Inflammatory Myofibroblastic Tumor in the Inguinal canal: A Rare Case Report

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Research Article

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Case Report

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Abstract

Background: Inflammatory myofibroblastic tumors, previously known as inflammatory pseudotumors, are rare soft tissue carcinomas with variable presentation and location. Due to non-specific symptoms and location, the diagnosis of this condition is often clinically challenging. Only a handful of case reports have been published in the literature describing this tumor, and there is still a lack of consensus on pathogenesis, risk factors, and treatment strategy. Most tumors have shown mutation in the anaplastic lymphoma receptor tyrosine kinase (ALK) gene. In this article, we describe a case of ALK-negative malignant inflammatory myofibroblastic tumor.

Case: A 46 years old male with no risk factors presented with a mass in the inguinal region. The ultrasound was suggestive of a mixed echoic mass suggestive of inguinal hernia, which led to surgical repair with resection of the tumor segment. Subsequently, histopathology and immunohistochemistry

confirmed that the mass was an inflammatory myofibroblastic tumor which then recurred in a few years and failed to respond to multiple chemotherapy regimens, and over time, it progressively metastasized to the anterior abdominal wall and lungs. The patient is currently receiving palliative chemotherapy and symptomatic treatment.

Conclusion: This rare soft tissue tumor has not received much attention, and clinicians often miss the diagnosis. We stress that further study should be carried out on these soft tissue tumors, and adequate diagnostic and therapy recommendations should be developed.

Keywords: Inflammatory Myofibroblastic tumor, pseudo tumors, soft tissue sarcoma, plasma cell granuloma, myofibroblastoma, pseudosarcomatous myofibroblastic proliferation.

Introduction:

Inflammatory myofibroblastic tumors (IMT) consist of neoplastic growth of mesenchymal myofibroblastic spindle cells along with infiltration of mesenchymal tissue with plasma cells, lymphocytes, and eosinophils [1]. It is a rare neoplasm described first in 1937, and it is seen commonly in pediatric and young adults with a prevalence of <1% of the world's population [2]. The pathogenesis is not entirely understood yet. It may present as a benign lesion with local recurrence or malignant tumor. Apart from genetic mutations, infections and autoimmune diseases can cause this tumor [3]. Prior abdominal surgery, trauma, radiation, and steroid exposure has been reported as an etiology of IMT [4]. Immunohistochemistry has demonstrated that 50% of IMT has a high expression of the ALK gene [5]. In Histopathology, there are characteristic myofibroblastic spindle cells with inflammatory cells in a background of a fibrotic collagenous matrix [6]. Clinical presentation varies depending upon the location of the tumor. However, it commonly presents with weight loss, malaise, fatigue, fever, and night sweats [7]. Here we present a case of IMT in a middle aged adult with ALK negative metastatic tumor.

Case Presentation:

We present the case of a 51-year-old Indian man who was initially diagnosed with **Inflammatory Myofibroblastic Tumor** at the age of 46 years. He initially presented at that time with complaints of right inguinal groin mass. The mass initially was irreducible in the groin area and was thought to be inguinal hernia. The ultrasound revealed mixed echoic mass in the inguinal canal with fluid collection in the scrotal sac. Open hernia surgery was done with excision of mass from the inguinal canal with right orchiectomy followed by hernioplasty with mesh repair.

Histopathology report of mass diagnosed a spindle cell neoplasm with storiform pattern and lymphoplasmacytic infiltrates and absent atypia *(figure 1)*. Immunohistochemistry was positive for Vimentin and SMA, S-100, CD34 + in blood vessels confirmed the presence of inflammatory myofibroblastic tumor.

A year later the patient developed a right scrotal abscess and received antibiotic treatment followed by incision and drainage. 2.5 years after the surgical excision, the patient complained of 8-10 kg weight loss and local fat loss with skin dimpling in the previously operated region. Investigation with PET-CT *(figure 2)* showed multiple nodules in the anterior abdominal wall, FDG avid lymph nodes involving the external iliac region, and a few subcentimeter sized pulmonary nodules.

Patient was commenced on Methotrexate and Prednisolone for one month. Genetic test report *(figure3)* of re-biopsied tissue was negative for any genomic alterations in gene related to cancer type soft tissue sarcoma as listed in NCCN guidelines with stable microsatellite status and low tumor burden. However, amplification of biomarker's CCND2, MDM2 and DDR2 was noted which affects cell cycle pathway, TP53 mediated apoptosis and receptor tyrosine kinase mediated signaling respectively. A CVP1B1 biomarker was present which targets drug metabolism *(figure 4)*.

Based on Genomic studies, guidelines approved therapy with gemcitabine, docetaxel and Palbociclib was initiated. Post chemotherapy PET-CT showed partial metabolic regression involving the right anterior abdominal wall and iliac lymph nodes. Unfortunately, new sub-centimeter sized parenchymal nodules of soft tissue density appeared in bilateral lungs. Failure of combination chemotherapy was noted and the patient was given additional cycles of Palbociclib for 6 months.

Compared to previous PET-CT, the tumor was noted to be increasing in size and number. A new second chemotherapy regime consisting of Imatinib and methotrexate was started. The patient continued to complain of difficulty in ambulation and breathlessness on exertion. Repeat chest x- ray, PET- CT and ultrasound showed progressive growth.

A third chemotherapy regimen of Lenvatinib and methotrexate was given subsequently.. New muscle deposits started to appear along with pelvic lymphadenopathy, suggesting treatment failure. After a failed response to multiple anticancer drugs Palbociclib, docetaxel, gemcitabine, imatinib and Lenvatinib, patient's condition continued to worsen with progressive spread of metastatic deposits leading to weight loss, breathlessness and new appearance of pneumothorax. Tumor also failed to respond to therapy with Cyclosporine, Adriamycin and Ifosfamide.

Currently the patient is receiving palliative chemotherapy with Irinotecan and bevacizumab with no significant improvement in response to therapy, making it a chemotherapy resistant carcinoma.

Discussion:

The etiology of IMT remains unknown. It was previously referred to as an inflammatory pseudotumor. Various names of the condition were suggested and used in literature like xanthomatous pseudotumor, plasma cell granuloma, myofibroblastoma, pseudosarcomatous myofibroblastic proliferation, and inflammatory Myo Fibrohistiocytic proliferation [10]. WHO classified this disease in 1994 as an intermediate-grade neoplasm with the potential to recur or undergo malignant transformation. It is challenging to predict malignant transformation even with the advancement of molecular and cytogenetic studies. In general, after tumor excision, inflammatory myofibroblastic tumors (IMTs) have a benign

course with a better outcome. They can be invasive, reoccur locally, or spread in some cases [10]. However, in our case, the tumor presented spontaneously in older adults as an inguinal mass and recurred after surgical excision.

Multiple studies have proposed that almost half of the time, genetic alterations on chromosome 2 cause overexpression of p80, and rearrangements of the anaplastic lymphoma kinase (ALK) gene to express oncoprotein in the spindle cells causes IMT [11,12]. Some researchers have also demonstrated and proposed that DNA aneuploidy and association of the lesion with oncogenic viruses such as Epstein-Barr virus, Human Herpes virus type 8, and overexpression of IL-6 are involved in the pathogenesis of the tumor[13]. A metastatic IMT has a poor prognosis [3]. An IMT can also be indolent, with prolonged survival despite multiple recurrences. Local recurrence rates of 15% to 37%, and distant metastasis rates up to 11%, have been reported [3]. Herein we presented a case of an ALK-negative metastatic tumor that recurred after excision and failed to respond to multiple chemotherapy regimens.

There is not much known about IMT, and there are no proper guidelines for the diagnosis and management of IMT. It is challenging to diagnose this tumor clinically. Certain features that favor its diagnosis are mass in the lung or soft tissue in children and young adults with histological features of inflammatory infiltrates consisting of plasma cells, ganglion-like cells demonstrating mild nuclear atypia [14]. The presence of lymphocytic infiltrates, severe atypia with hyperchromasia and evidence of necrosis do not favor the diagnosis of IMT [14].

In our case, the patient's age, location of the mass, the ambiguity of the clinical presentation, and the nonspecific imaging features all contributed to the exclusion of IMT from the preoperative diagnosis. Another diagnostic conundrum was the location of the mass. The lung is the most common anatomical location for IMTs. Malignant tumors such as MFH (malignant fibrous histiocytoma) and fibrosarcomas, on the other hand, should be considered in the differential diagnosis [7]. Benign or malignant spindle-cell tumors such as fibrous histiocytoma, fibroblastic/myofibroblastic tumor, and solitary fibrous tumor are among the possibilities for a differential diagnosis. Because of their similar morphology, spindle-cell morphology can be misdiagnosed as both benign reactive processes and malignant spindle-cell neoplasms [7]. Hence, histopathology and immunohistochemistry can aid in making the diagnosis of IMT. The lack of ALK reactivity has been linked to the development of metastases, however, further research is still needed [1]. Chemotherapy, radiotherapy, and corticosteroid administration have been proposed as treatment strategies with no practical results yet.

Conclusion:

IMTs are rare, genuine neoplasms of proliferating myofibroblast with an inflammatory component and its biological behavior ranges from benign to an aggressive cancer in most cases. Through this case report, we aim to add more to the literature about its unique presentation in middle-aged individuals as an inguinal mass. We also aim to create an appropriate awareness among surgeons and radiologists when evaluating soft tissue masses. Since there are no proper guidelines for treating metastatic malignant IMT, we suggest additional research on the topic. Following a thorough surgical resection of the primary tumor, long-term clinical and radiological surveillance is advised.

Declarations:

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Informed Consent: Informed consent is obtained from the individual included in the study. Participant has given consent to collect his case-specific details and has consented to publish the case report.
Authors' Contributions:
Conceptualization: Arpankumar Patel;
Methodology: Arpankumar Patel, Rutikbhai Desai ;
Acquisition of data: Arpankumar Patel, Hilloni Shah, Laseena Visyambath, Manozna Karri, ;
Formal analysis and Interpretation: Arpankumar Patel ;
Original draft preparation: Arpankumar Patel, Rutikbhai Desai ;
Writing/ Drafting of work: Hilloni Shah, Laseena Visyambath, Manozna Karri,
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Fig. 1 : Inflammatory myofibroblastic tumor demonstrating spindle cells (black arrow) with nuclear atypia and slender nuclei. The storiform pattern is seen along with lymphoplasmacytic infiltrates (red arrow) seen on histopathology.

Fig. 2: FDG PET scan demonstrating growth in right Inguinal region following tumor excision.

Fig. 3: The presence of genomic alterations in genes relevant to cancer type (Soft tissue sarcoma) as defined by NCCN recommendations.

Fig. 4: We identified CCND2 amplification in the patient. CCND2 gene codes for cyclin D2 which forms a complex with CDK4 and CDK6 and regulates the G1/S phase of the cell cycle. It phosphorylates and inhibits members of the tumor suppressor retinoblastoma (RB) protein family including RB1. Phosphorylation of RB1 causes dissociation of the transcription factor E2F from the RB/E2F complex and subsequent transcription of E2F target genes which are responsible for the advancement through the G(1) phase. CCND1 amplifications have been studied in various cancer types [8,9]. CDK4/CDK6 inhibitors like Palbociclib and clinical trials with Ribociclib have been mentioned.

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Figures

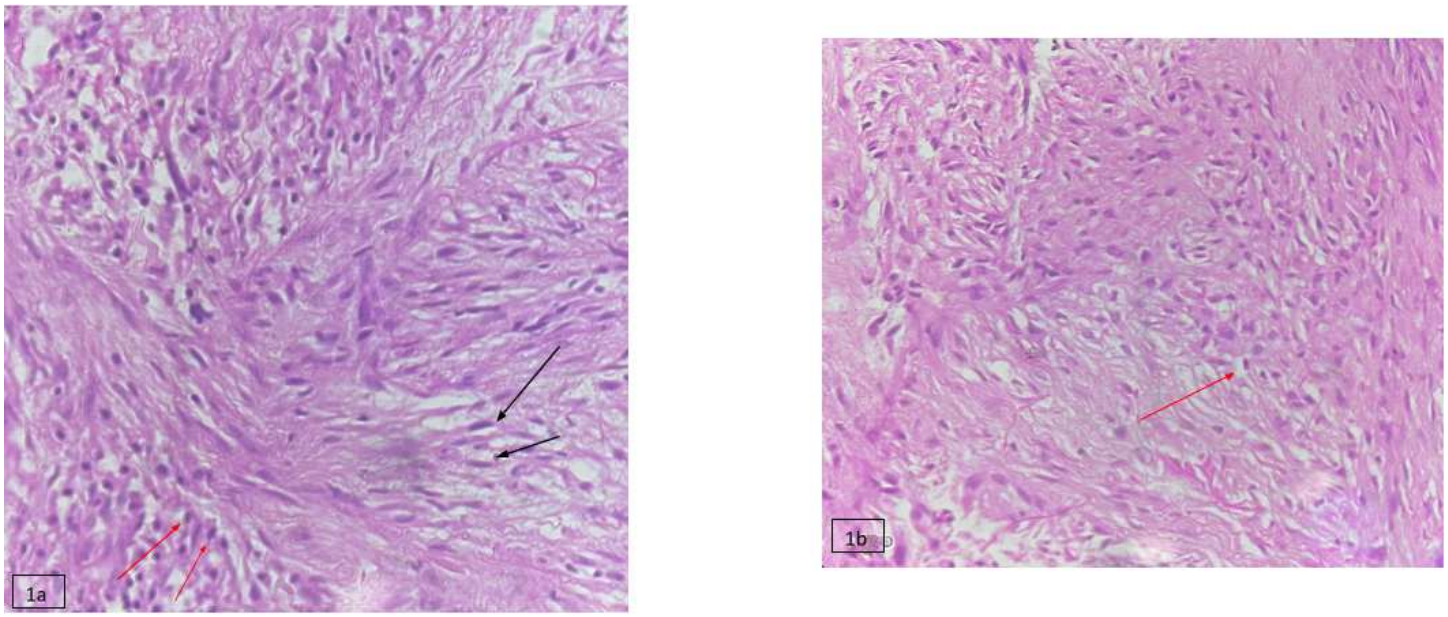


Figure 1

Inflammatory myofibroblastic tumor demonstrating spindle cells (black arrow) with nuclear atypia and slender nuclei. The storiform pattern is seen along with lymphoplasmacytic infiltrates (red arrow) seen on histopathology.

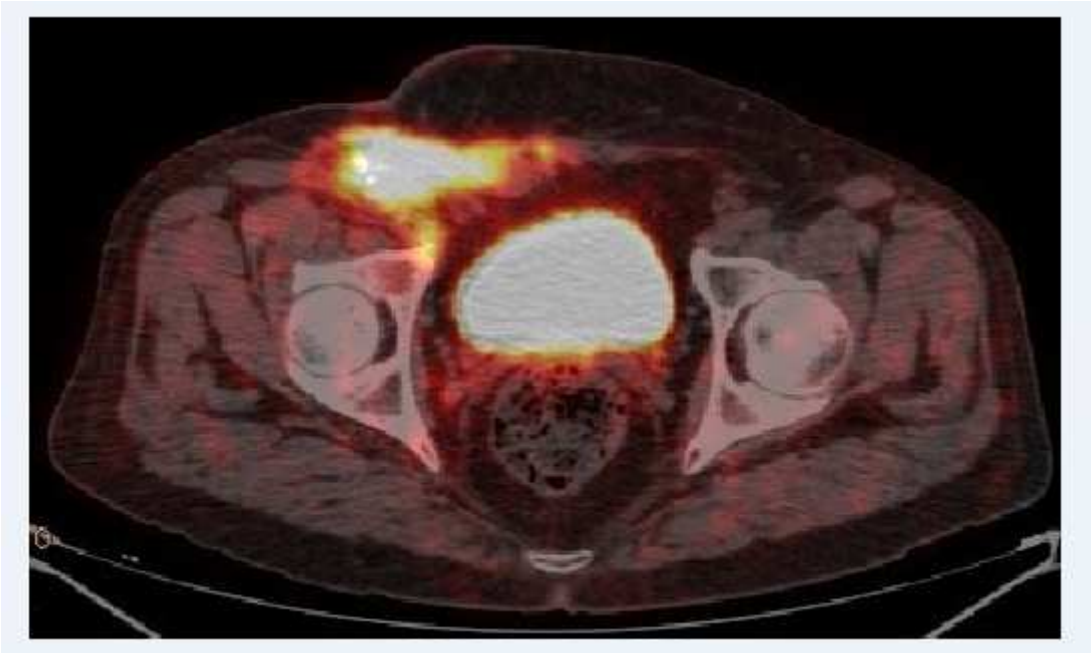
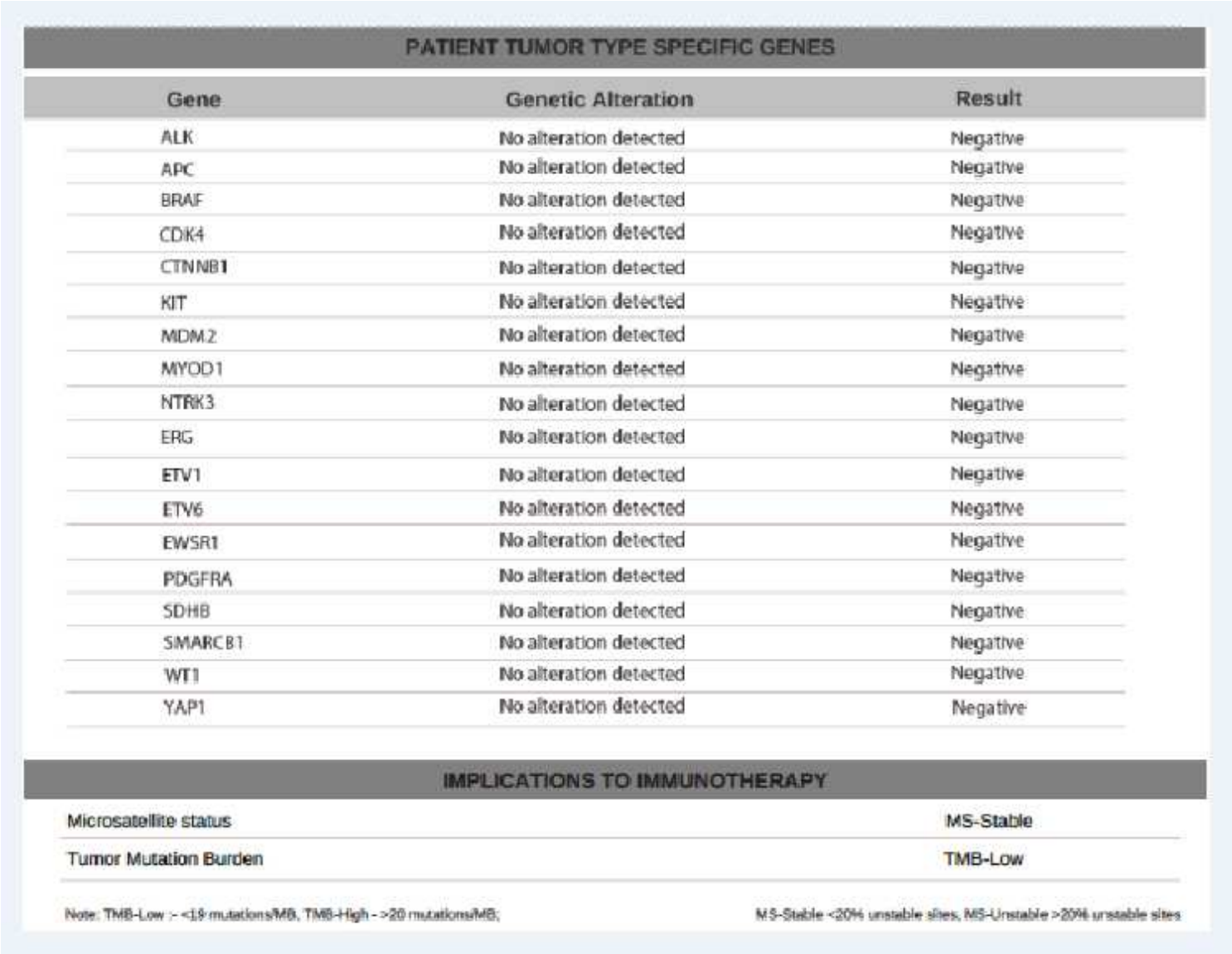


Figure 2

FDG PET scan demonstrating growth in right Inguinal region following tumor

excision.



PATIENT TUMOR TYPE SPECIFIC GENES

Gene	Genetic Alteration	Result
ALK	No alteration detected	Negative
APC	No alteration detected	Negative
BRAF	No alteration detected	Negative
CDK4	No alteration detected	Negative
CTNNB1	No alteration detected	Negative
KIT	No alteration detected	Negative
MDM2	No alteration detected	Negative
MYOD1	No alteration detected	Negative
NTRK3	No alteration detected	Negative
ERG	No alteration detected	Negative
ETV1	No alteration detected	Negative
ETV6	No alteration detected	Negative
EWSR1	No alteration detected	Negative
PDGFRA	No alteration detected	Negative
SDHB	No alteration detected	Negative
SMARCB1	No alteration detected	Negative
WT1	No alteration detected	Negative
YAP1	No alteration detected	Negative

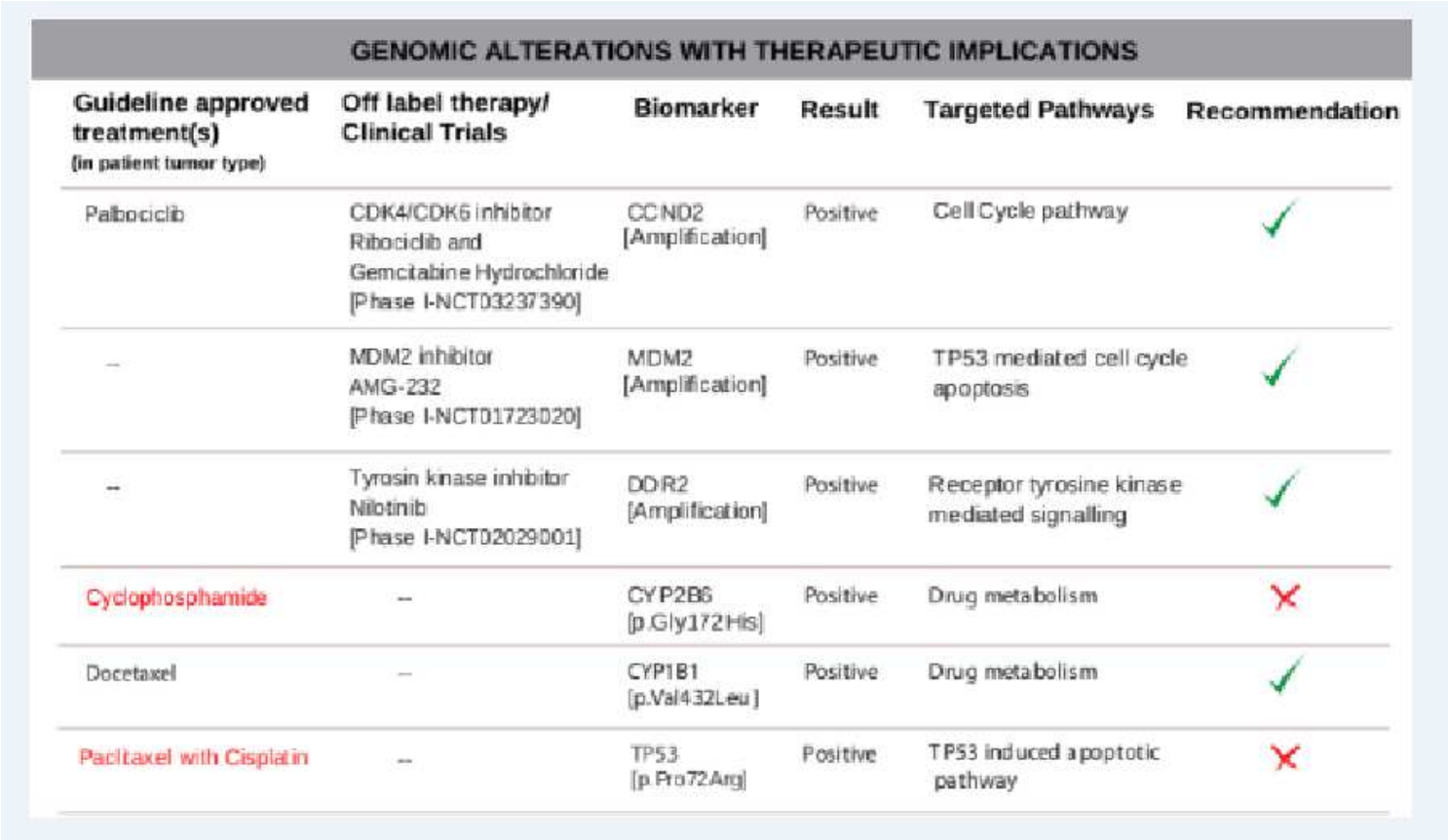
IMPLICATIONS TO IMMUNOTHERAPY

Microsatellite status	MS-Stable
Tumor Mutation Burden	TMB-Low

Note: TMB-Low :- <19 mutations/MB, TMB-High - >20 mutations/MB; MS-Stable <20% unstable sites, MS-Unstable >20% unstable sites

Figure 3

The presence of genomic alterations in genes relevant to cancer type (Soft tissue sarcoma) as defined by NCCN recommendations.



GENOMIC ALTERATIONS WITH THERAPEUTIC IMPLICATIONS

Guideline approved treatment(s) (in patient tumor type)	Off label therapy/ Clinical Trials	Biomarker	Result	Targeted Pathways	Recommendation
Palbociclib	CDK4/CDK6 inhibitor Ribociclib and Gemcitabine Hydrochloride [Phase I-NCT03237390]	CCND2 [Amplification]	Positive	Cell Cycle pathway	✓
–	MDM2 inhibitor AMG-232 [Phase I-NCT01723020]	MDM2 [Amplification]	Positive	TP53 mediated cell cycle apoptosis	✓
–	Tyrosin kinase inhibitor Nilotinib [Phase I-NCT02029001]	DDR2 [Amplification]	Positive	Receptor tyrosine kinase mediated signalling	✓
Cyclophosphamide	–	CYP2B6 [p.Gly172His]	Positive	Drug metabolism	✗
Docetaxel	–	CYP1B1 [p.Val432Leu]	Positive	Drug metabolism	✓
Paclitaxel with Cisplatin	–	TP53 [p.Pro72Arg]	Positive	TP53 induced apoptotic pathway	✗

Figure 4

We identified CCND2 amplification in the patient. CCND2 gene codes for cyclin D2 which forms a complex with CDK4 and CDK6 and regulates the G1/S phase of the cell cycle. It phosphorylates and inhibits members of the tumor suppressor retinoblastoma (RB) protein family including RB1. Phosphorylation of RB1 causes dissociation of the transcription factor E2F from the RB/E2F complex and subsequent transcription of E2F target genes which are responsible for the advancement through the G(1) phase. CCND1 amplifications have been studied in various cancer types [8,9]. CDK4/CDK6 inhibitors like Palbociclib and clinical trials with Ribociclib have been mentioned.

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