Genomic Characterization of Chondrosarcoma Reveals Potential Therapeutic Targets

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ABSTRACT

PURPOSE Chondrosarcomas are rare cancers of cartilage with limited systemic therapy options. To identify potential therapeutic targets, this study investigated the molecular and immune landscape of three chondrosarcoma subtypes using a large database of clinical-grade sequencing results.

METHODS Deidentified records from patients with a histologic diagnosis of conventional, dedifferentiated, or mesenchymal chondrosarcoma sequenced by the Tempus xT DNA assay were included. Microsatellite instability (MSI) and tumor mutational burden (TMB) were determined from sequencing data. The expression of PD-L1 and mismatch repair enzymes was evaluated in cases with available immunohistochemistry (IHC) data.

RESULTS Of the 149 patients, 103 had conventional chondrosarcoma, 31 dedifferentiated chondrosarcoma, and 15 mesenchymal chondrosarcoma. Across the cohort, 44% (n = 65) had an *IDH1* or *IDH2* mutation. No cases were MSI high. One conventional chondrosarcoma patient had a TMB >10 mut/Mb. Among 112 patients with available PD-L1 IHC, 10% of conventional (n = 7), 45% of dedifferentiated (n = 13), and 17% of mesenchymal cases (n = 2) were PD-L1–positive. The most common somatic alterations were in *IDH1* (34%) and *TP53* (28%) in conventional chondrosarcoma; *TP53* (68%), *TERT* (65%), *IDH1* (39%), *IDH2* (39%), *CDKN2A* (35%), and *CDKN2B* (35%) in dedifferentiated chondrosarcoma; and *HEY1-NCOA2* fusions (87%) and *CDKN2A* (20%) in mesenchymal chondrosarcoma. *MTAP* was deleted in >10% of each subtype, and potentially actionable *PDGFRB* mutations were identified in 13% of dedifferentiated chondrosarcomas.

CONCLUSION These findings reinforce therapeutic efforts to target IDH signaling in chondrosarcoma, provide insight into varied subpopulation response to immune checkpoint inhibitors, and identify new potential therapeutic targets for clinical development in chondrosarcoma.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

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INTRODUCTION

Chondrosarcomas are a rare group of cancers of cartilaginous origin. In adults, conventional chondrosarcoma is the most common, followed by mesenchymal, dedifferentiated, clear cell, and other ultra-rare subtypes.[1] Despite advances in treatment across cancer types, there is still no effective systemic treatment for conventional chondrosarcoma. Mesenchymal and dedifferentiated chondrosarcomas are often treated along Ewing sarcoma and osteosarcoma paradigms, respectively, but with limited evidence to support this use.[2-5]

After the identification of *IDH* mutations in chondrosarcoma,[6] IDH inhibitors are now being studied in this disease.[7] *COL2A1* alterations are present in over a third of chondrosarcomas, but these are not clinically actionable.[8] Reports of patients responding to immune checkpoint inhibitors are published, but without a clear mechanism for why some patients with chondrosarcoma respond to immunotherapy.[9-12] A prospective study of an immune checkpoint inhibitor in conventional chondrosarcoma was negative.[13]

Preclinical studies have suggested that some chondrosarcoma subtypes may be more responsive to immune-

CONTEXT

Key Objective

Chondrosarcomas are rare cancers of cartilage with limited systemic therapy options. We investigated the molecular and immune landscape of three chondrosarcoma subtypes using a large database of clinical-grade sequencing results.

Knowledge Generated

In addition to identifying the previously reported *IDH* mutations in chondrosarcoma, we found that *MTAP* was deleted in >10% of each subtype and potentially actionable *PDGFRB* mutations were identified in 13% of dedifferentiated chondrosarcomas. Forty-five percent of dedifferentiated chondrosarcomas were PD-L1–positive.

Relevance

These findings reinforce current therapeutic efforts to target IDH signaling in chondrosarcoma and identify other potential biomarkers including alterations in *MTAP, CDKN2A, PDGFRB,* and PD-L1 expression that can guide clinical trial design.

mediated therapies. One study found that 41% of dedifferentiated chondrosarcomas express PD-L1 exclusively in the dedifferentiated component, and PD-L1 expression was absent in the conventional, mesenchymal, and clear cell subtypes.[14] Similarly, separate studies identified PD-L1 positivity in higher grade chondrosarcomas, such as grade 3 or dedifferentiated, with no low- or intermediate-grade tumors having PD-L1 immunoreactivity.[15,16] A multiomic characterization of chondrosarcomas found that a dedifferentiated-like subtype of chondrosarcoma that the authors termed C6 had the highest expression of PDL1 and the highest level of intratumoral T cells.[17]

We sought to characterize the molecular and immune landscape of conventional, dedifferentiated, and mesenchymal chondrosarcomas using a large database of real-world clinical-grade sequencing results with the goal of identifying new therapeutic targets.

METHODS

Cohort

A sample of deidentified records from patients with a histologic diagnosis of conventional chondrosarcoma, dedifferentiated chondrosarcoma, or mesenchymal chondrosarcoma in the Tempus Database who had completed tissue DNA sequencing between November 2018 and May 2023 with the Tempus xT assay were included for this retrospective analysis (Tempus AI, Inc, Chicago, IL). This study was conducted on deidentified health information subject to an IRB exempt determination (Advarra Pro00072742) and did not involve human subject research.

Assigning Histological Grade and Pretreatment Status

Histologic grading was determined from curated clinical reports derived from a combination of structured data in electronic health record systems and unstructured data collected from patient records via technology-enabled chart abstraction. Due to the inclusion of unstructured data in the curation of these reports, clinical characteristics are often abstracted on the basis of a set of rules for interpreting a mixture of categorical and numerical data. In the case of histologic grading, categorical physician notes were assigned to a numerical grade on the basis of the inclusion of specific terms. For example, a note including the terms *differentiated, NOS* or *well differentiated* was classified as grade 1, whereas a note including *fairly well differentiated*, *intermediate differentiation*, *mid differentiated*, *partially differentiated*, *relatively well differentiated*, or similar terms was classified as grade 2. Likewise, notes such as *moderately poorly differentiated*, *poorly differentiated*, or *dedifferentiated* were classified as grade 3. In cases where multiple tumor characterization records were present for a given patient, the grade recorded closest to the sample collection date was selected. Any samples without complete tumor characterization date information, regardless of whether a grade was reported in the patient record, were considered to have an unknown grade.

Treatment information was similarly curated from clinical notes and reports. A treatment was defined as any antineoplastic therapy received, such as medications and cellular therapies, plus radiation therapies. Only patients with recorded treatment and treatment start dates were included in the analysis of sample collection date relative to treatment start date; all others were classified as having an unknown sample collection date relative to treatment start date.

DNA Sequencing

Ordering physicians were not required to order both sequencing and PD-L1 immunohistochemistry (IHC). Tempus xT next-generation sequencing assay results were analyzed as previously described.[18] Briefly, Tempus xT is a targeted, tumor/normal-matched panel that detects single-nucleotide variants, insertions and/or deletions, and copy

number variants in 596 or 648 genes depending on version number, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.

Microsatellite instability (MSI) was calculated as previously published.[18] Briefly, the Tempus xT panel derived MSI from 239 loci (each with minimum read thresholds). The proportion of unstable microsatellite loci was fed into a previously trained classification algorithm, resulting in four categories: microsatellite instability-high, microsatellite stable (MSS), microsatellite equivocal, or undetermined.

Tumor mutational burden (TMB) was calculated by dividing the count of all nonsilent mutations (including missense single-nucleotide polymorphisms/indels) by the total size of the Tempus xT panel coding region. Samples with TMB >10 mutations/Mb were considered TMB-high.

PD-L1 IHC

The expression of PD-L1 and mismatch repair enzymes was evaluated in cases with available IHC data using PD-L1 antibody 22c3 (Agilent Cat SK006, RRID:AB_2889976). Slides were scored by a pathologist using the tumor proportion score (TPS), calculated as the number of PD-L1–positive tumor cells divided by the total number of PD-L1–positive and PD-L1–negative tumor cells. PD-L1–positive is defined as a TPS of 1% or more.

Statistical Analysis

Oncoplot was made using the CoMut package for Python (RRID:SCR_008394).[19] Statistical comparisons were made using a *t*-test or analysis of variance (ANOVA) and graphs were made in GraphPad Prism v10 (RRID:SCR_002798). Chi-square tests were conducted in SPSS v28 (RRID: SCR_002865). Two-sided $P < .05$ were considered significant.

RESULTS

There were 149 patient records identified consisting of 103 conventional chondrosarcoma, 31 dedifferentiated chondrosarcoma, and 15 mesenchymal chondrosarcoma samples. Available patient demographics and tumor characteristics are reported in Table 1.

Of the total cohort (N = 149), 44% had either an *IDH1* or *IDH2* mutation (n = 65). *IDH1* mutations were present in 34% of conventional (n = 35), 38.7% of dedifferentiated (n = 12), and 0% of mesenchymal cases. *IDH2* mutations were identified in 5.8% of conventional (n = 6), 38.7% of dedifferentiated (n = 12), and 0% of mesenchymal cases. Collectively, 40% of conventional chondrosarcomas had a mutation in *IDH1* or *IDH2* and 77% of dedifferentiated chondrosarcomas had a mutation in *IDH1* or *IDH2*. In conventional chondrosarcoma, the most common somatic alterations were in *IDH1* (n = 35, 34%), *TP53* (n = 29, 28%), *CDKN2A* (n = 18, 17%), *CDKN2B* (n = 14, 14%), *TERT* promoter (n = 13, 13%), *MTAP* (n = 12, 12%), *IDH2* (n = 6, 6%), and *LRP1B* (n = 6, 6%). In dedifferentiated chondrosarcoma, the most common somatic alterations were in *TP53* (n = 21, 68%), *TERT* promoter (n = 20, 65%), *IDH1* (n = 12, 39%), *IDH2* (n = 12, 39%), *CDKN2A* (n = 11, 35%), *CDKN2B* (n = 11, 35%), *MTAP* (n = 6, 19%), and *PDGFRB* (n = 4, 13%). In mesenchymal chondrosarcoma, the most common somatic alterations were in *HEY1-NCOA2* fusions (n = 13, 87%), *CDKN2A* (n = 3, 20%), *CDKN2B* (n = 2, 13%), *MTAP* (n = 2, 13%), *FANCL* (n = 1, 7%), *GATA1* (n = 1, 7%), *KMT2C* (n = 1, 7%), and *RBM10* (n = 1, 7%; Fig 1). Copy number alterations were present in patients with or without *IDH1/2* mutations, with only 12 cases having any gene amplifications (Appendix Table A1). The copy number alterations seen in patients with *IDH1 or IDH2* mutations are presented in Appendix Table A2.

One patient with conventional chondrosarcoma had an activating *KIT* exon 11 mutation (V559A), and one had a *KRAS* G12D mutation. One patient with conventional chondrosarcoma had rearrangements involving *NTRK1* (*FAM20B-NTRK1* and *TPR-NTRK1* detected in the same patient; Table 2).

Of the six cases of dedifferentiated chondrosarcoma with any *PDGFRB* mutations, four are known to be pathogenic (N666S, N666K, D850V, R561C) and two were classified as variants of unknown significance located in the extracellular domain (T36I, S493I). One dedifferentiated chondrosarcoma case had a *DYNC1LI2-RAF1* fusion.

Among 112 patients with available PD-L1 IHC data, 10% of conventional (n = 7), 45% of dedifferentiated (n = 13), and 17% of mesenchymal cases (n = 2) had a TPS of ≥1 (Table 3). Only dedifferentiated chondrosarcoma cases had a PD-L1 TPS >50%. There was no difference in the likelihood of PD-L1 positivity between *IDH1/2* mutant tumors and *IDH* wild-type tumors (Appendix Fig A1; $\chi^2(2) = 0.567$; $P = .753$). Dedifferentiated chondrosarcoma had higher TPS compared with conventional chondrosarcoma (unpaired *t*-test; $P < .001$). The TPS difference between dedifferentiated and mesenchymal chondrosarcoma was nonsignificant (unpaired *t*-test; $P = .144$; Fig 2A). The median TMB was 1.533 mutations/Mb (95% CI, 1.168 to 1.898) for conventional, 2.307 mutations/Mb (95% CI, 1.533 to 3.460) for dedifferentiated, and 0.594 mutations/Mb (95% CI, 0.000 to 3.431) for mesenchymal. One patient with conventional chondrosarcoma had a high TMB (>10 mutations/Mb); no patients with dedifferentiated or mesenchymal chondrosarcoma had a high TMB (Fig 2B). TMB differences were not significant (ANOVA $P = .41$). All patients in each subtype were MSS.

DISCUSSION

We report the genomic and immune profile of three chondrosarcoma subtypes. These results redemonstrate the presence of *IDH* mutations in conventional and

TABLE 1. Patient Characteristics

Characteristic	Conventional Chondrosarcoma (N = 103)	Dedifferentiated Chondrosarcoma (N = 31)	Mesenchymal Chondrosarcoma (N = 15)	*P*[a]
Age at diagnosis, years				<.001
Median (IQR)	56 (43-64)	66 (63-71)	34 (24-46)	
Range	19-81	24-82	21-58	
Unknown	8	4	3	
Sex, No. (%)				.2
Male	72 (70)	23 (74)	7 (47)	
Female	31 (30)	8 (26)	8 (53)	
Race, No. (%)				.026
White	52 (93)	9 (75)	7 (70)	
Black or African American	1 (1.8)	1 (8.3)	2 (20)	
Other race	1 (1.8)	2 (17)	1 (10)	
Asian	2 (3.6)	0	0	
Not reported	47	19	5	
Ethnicity, No. (%)				.5
Not Hispanic or Latino	37 (36)	7 (23)	5 (33)	
Hispanic or Latino	3 (2.9)	1 (3.2)	1 (6.7)	
Unknown/not reported	63 (61)	23 (74)	9 (60)	
Tumor grade,[b] No. (%)				
Low	4 (8.7)	0	0	
Intermediate	27 (59)	3 (16)	0	
High	15 (33)	16 (84)	1 (100)	
Unknown/not reported	57	12	14	
Sample status with respect to systemic treatment or radiation therapy,[b] No. (%)				
Sample collected after treatment start	10 (36)	6 (75)	5 (100)	
Sample collected before treatment start	18 (64)	2 (25)	0	
Unknown/not reported	75	23	10	

[a]Kruskal-Wallis rank-sum test; Fisher's exact test.
[b]Samples that are unknown with respect to timing of treatment that may have been treated with surgery alone and effectively would be equivalent to those collected before treatment (see Methods: Assigning Histological Grade and Pretreatment Status).

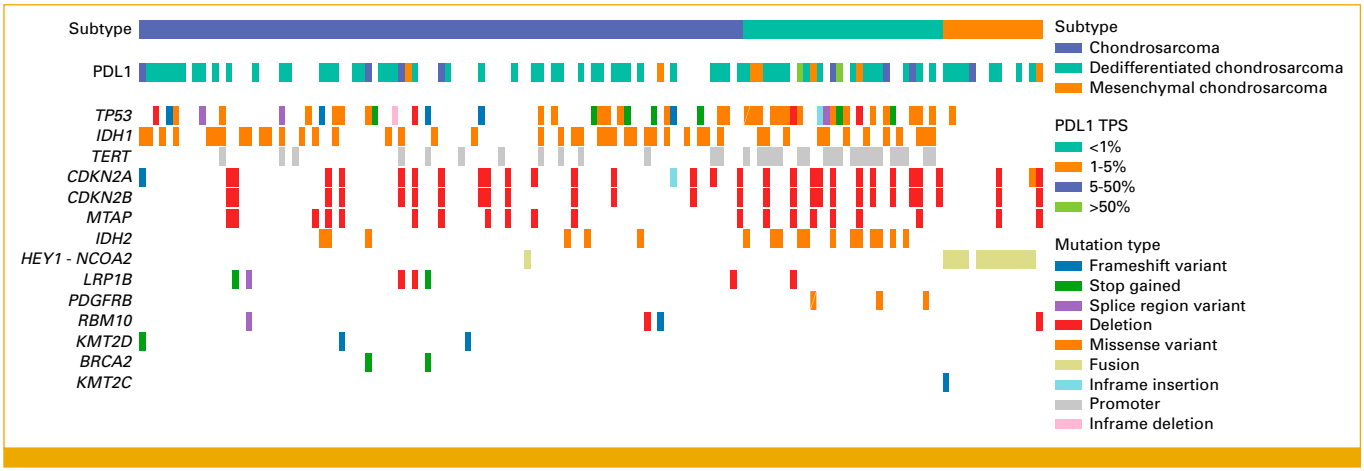

FIG 1. CoMut plot of somatic alterations in frequently altered genes in 149 patients with chondrosarcoma. Chondrosarcoma subtype and PD-L1 TPS (if known) are shown in the upper panels. Key to the right of the plot indicates subclassifications and specific alteration types. TPS, tumor proportion score.

dedifferentiated chondrosarcoma and identify less common alterations in genes such as *MTAP* in a subset of patients, which can inform future trial design. We also identify several targetable alterations that are not typically associated with chondrosarcoma but could lead to potential therapeutic options for patients with tumors that are generally considered unresponsive to current treatments. Although rare, one patient with conventional chondrosarcoma was identified to have a high TMB and all subtypes had some patients that were PD-L1–positive, suggesting possible mechanisms by which a small minority of patients with chondrosarcoma have been observed to respond to immune checkpoint inhibitors.

In other tumor types, *IDH* mutation status can affect the composition of the immune microenvironment. In high-grade gliomas, *IDH*-mutant tumors demonstrate reduced suppressive myeloid cells[20] and an abundance of microglia.[21] *IDH*-mutant cholangiocarcinoma has reduced T-cell infiltration, suggestive of a cold immune microenvironment.[22] We did not detect differences in PD-L1 expression between *IDH*-mutant and *IDH*-wild-type chondrosarcoma.

TABLE 2. Gene Rearrangements in Chondrosarcoma

Rearrangement	Conventional (n = 103)	Dedifferentiated (n = 31)	Mesenchymal (n = 15)
ANXA2-MYO5A	1	0	0
BCR-IGLL1	1	0	0
DYNC1LI2-RAF1	0	1	0
EWSR1-CREM	0	0	1
EWSR1-SMAD3	1	0	0
FAM20B-NTRK1			
TPR-NTRK1	1	0	0
TRIO-TERT (all in same case)			
FN1-ACVR2A	2	0	0
FN1-ACVR2B	1	0	0
HEY1-NCOA2	1	0	13
IGF2R-TMPRSS2	1	0	0
NRG1-LDAH	1	0	0
PICALM-ARHGAP42	0	1	0
RAF1-TMEM40	0	1	0
RASAL2-MYH7B	1	0	0
STK3-VPS13B	0	0	1
WNK1-EFR3A (concurrent with HEY1-NCOA2, reported separately)	0	0	1
WWP2-NQO1	1	0	0

TABLE 3. PD-L1 Expression in Chondrosarcoma

Total (N = 112)	PD-L1–Negative TPS <1 (%)	TPS 1-5 (%)	TPS >5 to <50 (%)	TPS ≥50 (%)	Total Positive TPS ≥1 (%)
Conventional (n = 71)	64 (90)	3 (4)	4 (6)	0	7 (10)
Dedifferentiated (n = 29)	16 (55)	6 (21)	2 (7)	5 (17)	13 (45)
Mesenchymal (n = 12)	10 (83)	1 (8)	1 (8)	0	2 (17)

Abbreviation: TPS, tumor proportion score.

To date and despite advances in our knowledge of biologic drivers of disease, no effective systemic treatments exist for metastatic chondrosarcoma. Systemic therapy of any type in dedifferentiated chondrosarcoma yielded a response rate of 9% with a median overall survival of 7.2 months.[10] *IDH1/2* mutations such as those identified in our data set are well characterized in cartilaginous neoplasms including enchondroma, conventional chondrosarcoma, and dedifferentiated chondrosarcoma. However, a prospective clinical trial of the IDH inhibitor ivosidenib yielded no radiographic responses and a progression-free rate at 6 months of 39.5%.[7] *CDKN2A/B* loss was found at a relatively high frequency, and these mutations have previously been reported in chondrosarcoma.[8,23] Although mechanistically *CDKN2A* loss would suggest susceptibility to CDK4/6 inhibitors, treatment with palbociclib was not effective in other tumor types with *CDKN2A* loss.[24] A recent genomic profiling effort of conventional and dedifferentiated chondrosarcoma had limited targeted gene coverage using retrospective sequencing results with over half of the patient data derived from a platform that only sequenced 50 genes and did not assess for some potentially actionable genes identified in our series.[23] Effective new therapeutic targets for chondrosarcoma are critically needed.

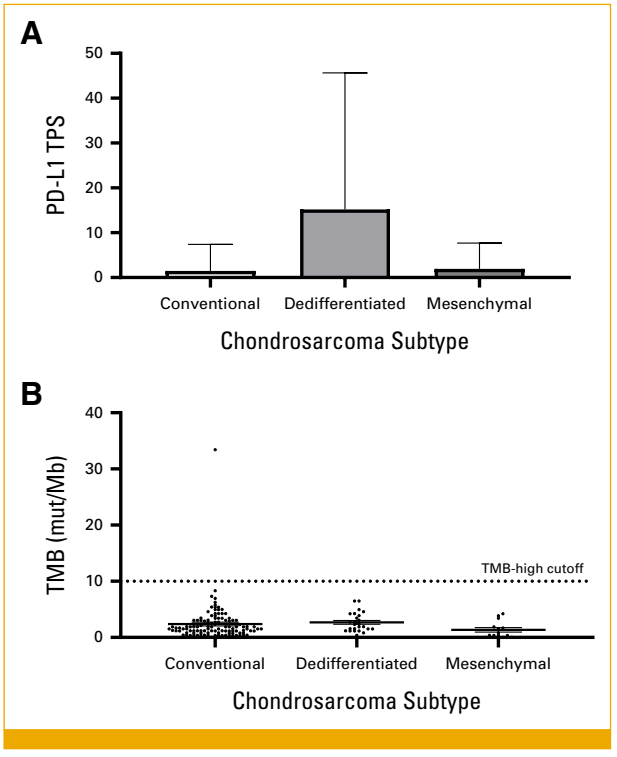

FIG 2. Immune profile of chondrosarcomas. (A) PD-L1 TPS among 112 patients with available PD-L1 IHC data. (B) Tumor mutation burden across the cohort (N = 149), one conventional chondrosarcoma case had a TMB >10 mut/Mb. IHC, immunohistochemistry; TMB, tumor mutational burden; TPS, tumor proportion score.

CDKN2A homozygous deletion often extends to the neighboring gene *MTAP*, resulting in increased levels of methylthioadenosine (MTA). MTA partially inhibits PRMT5, a methyltransferase involved in multiple essential biological functions.[25,26] MTA-cooperative PRMT5 inhibitors selectively bind MTA-PRMT5, thereby inhibiting PRMT5 in the tumor cells with high MTA levels and sparing the normal cells.[23] MTA-cooperative PRMT5 inhibitors are in clinical testing and have demonstrated clinical responses in multiple cancer types with *MTAP* deletion.[27] In our study, *MTAP* was deleted in 12% of conventional, 19% of dedifferentiated, and 13% of mesenchymal chondrosarcomas. Next-generation sequencing may underestimate the true incidence of *MTAP* deletion by missing subgenic *MTAP* deletions that may still abolish MTAP function. Furthermore, *MTAP* copy number alteration calls can be challenging in the context of marked aneuploidy, as is seen in high-grade chondrosarcomas. Thus, further studies investigating MTAP loss at the protein level are needed to determine the true incidence of *MTAP* deletion in this population. *MTAP* deletions have not been previously described in chondrosarcoma, and these results suggest a novel therapeutic vulnerability.

Nearly 20% of patients with dedifferentiated chondrosarcoma had *PDGFRB* alterations. A clinical trial of imatinib, a PDGFRA/B inhibitor, in chondrosarcoma was deemed a negative trial; however, no dedifferentiated chondrosarcomas were included.[28] Although *PDGFRA* mutations are relatively common in GI stromal tumor, *PDGFRB* mutations were only recently characterized in sarcomas.[29] Interestingly, *PDGFRB*-mutant myogenic tumors have a more aggressive clinical course than their counterparts, similar to how dedifferentiated chondrosarcoma compares with conventional chondrosarcoma. Given these findings, a future trial of imatinib in patients with *PDGFRB*-mutant sarcomas may be beneficial.

Dedifferentiated chondrosarcoma was most likely to be PD-L1–positive compared with conventional and mesenchymal chondrosarcoma. Notably, at least some examples of individuals with PD-L1 expression were found in each subtype,

compared with a previous report that only found PD-L1 expression in dedifferentiated chondrosarcoma and not in conventional or mesenchymal chondrosarcoma.[14] This is consistent with the reported activity of checkpoint inhibitors in chondrosarcoma, where several examples exist of responses in dedifferentiated chondrosarcoma,[10,30,31] and the rare response is reported in conventional chondrosarcoma.[9] One of the patients with dedifferentiated chondrosarcoma had a PD-L1 TPS of 7%.[10] Indeed, dedifferentiated chondrosarcomas in particular have been shown to have PD-L1 expression on the dedifferentiated component with associated T-cell infiltration and HLA class I expression.[14] Our finding that only dedifferentiated cases had PD-L1 TPS of 50% or greater is also consistent with the multiple previous reports of responses in this subtype and suggests that a study of immune checkpoint inhibition in dedifferentiated chondrosarcoma is warranted.

It is important to note that biomarkers other than TMB and PD-L1 status may be relevant in chondrosarcoma but were beyond the scope of this study. Conventional chondrosarcomas cluster into three immune categories: one with a high number of HLA-DR$^-$ CD14$^-$ myeloid cells, one infiltrated with exhausted T cells and dendritic cells, and one with little immune cell infiltration.[32] In a series of 12 patients with conventional chondrosarcoma treated with immune checkpoint inhibitors, one had a response and two patients were deemed to have benefit with durable stable disease; all were in the subgroup characterized by infiltration with exhausted T cells and dendritic cells.[32] Both T cells and PD-L1+ tumor–associated macrophages correlate with response to pembrolizumab in an unselected group of sarcomas.[33]

Strengths of this study include its relatively large sample for an ultra-rare disease, inclusion of different chondrosarcoma subtypes, and real-world applicability by incorporating patients from sites across the United States. Limitations include the finite number of genes sequenced, precluding our ability to identify genes that would be covered by whole-exome or whole-genome sequencing but are known to be mutated in chondrosarcoma (such as *COL2A1*). Although the cases were reviewed by pathologists, they were not centrally reviewed by sarcoma specialist pathologists, and for regulatory purposes we were unable to re-review the histology retrospectively and some cases may be misclassified. As an example, the previously described *HEY1-NCOA2* known to be associated with mesenchymal chondrosarcoma[34] was identified in 13 of 15 mesenchymal chondrosarcomas in this series, but was also found in one case classified as a conventional chondrosarcoma. Furthermore, these deidentified records are representative of the information available for each patient at the time a sample was submitted for sequencing. Due to the nature of retrospective, real-world data analyses where clinical characteristics are often abstracted from unstructured data, there is a high degree of missingness with clinical data that were not mandatory for the sample to be processed on the sequencing platform. Therefore, we cannot discuss clinical follow-up or treatment for the specific cases analyzed with certainty.

In conclusion, these findings reinforce current therapeutic efforts to target IDH signaling in chondrosarcoma and identify potentially actionable targets that to date have not been reported in chondrosarcoma, such as *MTAP* loss and *PDGFRB* mutations. Given PD-L1 expression in a minority of cases and one case with a high TMB, these data provide insight into why some patients respond to immune checkpoint inhibitors. Biomarker-driven trials are needed to understand the significance and potential applications of these results in clinical practice.

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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Gene Amplifications

Subtype[a]	Pathogenic Gene Amplifications	IDH1/2 Mutation Status
Conventional chondrosarcoma	*MCL1*	Wild type
Conventional chondrosarcoma	*CUL4A*	Wild type
Conventional chondrosarcoma	*BIRC3*	*IDH1*
Conventional chondrosarcoma	*KIT*, *PDGFRA*	Wild type
Conventional chondrosarcoma	*CKS1B*, *MCL1*	*IDH1*
Conventional chondrosarcoma	*MCL1*	Wild type
Conventional chondrosarcoma	*FGFR1*	Wild type
Conventional chondrosarcoma	*CDK4*, *FRS2*, *MDM2*, *STAT6*, *YEATS4*	*IDH2*
Dedifferentiated chondrosarcoma	*BIRC3*	*IDH2*
Dedifferentiated chondrosarcoma	*MYC*	*IDH2*
Dedifferentiated chondrosarcoma	*BIRC3*, *KDR*, *KIT*, *PDGFRA*	*IDH2*
Dedifferentiated chondrosarcoma	*CCND3*, *TFEB*, *VEGFA*	Wild type

[a]Each row represents an individual patient sample.

TABLE A2. Copy Number Landscape Among Patients With *IDH1* or *IDH2* Alteration

Characteristic	Conventional Chondrosarcoma (N = 41), No. (%)	Dedifferentiated Chondrosarcoma (N = 24), No. (%)
IDH1 (short variant)	35 (85)	12 (50)
IDH2 (short variant)	6 (15)	12 (50)
BIRC3 (amplification)	1 (2.4)	2 (8.3)
CDKN2A (deletion)	4 (9.8)	7 (29)
CDKN2B (deletion)	4 (9.8)	7 (29)
MTAP (deletion)	3 (7.3)	4 (17)
MYC (amplification)	0	1 (4.2)
BCL11B (deletion)	1 (2.4)	0
HNF1A (deletion)	1 (2.4)	0
LRP1B (deletion)	1 (2.4)	0
CKS1B (amplification)	1 (2.4)	0
KDM5C (deletion)	2 (4.9)	0
MCL1 (amplification)	1 (2.4)	0
PHF6 (deletion)	0	1 (4.2)
TP53 (deletion)	0	1 (4.2)
KDR (amplification)	0	1 (4.2)
KIT (amplification)	0	1 (4.2)
PDGFRA (amplification)	0	1 (4.2)
CDK4 (amplification)	1 (2.4)	0
FRS2 (amplification)	1 (2.4)	0
MDM2 (amplification)	1 (2.4)	0
STAT6 (amplification)	1 (2.4)	0
YEATS4 (amplification)	1 (2.4)	0
ATM (deletion)	0	1 (4.2)
GATA1 (deletion)	1 (2.4)	0
RBM10 (deletion)	1 (2.4)	0
SUFU (deletion)	1 (2.4)	0

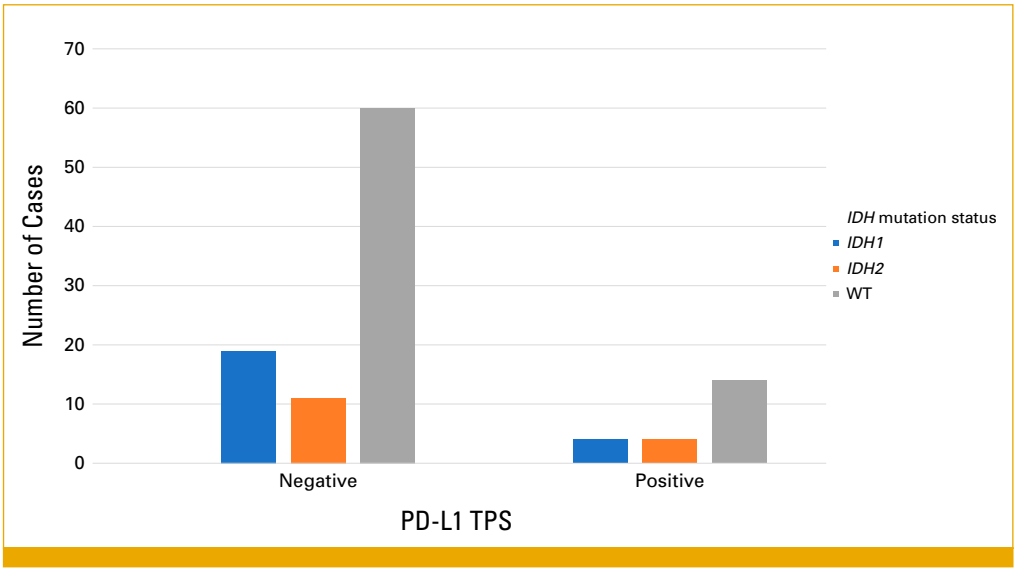

FIG A1. PD-L1 expression by *IDH1/2* mutation status. TPS, tumor proportion score; WT, wild-type.