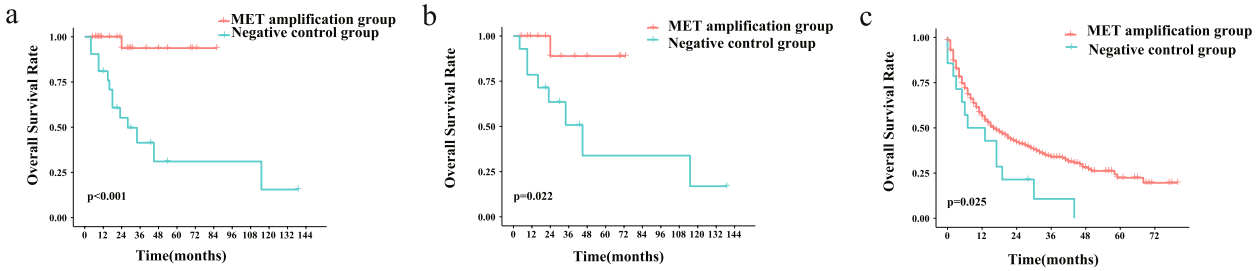

Fig. 3 Kaplan–Meier curves of the MET amplification group and NC group of patients receiving immunotherapy from multiple centers before (**a**) and after (**b**) PSM. Kaplan–Meier curves of the MET amplification group and NC group in the pancancer MSK-IMPACT cohort (**c**)

Table 4 Summary of characteristics of melanoma patients receiving immunotherapy from multicenter after PSM

	MET amplification group($n=14$)		Negative control group($n=14$)	
	NO	%	NO	%
Gender				$P=0.430$
Male	6	42.86	4	28.57
Female	8	57.14	10	71.43
Age(years)				$P=0.445$
< 60	5	35.71	7	50.0
≥ 60	9	64.29	7	50.0
Subtype				$P=0.147$
CM	6	42.86	5	35.71
ALM	1	7.14	5	35.71
MM	7	50.0	4	28.57

Abbreviations NO Numbers, *CM* Cutaneous melanoma, *ALM* Acral lentiginous melanoma, *MM* Mucosal melanoma

speculated that MET amplification may be the cause of therapy resistance.

In addition, we have compared the lactatedehydrogenase (LDH) of the MET amplification group and NC groups (Supplementary Material 2). The results showed that LDH was significantly higher in the MET amplification group than in the Negative control group ($p=0.0262$) (Supplementary Material 4).

Immune microenvironment of melanoma with MET amplification

If the tumor microenvironment shows a T-cell-inflamed phenotype and consists of infiltrating T cells, a type I interferon response, and a broad chemokine profile, innate immunity can be activated. In this study, using data from a TCGA cohort, we investigated the association between MET amplification and the tumor immune microenvironment in melanoma. We used CIBERSORT to evaluate the immune infiltration of 22 immune cell subsets, but we did not observe any differences between patients with and without MET amplification. The MET amplification group did not have a significantly higher proportion of any immunosuppressive cell or a significantly lower proportion of any immune-enhancing cell (Fig. 4). In summary, we are not sure whether the microenvironment of MET amplification is conducive to immunotherapy.

We have requested the surgical samples from Fujian Cancer Hospital for immunohistochemistry to assess the staining of PD-1, PD-L1, CD3 and CD8 (Supplementary Material 3). The expression of PD-1 or PD-L1 was correlated with tumor immunosuppression. While expression

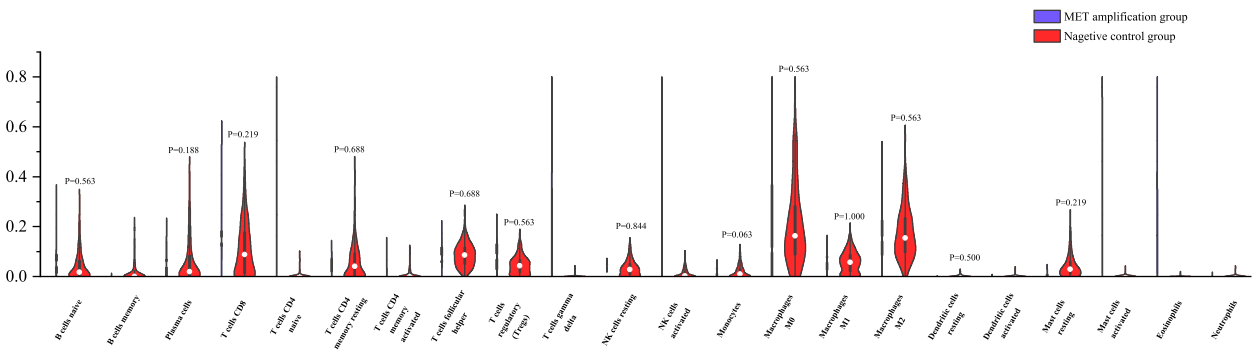

Fig. 4 Differences in infiltrating immune cell fractions estimated by the CIBERSORT algorithm between the MET amplification group and the NC group of melanoma patients

of CD3 is an immune cell (T cell or B cell) biomarker that promotes the tumor immune response. CD8-expressing T cells (CD8 + T cells) usually differentiate into cytotoxic T cells (CTLs) after activation and are able to specifically kill target cells. Due to the small number of surgical samples and most of the diagnoses are derived from pathology consultations on external data, only 4 cases of MET amplification with surgical macroscopic samples were deposited in our center. We additionally randomly matched 4 samples with no MET amplification for immunohistochemistry. The results showed that the CPS (Combined Positive Score) of PD-L1 in MET-amplified samples (CPS = 5 for 3/4 of the sample) was generally higher than that in MET-no amplification samples (CPS ≤ 2 for 3/4 of the sample). All samples were weakly positive (+) with scattered T cells expressing PD-1. The expression of CD3 in MET-amplified samples (≤ 5%) was lower than that in MET-no amplification samples (≥ 5%). The results showed that microenvironment of MET amplification is conducive to immunotherapy.

Association between MET mutation and survival after ICI treatment in patients with various cancers

ICIs have changed the management of many cancers [29]. MET exon 14 alteration is one of the actionable oncogenic drivers in NSCLC. Many highly selective MET inhibitors, such as tepotinib or capmatinib, have shown activity in cancer models and in patients with advanced NSCLC with MET exon 14 skipping mutation. In a previous study of NSCLC patients with MET exon 14 alterations, even though 76% (111/147) of patients expressed PD-L1 and received immune checkpoint inhibition, the ORR was low (17%), the median PFS was 1.9 months, and the median OS was 18.2 months [30]. We used 1109 cases from the MSK-IMPACT cohort from cBioPortal to analyze the association between MET amplification and OS in an immunotherapy cohort. Patients receiving immunotherapy in the MET amplification group had a trend toward worse OS than those without MET amplification ($P = 0.025$) (Fig. 3c). Therefore, MET amplification may be an indicator of poor immunotherapy efficacy across cancers as well as in melanoma.

Discussion

Immunotherapies and targeted therapies have revolutionized the treatment of tumors. Multiple studies have suggested that melanoma is an immune-responsive tumor. Anti-CTLA-4 and anti-PD-1 antibodies were first approved for the treatment of advanced metastatic melanoma in 2011 and 2014, respectively [31–33]. The success of immune checkpoint inhibitors in melanoma-related clinical trials has confirmed that these drugs are effective in reactivating the immune system to target disease. Statistics from the *New England Journal of Medicine* show that approximately 50% of patients with advanced melanoma are resistant to ICIs [34, 35]. Many trials of standard immunotherapy combined with other strategies, such as targeted therapy, chemotherapy, antiangiogenic therapy, and other agents, have been performed.

MET aberrations, including amplifications, mutations, and fusions, have been well documented as drivers of oncogenesis across cancers. Approximately 1%-5% of NSCLC cases and 1%-10% of gastric cancers cases show MET aberrations [1]. MET amplification has been regarded as a biomarker of survival in gastroesophageal adenocarcinoma [36]. Lung cancers with MET amplification are resistant to immune checkpoint blockade [37].

MET inhibitors have shown welcome results in inhibiting melanoma in preclinical studies. But MET inhibitors as single-therapy agents in melanoma have been largely unfruitful. Surriga has found that crizotinib inhibited cell migration at a concentration sufficient for preventing phosphorylation of the MET receptor in uveal melanoma and strongly inhibited the development of metastasis of uveal melanoma in a metastatic mouse model. In a multicenter, single-arm trial (Clinical Trial Information: NCT02223819), adjuvant treatment with crizotinib in patients with high-risk UM did not reduce the recurrence rate. Approximately 28% (9/32) of patients required dose adjustment or discontinuation due to a treatment-related adverse event, which may have limited efficacy. Further study of adjuvant treatment options is warranted. In a clinical trial of patients with metastatic melanoma (NCT00940225), the median PFS (progression-free survival) with cabozantinib treatment (5.7 months) was longer than that in patients receiving placebo (3 months). That study covered patients with cutaneous/mucosal subtypes of melanoma (70%) and uveal melanoma (30%). These clinical studies suggest the efficacy data are still limited. Possibly due to the complex crosstalk of the HGF/MET pathway with other oncogenic pathways. Better stratification of patients based on molecular characteristics may help in the development of these therapies.

Our study, which covers a large database of melanoma in the Chinese population, is the first to report the epidemiology of MET amplification, which was found to be different from that in Europe and the United States. Our retrospective study of melanoma patients from multiple centers revealed that MET amplification is a poor prognostic factor for OS in patients treated with immunotherapy as the first-line treatment. Our univariate Cox regression analysis and survival analysis results suggest that clinicians can test for MET gene alterations to predict the efficacy of immunotherapy. If MET amplification is detected in cases of melanoma, MET-related targeted therapeutic agents should be considered. The

retrospective cohort data of this study has included the largest melanoma clinic in China, but still lacks sufficient sample size for MET amplification. This is a limitation of this study. We will continue to follow up new MET-amplified cases and analyse clinical data and multi-omics sequencing data.

A previous study sequenced 524 American Joint Committee on Cancer stage I-III primary melanomas and revealed that NF1, NRAS, EGFR, TLR4, ARHGAP21 and GABRA6 mutations were mutually exclusive with BRAF mutation [38]. By analyzing multiple published databases and retrospective cohorts, we found that of cases comutation of MET and other common driver genes, such as BRAF, RAS, and KIT, exists in melanoma. Therefore, we suggest that MET amplification can serve as an independent molecular subtype of melanoma. The mechanism by which MET amplification or comutation of MET with other driver genes affects the efficacy of immunotherapy in patients with melanoma needs to be further investigated.

Conclusion

The main MET aberrant type in melanoma is amplification. Melanoma patients with MET amplification have similar immunotherapy efficacy regardless of BRAF mutation status. MET amplification is associated with poor outcome in melanoma patients who receive immunotherapy as the first-line treatment.

Abbreviations

MET	Mesenchymal epithelial transition factor
PSM	Propensity score matching
OS	Overall survival
NC	The negative control
CM	Cutaneous melanoma
MM	Mucosal melanomas
ICI	Immune checkpoint inhibitor
WGS	Whole-genome sequencing
NSCLC	Non-small cell lung cancer
TCGA	The Cancer Genome Atlas
MSKCC	Memorial Sloan Kettering Cancer Center
HR	Hazard ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13163-z.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions

Y.C. and L.S.; Y.C. was responsible for project funding. X.C, C.L, J.L, T.X, C.C, B.L, X.W, S.B, Y.H, H.Z collected and processed the data. X.C wrote the manuscript with input from all co-authors.

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Data availability

The Geneplus cohort that support the findings of this study are available in Supplementary Material 1. Retrospective analysis of melanoma cases from multiple centers are available Supplementary Material 2. The TCGA and MSKCC data that support the findings of this study are openly available at http://cbioportal.org.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Fujian Cancer Hospital (K2023-097–01) in accordance with the Declaration of Helsinki. The patients in this manuscript have given written informed consent to publication of their case details.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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