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High Grade Sarcomas with Myogenic Differentiation Harboring Hotspot *PDGFRB* Mutations

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Abstract

PDGFRB activating mutations have been reported in pediatric myofibroma or myofibromatosis. However, recurrent gain-of-function *PDGFRB* mutations have not been documented in sarcomas with myogenic differentiation. Driven by occasional sarcomas harboring *PDGFRB* mutations, we investigate their prevalence, clinicopathologic and genomic features in a large cohort of sarcomas. An institutional targeted DNA next-generation sequencing database was searched for sarcomas with hotspot *PDGFRB* gene alterations. Among 3,300 patients with sarcomas, 21 (0.6%) sarcomas with myogenic differentiation were identified (17 females, 4 males) with an age range of 35–88 years. The site distribution included 13 gynecologic tracts (12 uteri, 1 vagina), 4 bone and soft tissue, and 4 viscera. All except one were high grade. Most cases were diagnosed as sarcomas with myogenic differentiation based on partial staining for one/more muscle markers, while 6 were labeled as LMS. Most tumors showed monomorphic spindle morphology, with either heterogeneous features of myofibroblastic and smooth muscle differentiation or an undifferentiated phenotype. Hormone receptors were negative in all uterine cases. PDGFRB immunostaining in all cases tested was strong and diffuse, while PDGFRA was negative/focal. The most frequent *PDGFRB* mutations were exon 12 (43%), exon 14 (N666K/S/T) (38%), and exon 18 (D850Y/H/V or insertion/deletion) (19%). The most frequent co-existing genetic alterations (26–37%) occurred in *CDKN2A/B, TP53, TERT*, and *MED12*. Moreover, PDGFRB-mutant sarcomas had an overall distinct genomic landscape compared to both uterine and soft tissue LMS control groups. These tumors were associated with a highly aggressive

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Author Contribution Statement

JKD performed study design, data acquisition, data analysis and interpretation, writing, and revision of the paper. SC, MH, WT performed data acquisition and critical review of the paper. CRA performed study design and conception, analysis and interpretation of data, writing, review, and revision of the paper. All authors read and approved the final manuscript.

Ethics Approval / Consent to Participate

This study was approved by the Memorial Sloan Kettering Cancer Institute Institutional Review Board.

Conflict of Interest Statement

All authors report no conflict of interest related to this study.

clinical course, with frequent distant metastases (81%) and death (76%), regardless of anatomic location, and worse overall survival compared to the two LMS control groups. This is the first study documenting recurrent hotspot *PDGFRB* alterations in high grade sarcomas, which show predilection for uterine location and myogenic differentiation that fall short of the diagnostic criteria for LMS. Further studies are needed to investigate the therapeutic potential of kinase inhibitors in this group of tumors.

Keywords

PDGFRB; sarcoma; myogenic differentiation; molecular profiling

Introduction

Platelet-derived growth factor receptor-B (PDGFRβ) is a transmembrane receptor tyrosine kinase encoded by the *PDGFRB* gene on 5q32.[1] PDGFRβ is primarily expressed in cells of mesenchymal origin, including vascular smooth muscle cells, and studies on genetically engineered mouse models demonstrated PDGFRβ to be essential for embryonic development in part by controlling perivascular cell accumulation/localization.[2,3] *PDGFRB* activating mutations have been reported in a subset of pediatric myofibroma or myofibromatosis.[4–6] Moreover, the vast majority of families with autosomal-dominant infantile myofibromatosis harbor germline variants in *PDGFRB*,[7,8] which primarily occur at 2 hotspots, exon 12 p.R561C, and exon 14 p.N666K. These mutations were also reported in sporadic infantile myofibromatosis.[9] Most of these hotspot *PDGFRB* alterations were shown to be sensitive to imatinib and other receptor tyrosine kinase inhibitors (TKI).[10–12] However, recurrent gain-of-function *PDGFRB* mutations have not been documented in malignant pericytic or myofibroblastic lesions or sarcomas with myogenic differentiation. Driven by the observation of occasional sarcomas harboring *PDGFRB* mutations, we sought to investigate their prevalence in a large cohort of sarcomas to better define their clinicopathologic features and associations with other genomic alterations.

Materials and Methods

Case Selection and Study Cohort

An institutional targeted DNA NGS assay database for solid tumors was searched for sarcomas (soft tissue, bone, gynecologic tract, etc.) with *PDGFRB* gene alterations. Among a total of 3,300 patients with sarcomas, *PDGFRB* mutations were detected in 42 (1.2%) patients. After excluding cases with other known oncogenic drivers (e.g., gene fusions, *MDM2/CDK4* amplification) or established mesenchymal tumor entities, a total of 21 sarcomas harboring *PDGFRB* hotspots were identified. *PDGFRB* hotspots were defined based on recurrently mutated positions in relevant tumor types (myofibromas, myofibromatosis), pathogenicity/oncogenicity from germline and somatic variant databases (ClinVar, COSMIC, Oncokb, etc.), and equivalence to known *PDGFRA* hotspots. For comparative genomic analysis, control cohorts of comparable sample sizes with MSK-IMPACT profiling between 2021-2022 were randomly selected without prior knowledge of their immunohistochemical and molecular profile or clinical features: 24 uterine

leiomyosarcomas (ULMS) and 22 soft tissue leiomyosarcomas (STLMS) (12 with clinically documented association with large retroperitoneal blood vessels). Each of these cases was individually reviewed by one of the authors (CRA) to ensure accurate histopathologic classification.

Immunohistochemistry

The relevant antibodies and the dilutions used in this study are as follows: pan-cytokeratin (AE1/AE3) (Dako, clone M3515, 1:1600), CD10 (Ventana clone SP67, undiluted), cyclin D1 (Thermo Fisher, clone SP4, 1:200), desmin (Ventana, clone DE-R-11, undiluted), ER (Leica Biosystems, clone 6F11, undiluted), H-caldesmon (Cell Marque, clone E89, undiluted), MSA (Ventana, clone HHF35, undiluted), PDGFR-A (Novus Biochemical, clone 1C10, 1:400), PDGFR-B (Abcam, clone Y92, 1:1000), PR (Leica Biosystems, clone 16, undiluted), S100 (Cell Marque, clone 4C4.9, 1:600), SMA (Cell Marque, clone 1A4, undiluted), and SOX10 (Biocare, clone BC34, 1:50). For clinical validation of PDGFRB and PDGFRA antibodies: PDGFRB was validated on 10 *PDGFRB*-mutant myofibroma(tosis). PDGFRA was validated on 10 PDGFRA-mutant gastrointestinal stromal tumors (GIST). For negative controls, 10 other spindle cell neoplasms (leiomyoma, schwannoma, desmoid) were used for PDGFRB, and 10 *KIT*-mutant or wild-type GISTs were used for PDGFRA.

Targeted DNA sequencing for mutational and copy number profiling

detailed descriptions of MSK-IMPACT workflow and data analysis, a matched tumor-normal, hybridization capture-based targeted DNA next-generation sequencing (NGS) assay for solid tumors were described previously. All mutational and copy number calls were generated by the standard MSK-IMPACT pipeline.[13] Genetic alterations included copy number deletion, intragenic deletion, nonsense mutation, frameshift insertion/deletion, most splice site mutations, missense mutations [single nucleotide variants (SNV)], and in-frame insertions/deletions (Insdel).

Data analysis was performed using R version 4.1.0. Mutations and gene-level copy number alterations were visualized and summarized using the R package “ComplexHeatmap” version 2.8.0.[14]

Survival analysis

Survival analysis by comparison of hazard ratios using log rank *P* testing and visualization of Kaplan-Meier curves were performed using R packages “survminer” version 0.4.9 and “survival” version 3.2.13. Clinical charts were manually reviewed to document the date of initial presentation, disease progression, and survival status. Median time (in years) to disease progression was defined as the time interval between initial presentation (presence of tumor seen radiographically or on pathologic examination) and the first instance of tumor recurrence or distant metastases after initial surgical resection and/or chemoradiation therapy with radiographically negative evidence of residual tumor. Survival analysis was also investigated in the two control leiomyosarcoma cohorts to establish potential differences in biologic behavior with the study cohort.

Results

Clinical summary

Twenty-one sarcomas with hot spot *PDGFRB* mutations and myogenic differentiation were identified (17 females, 4 males) with an age range of 35-88 years (median 62 years old). Thirteen cases (12 uteri, 1 vagina) occurred in the gynecologic tract. Eight cases presented outside of the gynecologic tract: 4 bone and soft tissue and 4 viscera (pancreas, liver, breast) (Table 1). Greatest dimensions of the tumors ranged from 3.5 to 20.0 cm (median 10.8 cm). Surgical resection margins were negative in 17 of 18 cases when applicable/available.

Histopathologic features

The majority of the tumors received an original diagnosis of “high-grade sarcoma with myogenic differentiation”, based on a combination of morphologic features and partial staining for one/more muscle markers. In only 6 cases, diagnostic features consistent with leiomyosarcoma were found.

Histologically, most tumors showed monomorphic spindle morphology, with either heterogeneous features of myofibroblastic and smooth muscle differentiation or an undifferentiated phenotype. In 9 cases, the neoplastic cells demonstrated myofibroblast-like features including stubby to fusiform nuclei with open to vesicular chromatin and small nucleoli, amphophilic cytoplasmic processes, and extracellular collagen deposition and focal myxoid or fibromyxoid stroma (Figure 1A–H, Figure 2A–D). In 6 cases, the cells demonstrated cigar-shaped nuclei and brightly eosinophilic cytoplasm, often arranged in intersecting fascicles and bundles that are more reminiscent of a leiomyosarcoma (Figure 2A, B). While the majority of the cases demonstrated monomorphic neoplastic cells, the gynecologic cases showed a wider morphologic spectrum. A few cases contained predominantly epithelioid to ovoid cells (Figure 2E, F). However, severe nuclear atypia including marked pleomorphism and atypical mitoses were identified in 6 cases (pleomorphism diffuse in 3, focal in 3) (Figure 2G, H).

All except one case (case 1) were high-grade. The majority of the tumors were highly mitotic active: mitotic rate was greater than 10 per 10 (range 10-65) high power fields in 16/19 (84%) cases. Lymphovascular invasion was present in 8/19 (42%) cases. Tumor cell necrosis was identified in 19/21 (90%) cases (Supplementary Table 1).

Immunohistochemical features

The tumors demonstrate variable staining for myogenic markers. SMA was diffusely positive in 7/19 (37%) cases, focal/patchy in 9/19 (47%), and negative in 3/19 (16%) cases. Desmin was diffusely positive in only 1/21 (5%) case, focal/patchy in 5/21 (24%) cases, rare in 1/21 (5%) case, and negative in 14/21 (67%) cases. H-caldesmon was diffusely positive in 8/13 (62%) cases, focal in 1/13 (8%) case, and negative in 4/13 (31%) cases. ER and PR were negative in all 12 gynecologic cases tested. In contrast, ER was positive in 13 of 17 (76%) cases of ULMS where it was performed. In 14 cases, immunostaining for PDGFRB and PDGFRA was performed. PDGFRB demonstrated diffuse and strong membranous staining in 11 (79%) cases and focal in 3 (21%) cases, while PDGFRA was

negative in 11 (79%) cases and focal/rare in 3 (21%) cases (Figure 3, Table 2). Additionally, HMB45, Melan A, myogenin, and MyoD1 were performed in 4 cases, 2 cases, 3 cases, and 1 case, respectively; all were negative.

Molecular Findings

The most frequent *PDGFRB* (NM_002609) mutations were located at exon 12 (SNV/insdel) (9 cases, 43%), which corresponds to the juxtamembrane domain of PDGFRβ, and exon 14 (N666K/S/T) (8 cases, 38%) and exon 18 (D850Y/H/V or insdel) (3 cases, 19%), both of which are located on the receptor protein tyrosine kinase domain of PDGFRβ. Variant allele frequencies of the *PDGFRB* mutations ranged from 5 to 72% (median 35%). Three patients had two concurrent *PDGFRB* hotspot alterations: two with exon 12 + exon 14 mutations, and one with exon 12 + exon 18 mutations (Figure 4A, Table 2).

Among gynecologic *PDGFRB*-mutant sarcomas, the most frequent co-existing genetic alterations occurred in *CDKN2A/B* (54%), *TP53* (38%), *TERT* promoter (23%), and *MED12* (38%). In contrast, ULMS harbored a much higher frequency of alterations in *TP53* (94%), *RB1* (69%), and *ATRX* (44%), the majority being loss-of-function mutations or deletions (Figure 4B).

Among non-gynecologic *PDGFRB*-mutant sarcomas, the most frequent co-existing genetic alterations occurred in *TERT* promoter mutations (38%). Other alterations (25% each) included *TP53*, *PIK3CA*, *ALK*, *ARID1B*, *KMT2D*, and *B2M*. In contrast, STLMS harbored a much higher frequency of alterations in *TP53* (80%), *RB1* (35%), and *ATRX* (25%), the majority being loss-of-function mutations or deletions (Figure 4C).

Compared to the 15 cases without pleomorphism/atypia, *TP53* and *RB1* alterations (67 vs 13% and 50 vs 0%, respectively) were significantly more frequent among the 6 cases with pleormorphism/atypia (Mid-P exact one-tailed $P = 0.006$ and 0.036, respectively). There were no significant differences in the fraction of genome with copy number alterations in both gynecologic or non-gynecologic *PDGFRB*-mutant sarcomas compared to ULMS and STLMS, respectively (Supplementary Figure S1).

Clinical Outcome

Over a follow-up period of 6 to 134 months (median 18 months), distant metastases were documented in 17 (81%) cases and local recurrence in 2 (10%) cases. Metastatic sites included lungs (16, 94%), liver (6, 35%), brain (8, 47%), and bone (7, 41%). All but five patients received conventional sarcoma chemotherapy regimen (gemcitabine/docetaxel, n=13, trabectedin, n=3; dacarbazine plus doxorubicin, n=3, etc.). Five (24%) patients received multi-kinase inhibitors, one of whom showed response to treatment before further progression, one had stable disease before further progression, and three showed no benefits from kinase inhibitor treatment. Four of these patients received multiple rounds of conventional sarcoma chemotherapy in addition to kinase inhibitor. At last follow-up, 16 (76%) patients had died of disease; 2 (10%) were alive with disease; 3 (14%) were alive without disease (Table 1). There were no statistically significant differences in overall survival (OS) or progression-free survival (PFS) between gynecologic versus non-gynecologic *PDGFRB*-mutant sarcomas (Supplementary Figure S2).

On the other hand, for the gynecologic *PDGFRB*-mutant sarcomas, although there was no statistically significant difference in PFS compared to ULMS (median PFS: 0.37 vs 0.65 years, log-rank $P = 0.61$), the OS of gynecologic *PDGFRB*-mutant sarcomas (median OS: 1.80 years) was significantly worse compared to ULMS (median OS > 3 years) (log-rank $P = 0.028$) (Figure 5A). Two-year and five-year OS probability were 42% and 11%, respectively, for gynecologic *PDGFRB*-mutant sarcomas, versus 76% and 51%, respectively, for ULMS.

Similarly, for the non-gynecologic *PDGFRB*-mutant sarcomas, although there was no statistically significant difference in PFS compared to STLMS (median PFS: 0.85 vs 1.09 years, log-rank $P = 0.19$), the OS of non-gynecologic *PDGFRB*-mutant sarcomas (median OS: 1.93 years) was significantly worse compared to STLMS (median OS: 6.43 years) (log-rank $P = 0.03$) (Figure 5B). Two-year and five-year OS probability were 44% and 22%, respectively, for non-gynecologic *PDGFRB*-mutant sarcomas, versus 90% and 75%, respectively, for STLMS.

Discussion

Deregulated activation of PDGFRβ has been described in human cancers, mainly driven by oncogenic fusions. *PDGFRB* gene rearrangements have been reported in myeloid/lymphoid neoplasms, frequently associated with eosinophilia.[15–17] An additional mechanism of oncogenic PDGFRβ activation is through an autocrine/paracrine stimulation by increased expression of its ligand, PDGFβ, as seen in *COL1A1::PDGFB* fusion in dermatofibrosarcoma protuberans.[18] In contrast, fewer human cancers have been described to harbor kinase-activating *PDGFRB* mutations, so far limited to benign myofibroblastic or pericytic neoplasm, in which both somatic and germline missense mutations have been reported. This finding is significant as PDGFRβ is typically expressed in vascular smooth muscle cells and pericytes, with PDGFRβ signal transduction being required for their proliferation and migration, while loss of either PDGFRβ or PDGFβ resulting in a decrease in the number of pericytes and vascular smooth muscle cells.[19] Germline *PDGFRB* gain-of-function mutations occur in the majority of infantile myofibromatosis familial cases,[8] and a substantial fraction of patients with sporadic multifocal disease have either germline, somatic, or mosaic gain-of-function mutations.[9] The majority of the *PDGFRB* mutations described to date in benign myofibromas and infantile myofibromatosis alter the juxtamembrane domain or the kinase domain, presumably resulting in constitutive activation and are sensitive to imatinib inhibition.[4,9,10,11,12]

To date, *PDGFRB* activating mutations have not been reported in the malignant counterparts of myofibroma/myopericytoma. Although among a large cohort of sarcoma types tested on our IMPACT panel, *PDGFRB* mutations were rare events, occurring only in 1.2% of cases, many of the hotspot mutations showed a striking association with high grade sarcomas with myogenic differentiation. This finding raises the question of whether these *PDGFRB*-mutant sarcomas represent a distinct pathologic entity or a LMS subset characterized by a poorly differentiated/incomplete smooth muscle immunophenotype. This consideration is particularly justified as most of these primary tumors were located in the gynecologic tract, where it is known that uterine LMS may show a variable or partial expression

of smooth muscle markers, including desmin, compared to soft tissue counterparts.[20] However, upon careful morphologic review, the overwhelming majority of cases did not show diagnostic features of LMS, lacking the typical intersecting fascicles and bundles of spindle and pleomorphic cells with abundant fibrillary/brightly eosinophilic cytoplasm. We do acknowledge that sometimes the distinction between “sarcomas with myogenic differentiation” versus “leiomyosarcomas” could be subjective and variable among different pathologists. Moreover, 95% of the cases in our cohort were either completely negative or only focally positive for desmin, compared to STLMS and ULMS, among which this marker is overwhelmingly positive.[21,22] Nonetheless, a significant subset of leiomyosarcomas lacks desmin expression, and thus its absence does not rule out a leiomyosarcoma. Also, none of our uterine/vaginal *PDGFRB*-mutant sarcomas expressed hormonal receptors, while 76% of the control ULMS showed ER immunopositivity.

Next, we compared the genomic profile of our *PDGFRB*-mutant study cohort with two control groups of ULMS and STLMS displaying typical histologic and immunohistochemical features. Compared to ULMS and STLMS, both of which frequently harbored *TP53*, *RB1* and *ATRX* alterations in our study and the TCGA sarcoma landscape study,[23,24] the gynecologic *PDGFRB*-mutant sarcomas harbored a higher frequency of *CDKN2A/B* deletion, *TERT* promoter mutation and *MED12* mutations, while the non-gynecologic *PDGFRB*-mutant sarcomas harbored higher frequency of *TERT* promoter mutations. Both types of *PDGFRB*-mutant sarcomas showed much lower frequencies of *TP53*, *RB1*, and *ATRX* alterations. Moreover, the TCGA sarcoma study showed overall similarity and lack of discriminatory somatic copy-number alterations among ULMS and STLMS, but had significantly distinct methylation and mRNA expression signatures, with ULMS showing a higher DNA damage response score (p=0.005), and hypomethylation of ESR1 target genes, while STLMS had a more prominent HIF1 α signaling signature.[23]

Importantly, despite having similar PFS, the OS of *PDGFRB*-mutant sarcoma patients was significantly worse than both ULMS and STLMS patients: less than 2 years regardless of anatomic locations compared to 3 to 6 years in the latter two groups, suggesting that *PDGFRB*-mutant high-grade sarcoma may be a distinct pathologic and clinical entity. Additionally, our cohort seems to have a much higher propensity for distant metastasis to the brain [6 of 11 (55%) among gynecologic cases], compared to ULMS, which has a reported distant metastatic rate of 4% to the brain.[25] Moreover, none of the 13 patients treated with gemcitabine/docetaxel chemotherapy, a standard first- or second-line treatment for ULMS,[26–28] showed any clinical response. On the other hand, two of the five patients treated with TKI showed evidence of clinical response or disease stabilization before further progression.

This is the first genomic study documenting recurrent hotspot *PDGFRB* alterations in high grade sarcomas. Our results show a predilection for uterine location and tumors with myogenic differentiation that fall short of the usual diagnostic criteria of LMS. One should consider this diagnosis when encountering a high-grade sarcoma with relatively monomorphic cytology that shows heterogeneous myofibroblastic and smooth muscle histologic features and an incomplete smooth muscle immunoprofile. *PDGFRB*-mutated sarcomas with myogenic differentiation were associated with a highly aggressive clinical

course, with frequent distant metastases, including to the brain, and significantly worse overall survival compared to leiomyosarcomas. These findings may support testing PDGFR-targeted agents in patients with this rare subtype of sarcomas. Further studies are needed to investigate the therapeutic potential of kinase inhibitors in this group of tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The raw data generated are not publicly available due to lack of access to indefinite hosting capabilities, but are available from the corresponding author on reasonable request.

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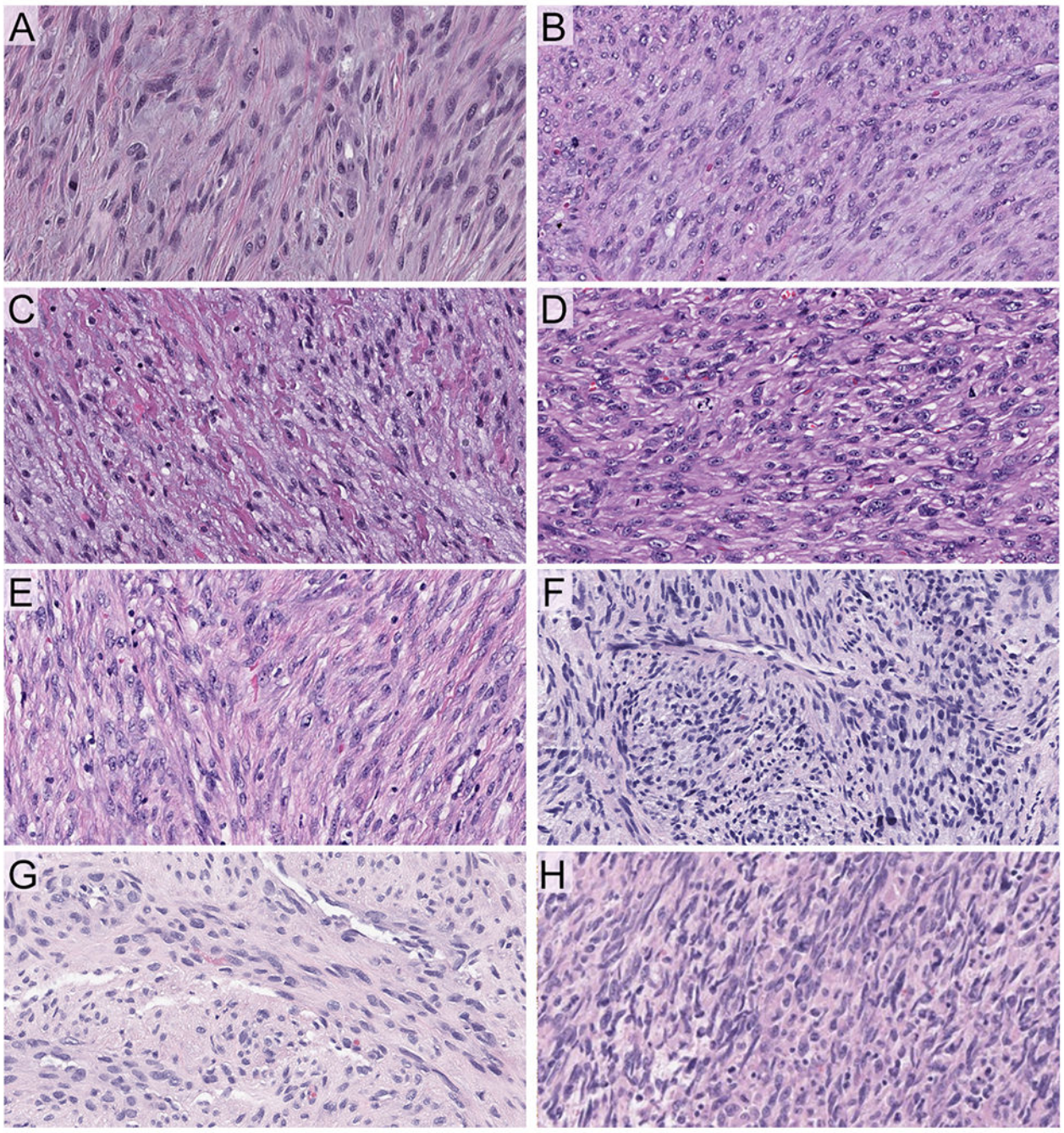

Figure 1. Morphology of non-gynecologic *PDGFRB*-mutated sarcomas.

Monomorphic spindle cell neoplasm with heterogeneous myofibroblastic and leiomyosarcomatous features. Arranged in fascicles, the spindle cells display ovoid to fusiform nuclei with vesicular chromatin and small to inconspicuous nucleoli. Some cases show a more myofibroblastic phenotype, with amphophilic cytoplasm and evidence of extracellular collagen deposition (A-E), while others are more reminiscent of smooth muscle differentiation, showing spindle cells with elongated nuclei and fibrillary cytoplasm arranged in intersecting bundles (F-H). A-H: hematoxylin & eosin, 200X. A: case 7, breast;

B: case 8, breast; C: case 1, epidural soft tissue; D: case 4, lung metastatic tumor; E: case 3, iliac bone; F: case 5, liver; G: case 6: pancreatic tumor metastatic to lung; H: case 2, pelvis/retroperitoneum.

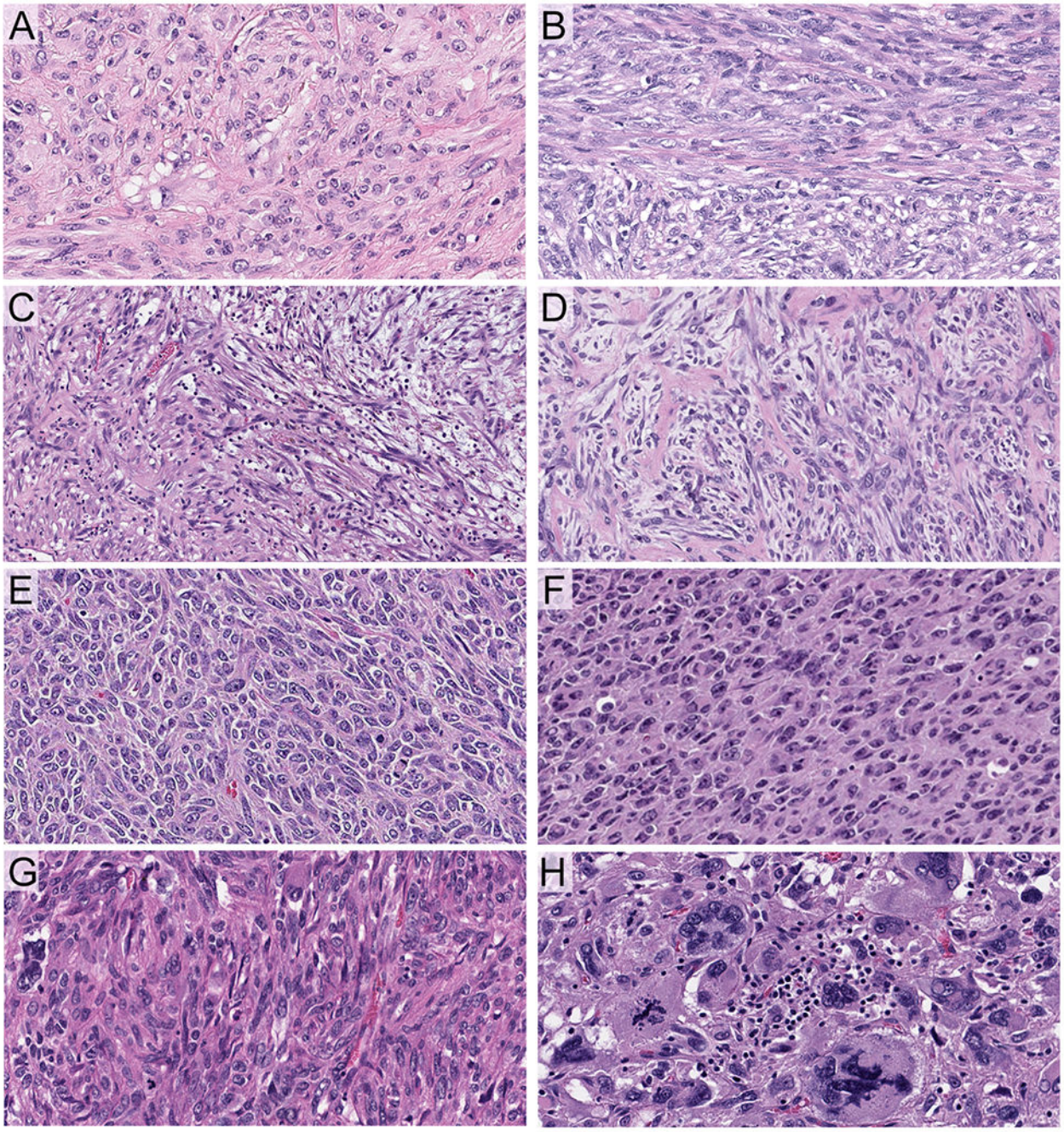

Figure 2. Morphology of gynecologic *PDGFRB*-mutated sarcomas.

The gynecologic cases show a wider morphologic range. Most show monomorphic spindle cell morphology (A-F). The spindle cells range from LMS-like: having ovoid to elongated blunt ended nuclei with fibrillary pink cytoplasm (A, B) to more myofibroblastic: showing stubby, fusiform nuclei with amphophilic cytoplasm and extracellular collagen deposition (C, D). Some cases show predominantly epithelioid to ovoid cells (E, F). A subset of cases was frankly pleomorphic and anaplastic cytologic features (G, H). A-H: hematoxylin &

eosin, 200X. A: case 13; B: case 9; C: case 21; D: case 12; E: case 15; F: case 10; G: case 17; H: case 20.

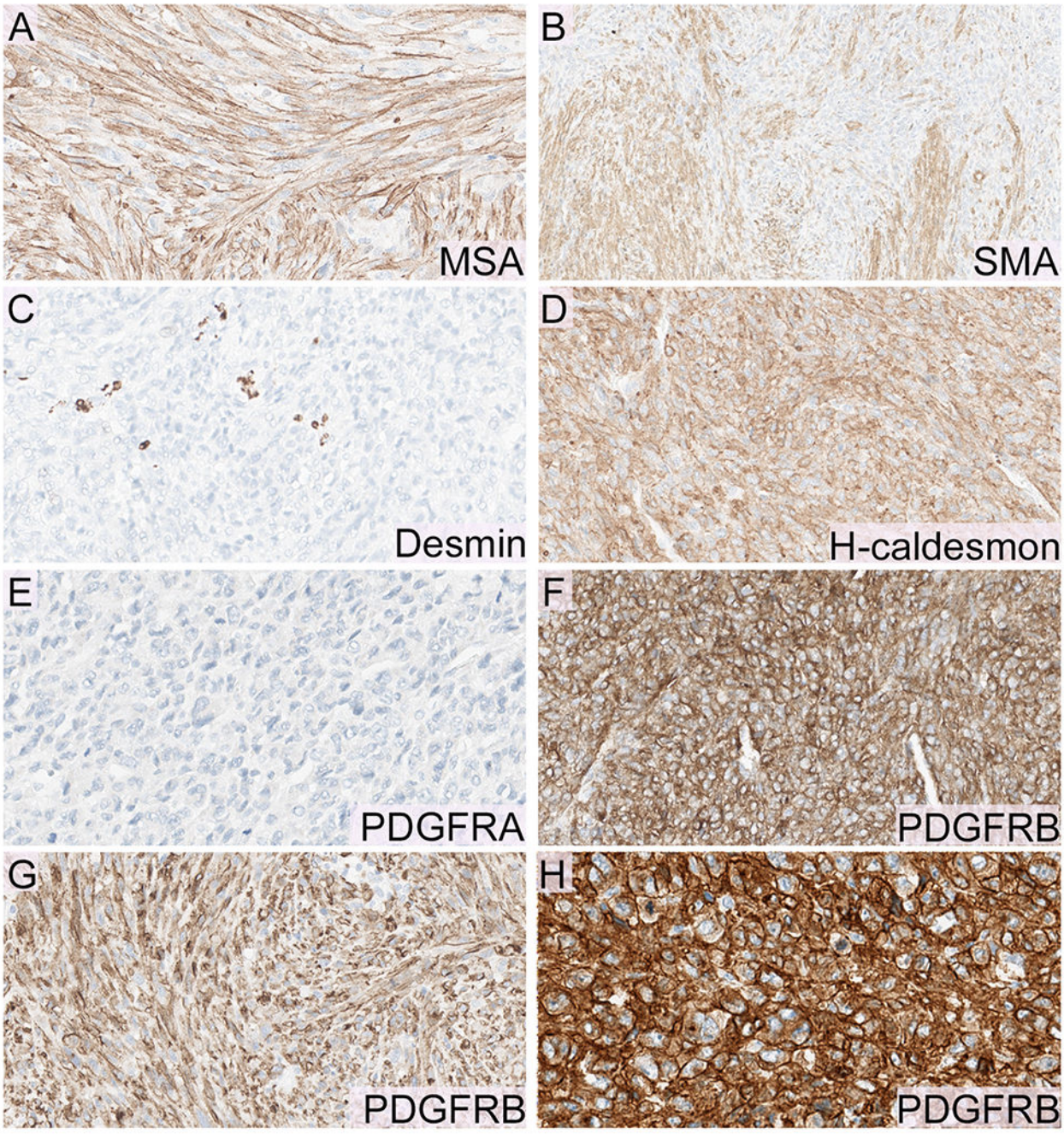

Figure 3. Immunohistochemical features of *PDGFRB*-mutated sarcomas.

Patchy to focal immunohistochemical expression for myogenic markers, including muscle specific actin/HHF35 (A, case 9), smooth muscle actin (B, case 11), desmin (C, case 16, and h-caldesmon (D, case 16). The tumors are predominantly negative for PDGFRA (E, case 10) but expressed strong and diffuse membranous PDGFRB immunostaining (F, case 16; G, case 9; H, case 10).

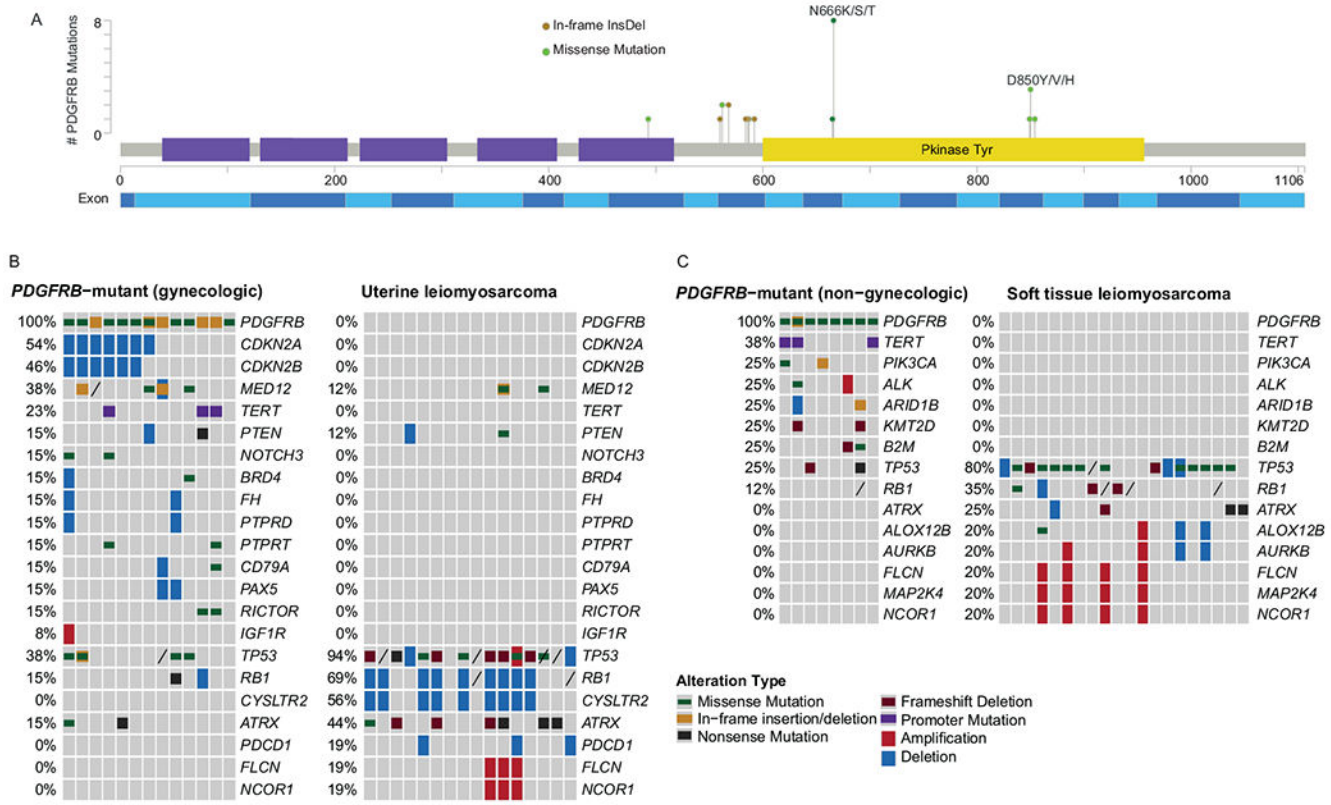

Figure 4. Mutational profile of *PDGFRB*-mutated sarcomas compared to leiomyosarcomas.

A, Lollipop plot illustrating the location and counts of *PDGFRB* mutations and the corresponding protein domains and exons. Number on the horizontal axis denotes amino acid position. Ig: immunoglobulin-like domain; Pkinase Tyr: protein tyrosine kinase domain. B and C, Oncoprint illustrating the frequency and distribution of recurrent genetic alterations (mutations, copy number changes) in gynecologic *PDGFRB*-mutant sarcomas versus uterine leiomyosarcoma (B) and non-gynecologic *PDGFRB*-mutant sarcomas versus soft tissue leiomyosarcomas (C).

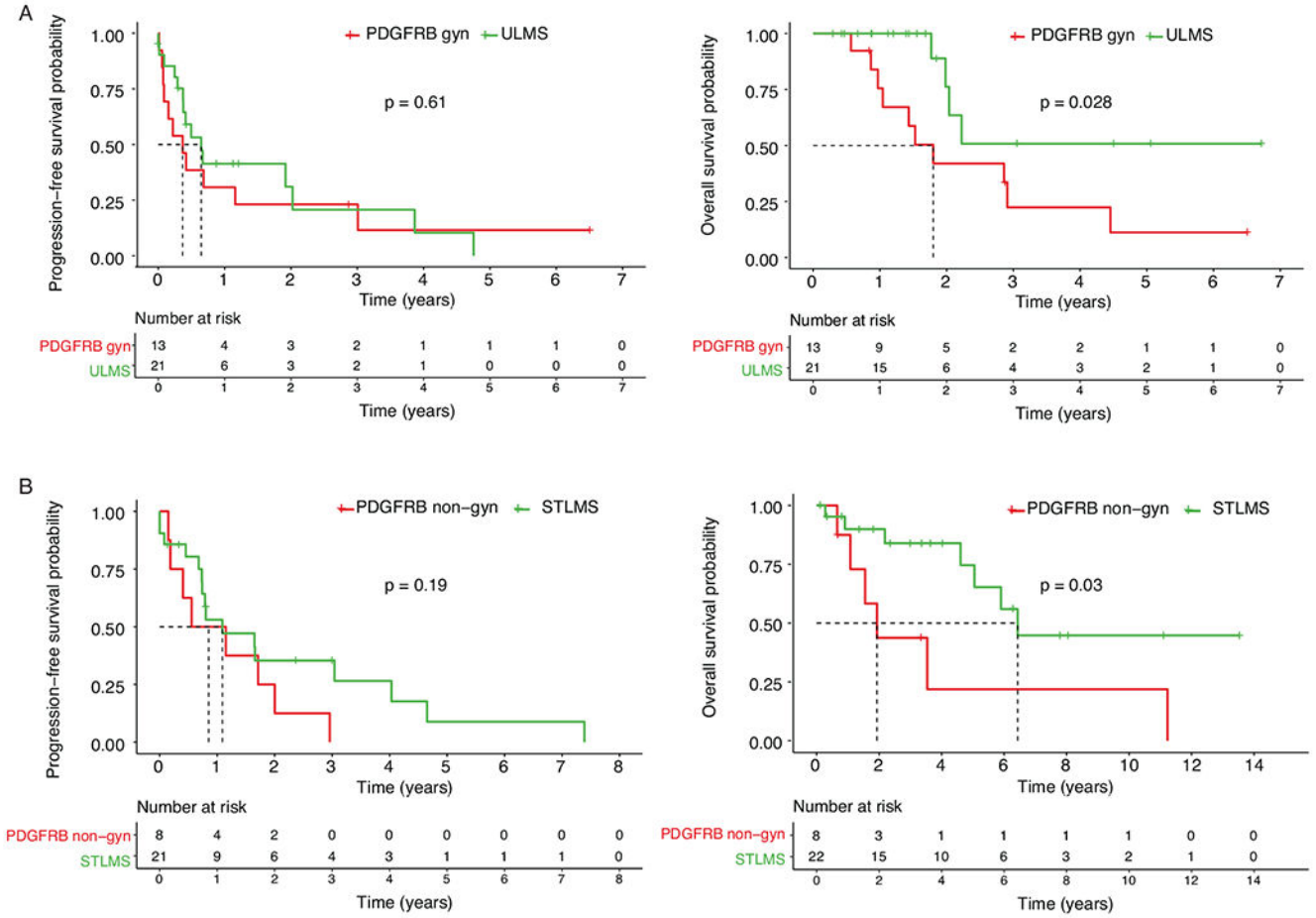

Figure 5. Survival of *PDGFRB*-mutated sarcomas

Kaplan Meier plots showing progression-free survival and overall survival of gynecologic *PDGFRB*-mutant sarcomas versus uterine leiomyosarcoma (A) and non-gynecologic *PDGFRB*-mutant sarcomas versus soft tissue leiomyosarcomas (B) [log-rank P value].

Table 1.

Patients Demographics, Pathologic Findings and Clinical Follow-up

Case	Age	Sex	Primary Site	Metastatic Site	TNM	Chemotherapy	PDGFRB Inhibitor	Progression	Status at Last Follow-up
1	51	Male	Soft tissue (epidural)	bone (skull base), subcutaneous tissue		None	no	Distant metastasis	DOD
2	62	Male	Soft tissue (pelvis, retroperitoneum)	pelvic (extension to thigh/ retroperitoneum)		Neoadiuvant AIM, gem/doce	no	Local recurrence	AWD
3	88	Female	Soft tissue (right iliac)	bone, lung	pT2N0	Gem	no	Distant metastasis	DOD
4	73	Male	Bone (fibula)	lung, liver		Gem/doce, DTIC	yes – stable disease	Distant metastasis	DOD
5	73	Male	Unknown primary	lung, liver, bone, brain		DTIC+dox, gem/doce	no	Distant metastasis	DOD
6	52	Female	Pancreas	lung, skin, liver, bone, brain		Gem/doce, dox + DTIC	no	Distant metastasis	DOD
7	61	Female	Breast	lung		None	yes – POD/no benefit	Distant metastasis	DOD
8	82	Female	Breast	N/A		None	no	Local recurrence	ANED
9	54	Female	Uterus	lung, brain	T1	AIM, gem/doce	no	Distant metastasis	AWD
10	60	Female	Uterus	N/A	T1bN0M0	None	no	None	ANED
11	59	Female	Uterus	liver, lung	T2bNxM1	Gem/doce, olaratumab	yes – POD/no benefit	Distant metastasis	DOD
12	52	Female	Uterus	brain, lung		Gem/doce, RT	no	Distant metastasis	DOD
13	69	Female	Uterus	lung, brain		Gem/doce, letrozole, trabectedin	no	Distant metastasis	DOD
14	71	Female	Uterus	bone, lungs, lymph node, pelvis		Gem/doce, trabectidin	yes – POD/no benefit	Distant metastasis	DOD
15	68	Female	Uterus	brain, lung, bone	T1bN0M1	Doxi/olaratumab	no	Distant metastasis	DOD
16	53	Female	Uterus	lung, brain	T2aNxM1	Gem/doce	no	Distant metastasis	DOD
17	68	Female	Uterus	lung, stomach, liver		Gem/doce; RT; trabectedin	no	Distant metastasis	DOD
18	64	Female	Uterus	lung, liver	T1b	Gem/doce	no	Distant metastasis	DOD
19	67	Female	Uterus	lung,bone	T1N0M1	Letrozole, gem/doce, pembro, dox + DTIC	yes – RECIST response	Distant metastasis	DOD
20	58	Female	Uterus	lung, brain	T1NxM1	Gem/doce, pembro	no	Distant metastasis	DOD
21	35	Female	Vagina	N/A		None	no	None	ANED

AIM: Adriamycin, ifosfamide, mesna; AWD: alive with disease; ANED: alive with no evidence of disease; DOD: dead of disease; dox: doxycycline; DTIC: dacarbazine; gem/doce: gemcitabine/docetaxel; N/A, not applicable; pembro: pembrolizumab; POD: progression of disease; RECIST: Response Evaluation Criteria in Solid Tumors; RT: radiation therapy.

Table 2.

Immunohistochemical and Molecular Findings

Case	PDGFRB	PDGFRA	SMA	MSA/ HHF35	Desmin	H caldesmon	ER	PR	PDGFRB Mutation Exons	PDGFRB Mutation (p.)	VAF
1	ND		Diffuse	ND	Focal	Negative	ND	ND	18	D850H	0.20
2	Diffuse and strong membranous staining	Negative	Focal		Diffuse	Diffuse	ND	ND	14	N666S	0.05
3	ND	ND	Focal	ND	Negative	ND	ND	ND	12, 14	L587P, N666T	0.15, 0.08
4	ND	ND	Diffuse	ND	Negative	Negative	ND	ND	12	V568E	0.36
5	Focal	Focal	Diffuse	Diffuse	Negative	Diffuse	Negative	Negative	18	D850Y	0.27
6	ND	ND	Focal	ND	Negative	ND	ND	ND	14	N666K	0.45
7	Focal	N	Diffuse	Focal	Negative	ND	Negative	Negative	14	V665A	0.08
8	Diffuse and strong membranous staining	Negative	Negative	Focal	Rare	Diffuse	Negative	Negative	12, 14	V568_I569delinsP, N666K	0.48, 0.57
9	Diffuse and strong membranous staining	Focal	Focal	Diffuse	Negative	Diffuse	Negative	Negative	14	N666K	0.34
10	Diffuse and strong membranous staining	Negative	Negative	ND	Negative	Diffuse	Negative	Negative	14	N666K	0.44
11	Diffuse and strong membranous staining	Negative	Negative	ND	Negative	Diffuse	Negative	Negative	12	Y562C	0.67
12	ND	ND	Diffuse	ND	Negative	Negative	Negative	Negative	12	Q586-T592	0.45
13	ND	ND	ND	ND	Focal	ND	Negative	Focal	14	N666K	0.33
14	ND	ND	ND	ND	Focal	ND	ND	ND	14	N666K	0.72
15	Diffuse and strong membranous staining	Negative	Focal	Negative	Negative	Negative	Negative	Negative	12	P560_Y562delinsM	0.12
16	Diffuse and strong membranous staining	Negative	pend	ND	focal	pend	Negative	Negative	12, 18	Q586_L587del, D854G	0.32, 0.39
17	Diffuse and strong membranous staining	Negative	pos	ND	Negative	ND	Negative	Negative	18	I851_D854del	0.50
18	ND	ND	Focal		Negative	ND	Negative	ND	10	S493I	0.22
19	Diffuse and strong membranous staining	Negative	Focal	ND	Negative	Diffuse	Negative	Negative	12	M585_T592del	0.52
20	Diffuse and strong membranous staining	Negative	Focal	ND	Focal	Focal	Negative	Negative	12	Y562S	0.50

Case	PDGFRB	PDGFRA	SMA	MSA/ HHF35	Desmin	H caldesmon	ER	PR	PDGFRB Mutation Exons	PDGFRB Mutation (p.)	VAF
21	Diffuse and strong membranous staining	Focal	Diffuse	ND	Diffuse	Diffuse	weak/rare	Focal	18	D850V	0.20

ER: estrogen receptor; MSA: muscle-specific actin; ND: not done; PR: progesterone receptor; SMA: smooth muscle actin; VAF: variant allele frequency