Overview of « druggable » alterations by histological subtypes of sarcomas and connective tissue intermediate malignancies

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ARTICLE INFO

ABSTRACT

We summarize herein the literature data about molecular targeted therapies in sarcomas and conjunctive tissue intermediate malignancies. For each clinical setting, the level of evidence, the mechanism of action and the target are described. The two major axes include (i) identification of subgroups of tumors with druggable alteration irrespective of the histological diagnosis (e.g. NTRK), and (ii) druggable target of pathway related to the physiopathology of the tumor: denosumab and bone giant cell tumor, imatinib and soft tissue giant cell tumor, mTOR inhibitor and PECOMA.

1. Introduction

Sarcomas represent a myriad of clinico-bio-pathological entities (with more than 100 types), with a heterogenous natural course and different sensitivity to systemic treatment. These entities represent approximately 2 % of adult malignancies and 15 % of pediatric cancers. Nevertheless, recent epidemiological data suggest that sarcoma are twice more frequent than usually estimated (Amadeo et al., 2020). Despite intense clinical research, doxorubicin and doxorubicin-based regimes remain the overall best first-line treatment in 2020. However, the median overall survival of advanced sarcoma remains poor, at about 18 months. Therefore, extensive efforts have been made in the past two decades to identify potentially druggable alterations in these diseases. Regarding the number of clinic-pathological entities, the number of potential targets and pathway, and the number of potential targeted therapies, so attempt to summarize the recent available studies. These studies are based on two different approaches.

First, new techniques such as next generation sequencing (NGS) could be applied to these entities irrespective of the primary and the histological entities. Several teams have embarked on these impressive "fishing expeditions" (Boddu et al., 2020; Cote et al., 2018; Groisberg et al., 2017; Gounder et al., 2017; Harris et al., 2016; Italiano et al., 2017; Jour et al., 2014). It is of note that the largest series (accounting for 5746 patients) is yet to fully conclude their report (Gounder et al., 2017). Overall, the rate of potentially actionable target ranged from 30 % to 60 % according to the series. In the Gounder et al. study, (excluding misdiagnosed gastro-intestinal stromal tumors and dermatofibrosarcomas), 546 of 5746 patients could be potentially treated with available drugs (9.5 %) and 2289 other patients could be treated with new investigational drugs (39 %).

When potentially actionable target is identified, about 12–15 % received matched molecular targeted therapy within clinical trials or off-label (Boddu et al., 2020; Groisberg et al., 2017; Gounder et al., 2017). Clinical benefit (at least stable disease) has been reported in 25–50 % of patients treated with molecular targeted therapies according to the identified potentially actionable target.

The second approach is based on better characterization of the different clinico-pathological entities that is sometimes associated with the discovery of "druggable" alterations allowing personalized approach for some entities.

We aimed to summarize available data using systematic research with Medline (last issue 1st November 2019). We have included all successive prospective studies focusing sarcomas or and connective tissue intermediate malignancies, excluding gastro-intestinal stromal tumors. In this review, we did not include the following treatment modalities: hormonal therapies (Pannier et al., 2019), immunotherapies and multi-tyrosine kinase inhibitors that act mainly as anti-angiogenetic agent (e.g., sunitinib, sorafenib, and regorafenib). We have added some preclinical or retrospective studies that constitute the background of clinical use of the different targeted therapies.

2. Results

2.1. Successful druggable alterations associated with some histological subtypes

2.1.1. Diffuse-type tenosynovial giant-cell tumors (dt-TGCTs)
2.1.1.1. *The tumor.* Dt-TGCTs, so-called diffuse pigmented villonodular synovitis are rare connective tissue intermediate malignancies (with < 2 cases per million inhabitants), arising from

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joint or para-articular tendon sheath. They are invasive, destructive, and usually slow growing. Lung metastasis are exceptional. Dt-TGCTs are characterized by proliferation of synovial cells associated with inflammatory multicellular stroma, including histiocytes and hemosiderin-containing macrophages. Dt-TGCTs arise mostly in the knee, but could also affect the hip, ankle, and foot. Dt-TGCTs are diagnosed between 25–40 years and cause severe impairment. Surgery remains the cornerstone of treatment. Adjuvant isotopic synoviorthesis using Yttrium 90 or Rhenium 186 may be an option. Nevertheless, some bulky or relapsing TGCTs are not accessible to non-mutilating curative-intent surgery (Martin et al., 2000Cupp et al., 2007).

2.1.1.2. The pathway. Dt-TGCTs display a specific translocation t (1;2) involving colony-stimulating factor 1 (CSF1) gene (located on chromosome 1p13), also known as macrophage colony-stimulating factor (M-CSF), and COL6A3 gene (located on chromosome 2q35). This results in the over-expression of CSF1 and can explain the massive inflammatory pattern of the tumor (Cupp et al., 2007).

2.1.1.3. Clinical evidences. Four molecules have been studied as potential treatment for dt-TGCTs all of which inhibit the CSF1-receptor: imatinib, nilotinib, emactuzumab, and pexidartinib. Blay et al. first reported a complete response of bulky dt-TGCT treated with imatinib (Blay et al., 2008). In 2012, Cassier et al. reported the results of a retrospective multicenter study with 29 patients (Cassier et al., 2012). Five of 27 evaluable patients experienced objective responses (overall response rate (ORR), 19 %; 1 complete response and 4 partial responses), and 20 of 27 patients (74 %) had stable disease. Symptomatic improvement was noted in 16 of 22 assessable patients (73 %). The 12-month progression-free rate was 80 %. Given these encouraging findings, a phase II trial has been conducted with another tyrosine kinase inhibitor acting on CSF1-R, nilotinib (400 mg twice per day; NCT01261429). The primary objective was the rate of patients who were progression free at 12 weeks, with central review and according to RECIST 1.1 (Gelderblom et al., 2018). In this trial, 56 patients were enrolled, including 51 patients with an evaluable primary endpoint. The rate of patients who were progression free at 12 weeks was 93 %. This study highlighted the difficulty in assessing objective response in such malignancy. Emactuzumab is a monoclonal antibody directly acting on CSF1-R. Cassier et al. reported the results of a dose-escalating phase I trial (NCT01494688), with promising activity in dt-TGCT patients (an objective response was achieved by 86 % of 28 patients, with a complete response in 7 % and a partial response in 79 %). Most toxicities were grade 1 and 2 and most of the toxicities were of cutaneous types (Cassier et al., 2015). Pexidartinib is a selective inhibitor of CSF1-R. In a non-randomized phase II trial, among 23 assessable patients, there were 12 partial responses and 7 stable diseases. This trial stressed that most objective responses occurred within the first 4 months, and that liver toxicity was the major safety concern (Tap et al., 2015). ENLIVEN (NCT02371369) was a large international double-blind placebo-controlled phase 3 trial assessing the safety and activity of pexidartinib in TGTs that were not treatable by non-mutilating surgery. The primary endpoint assessed in all intention-to-treat patients was overall response at week 25 (centrally reviewed by RECIST, version 1.1). Overall, 120 patients were randomized and included. Because of liver toxicity, the pexidartinib dose was decreased from 1,000–800 mg/day. After 25 weeks of treatment, the ORR was 38 % with a 15 % complete response rate and a 23 % partial response rate. Common side effects of pexidartinib included increased levels of lactate dehydrogenase, cholesterol and aspartate/alanine aminotransferases and hair color changes. Eight patients (13 %) discontinued pexidartinib therapy because of hepatic adverse events, and 4 patients had serious nonfatal adverse events with increased bilirubin, one lasting about 7 months (Tap et al., 2018).

To the best of our knowledge, there is no further development in the therapy involving imatinib, nilotinib and emactuzumab for dt-TGCT. In August 2019, the Food and Drug Administration (FDA) approved pexidartinib (400 mg twice daily) for adult patients with symptomatic dt-TGCTs associated with severe morbidity or functional limitations and not amenable

to improvement with surgery. Regarding liver toxicity, the risk/benefit ratio must be carefully weighed.

2.1.2. Giant cell tumor of bone (GCT-b)
2.1.2.1. The disease. GCT-b is a locally aggressive, rapidly growing and destructive primary bone tumor, with possible extension to surrounding tissues. Metastasis occurs in less than 3% of cases, primarily to the lung. Its estimated yearly incidence is about 2 cases per million inhabitants. GCT-b affects mainly young adults. GCT-b arise mainly in the epiphyseal portions of long bones but can also arise in the axial skeleton. The standard of care involves surgery that aims for complete removal of the tumor by curettage without causing functional impairment. Extensive surgery or amputation are rarely required. Nevertheless, surgery of axial skeleton primaries or cases with massive soft tissue extension are particularly challenging. Furthermore, some cases such as skull base GCT-b or massive sacral GCT-b are definitively inoperable (Balke et al., 2008Klenke et al., 2011). After surgery, local recurrence occurs in 20–50 % of cases and usually arises within 2 years. Local recurrences are usually treated by re-curettage if possible (Balke et al., 2008; Klenke et al., 2011). There is no adjuvant treatment that is able to reduce the risk of local recurrence. Rarely, GCT-b can undergo malignant transformation.

2.1.2.2. The RANK/RANK ligand pathway. GCT-b is characterized by co-existence of two tumor cells populations. The true "malignant" cells are small spindle cells that overexpress and secrete RANK-ligand (receptor activator of nuclear factor kappa B). These tumor cells display H3F3 mutation in about 85 % of cases (Kervarrec et al., 2017). RANK-Ligand (RANK-L) overexpressed and secreted by tumor cells activate normal bone cells and osteoclast-like giant cells that express RANK (Atkins et al., 2006), that destroy bone. Thus, osteoclastosis is deregulated in GCT-b. Denosumab or zoledronate inhibits the RANK/RANK-ligand interaction and reduce the osteoclast-induced bone destruction. However, these drugs act only on the reactive osteoclast-bone destruction without any impact on the true "malignant" cells.

2.1.2.3. The clinical evidences. The activity of denosumab (120 mg administered subcutaneously every 28 days with 2 loading doses on days 8 and 15) was first assessed in a multicenter phase 2 trial with 37 patients with GCT-b (Thomas et al., 2010). Clinical benefit was documented in 30 of 35 assessable patients (86 %). Responses were associated with pain relief, functional improvement, tumor shrinkage in some cases and bone lysis recalcification. However, clinical tumor response criteria (such as RECIST) are not appropriate for clinical benefit assessment. A second and larger phase II trial was launched, including 3 different strata: patients with sacral and spinal GCT-b or those with lung metastasis (stratum 1), patients with planned morbid surgery (including procedures with high risk of neurological sequelae) (stratum 2), and the patients enrolled in the prior trial (stratum 3). Several results have been reported from the trial (NCT00680992). An interim analysis had been reported in 2013. In stratum 1, 163/169 (96 %) did not experience disease worsening. In the stratum 2, surgical downstaging was feasible in 16 of 26 patients requiring surgery (62 %) and surgery could be avoided in 74 of 100 patients (Chawla et al., 2013). This trial was then expanded. Finally, the total number of patients enrolled in stratum 1 was 267 and those in stratum 2 was 253. The median follow-up was about 58 months. In stratum 1, the median time to progression was not reached, since 28 out 262 patients experienced disease progression or recurrence (11 %). Of 248 patients enrolled in stratum 2, only 21 required surgery within the 6 months of the study (8 %). Longer follow-up allows a better description of safety profile of long-lasting denosumab treatment. Most common grade 3 toxicities were as follows: hypophosphatemia (5 %) osteonecrosis of the jaws (3 %), anemia (2 %), pain (2 %) and fracture (2 %). Hypercalcemia occurring after denosumab discontinuation was reported in 4 patients (1 %) (Chawla et al., 2019). Furthermore, Japanese colleagues have reported a non-randomized phase 2 trial assessing denosumab in GCT-b patients. The response rate was 88 % in 17 patients (Ueda et al., 2015). Denosumab is currently approved by the

European Medicines Agency (EMA) and FDA for the management of inoperable GCT-b or GCT-b requiring mutilating surgery. However, there are unresolved questions about denosumab use in GCT-b patients. The risk/benefit ratio of prolonged administration of denosumab is a key question. Denosumab is not a curative-intent treatment since denosumab acts only on osteoclast-like cells and did not affect the true tumor cells. Girolami et al. have demonstrated that denosumab administration did not change the H3F3A cell density in post-treatment versus pre-treatment bone specimen of GCT-b (Girolami et al., 2016). This suggested that denosumab treatment must be maintained as long as possible. Progressive disease occurs usually within the 9 months following denosumab withdrawal. Nevertheless, long-term administration is associated with increasing severe toxicity such as osteonecrosis of the jaws and stress fractures. The drug-holiday, the use of denosumab every 3 months rather than monthly, and the use of bone remodeling biomarkers (Watanabe et al., 2014) to optimize the treatment are still questionable.

The therapeutic role of zoledronate have been also explored. Gouin et al. reported a non-randomized phase 2 trial assessing 5 cycles of zoledronate as adjuvant treatment of resected GCT-b; 24 patients were enrolled, the local relapse-free survival was 82 % at 60 months (Gouin et al., 2014). Lipplaa et al. reported a randomized phase 2 assessing the use of zoledronate as adjuvant treatment of resected high-risk GCT-b; however, only 14 patients were enrolled. Overall, the 2-year recurrence rate was 38 % (3/8) in the intervention versus 17 % (1/6) in the control group ($p = 0.58$) (Lipplaa et al., 2019).

To conclude, denosumab an active treatment for GCT-b could lead to long-lasting tumor control with symptomatic improvement, however denosumab is not able to cure GCT-b.

2.1.3. Dermatofibrosarcoma protuberans (DFSP)

2.1.3.1. The tumor.
The estimated incidence of Dermatofibrosarcoma protuberans (DFSP) is in the range of 0.8–4.2 cases/million inhabitants per year (Criscione VD, Weinstock MA, 2007). Given the possibility of diagnostic confirmation by molecular biology, the incidence is higher in recent decades. Diagnosis is made usually between 30 and 50 years of age. Pediatric forms are rare (less than 6% of DFSPs) and must be confirmed by an experienced pathologist. They classically present as the "giant cell fibroblastoma" variant of DFSP. There is a very slight male predominance (Bowne et al., 2000; Rutgers et al., 1992).

Surgery is the only curative-intent treatment of DFSPs. It has a local malignant pathology with a 20–40 % risk of local relapse; these relapses may be late and require prolonged clinical follow-up. The risk of metastatic relapse is low in the order of 5 % (Chang et al., 2004; Fiore et al., 2005). Overall the prognosis is good with an overall survival of 92 % at 5 years. Furthermore, this prognosis is directly related to the quality of care (Corey et al., 2014).

On macroscopic examination the lesion is centered on the dermis but it infiltrates the depth. It is a homogeneous limited lesion. Proliferation involves moderately atypical monomorphic fusiform cells with a low or moderate mitotic index (< 7 mitoses per 10 high power fields), tumor cells are often short or storiform. These tumors strongly express CD34 in immunohistochemistry (Weiss and Nickoloff, 1993). They do not express factor XIIIa, cytokeratin, desmin, smooth muscular actin or S100 protein. There are numerous atypical forms including myxoid, myofibroblastic, and pigmented forms.

The transformation into fibrosarcoma occurs in 10 % of cases, either de novo or after a long-term history of the disease. In these cases, the tumor loses its homogeneous and fascicular organization. Cellular atypia and mitosis are more numerous (more than 5 mitoses/10 high power fields). CD34 expression may be lost (Wrotnowski et al., 1988; Goldblum, 1995). Transformed forms are associated with a significant risk of local and metastatic relapse and therefore a poor prognosis (Liang et al., 2014).

2.1.3.2. The target.
About 90 % of DFSPs have reciprocal translocation t (17;22) (q22;q13) (COL1A1; PDGFB : Platelet Derived Growth Factor subunit B), which presents (especially in adults) as a supernumerary ring chromosome where segments of chromosomes 17 and 22 are duplicated resulting in an amplification of the fusion gene leading to PDGFB over-expression driven by the COL1A1 promoter. This in turn is responsible for tumor susceptibility to imatinib. This fusion gene can be detected by fluorescence in situ hybridization (FISH), or with comparative genomic hybridization (CGH) analysis (Patel et al., 2008). The fusion gene can be found in fibrosarcoma derived from DFSPs. In routine practice, molecular investigation is not necessary for the diagnosis except in the challenging cases of fibrosarcoma transformation and giant cell fibroblastoma in children.

2.1.3.3. Clinical evidences.
This tumor is regarded as chemo-resistant although anecdotal responses have been reported with methotrexate. Imatinib inhibits PDGFRB receptor. The first cases reported in the literature showed that only tumors with fusion gene respond to imatinib.

Two clinical trials assessed the activity of imatinib for inoperable or metastatic locally advanced DFSPs (American trial B2225; imatinib 400 mg/day) and European EORTC trial (imatinib 800 mg/day). These two trials with small numbers were pooled (Rutkowski et al., 2010). A total of 24 patients were included in these 2 trials. The objective response rate at 12–14 weeks was 46 % (11/24). The control rate of the disease was 64 %. The median time up to progression was 1.7 years; the 1-year non-progression rate was 57 %. One-year survival was 87 %.

An Italian retrospective study of patients with metastatic disease showed that metastatic forms were almost always associated with a transformation into fibrosarcoma; and even when the fusion gene was present the duration of activity of the imatinib seemed less: 8 objective responses out of 10 occurred with a median without progression of 11 months (Stacchiotti et al., 2016).

Two trials assessed the role of imatinib as a neo-adjuvant treatment. Ugurel et al. reported a trial involving 16 patients treated with imatinib 600 mg/day (Ugurel et al., 2014). The median treatment time was 3 months. The objective response rate was 57 % (including 7 % of complete response). Only one patient experienced disease progression on treatment. Thirteen patients underwent surgery. Another trial evaluated a neo-adjuvant treatment at 600 mg/day over a 2-month period in 25 patients, the objective response rate was 36 % (Kerob et al., 2010). These data though interesting have not established the place of imatinib in neo-adjuvant situations; thus, it cannot be recommended routinely without more precise data on the clinical benefit (i.e., reduction in tumor volume, improvement in resectability, and rate of R0 margins)

A phase II trial was conducted with pazopanib, a multi-kinase inhibitor. The objective response rate was 30 % with a median follow-up of 6 months (Delyon et al., 2018). For DFSPs with presence of fusion gene but refractory to imatinib, anecdotal benefit with sunitinib or sorafenib has been reported. For fibrosarcomas without gene fusion, anthracycline-based chemotherapy is usually performed.

2.1.4. Inflammatory myofibroblastic tumor (IMT)

2.1.4.1. The tumor.
IMT is an exceptional conjunctive tumor occurring in children or adolescents/young adults. Most primaries occur in the lung, retroperitoneum, or abdominal or pelvic areas. Tumors may be multifocal, and rarely some tumor spread by metastasis. It is composed of homogeneous myo-fibroblastic spindle cells surrounded by myxoid and collagenous stroma infiltrated by plasma cells and lymphocytes. IMT is regarded as borderline malignancy, since local relapse is common but metastatic spreading is rare (Coffin et al., 1995; Pettinato et al., 1990). Large-en-bloc surgery is the cornerstone treatment. In case of local or multifocal relapse there is no consensual treatment.

IMT could be misdiagnosed with other benign or malignant conjunctive tumors. For example, a large retrospective study demonstrated that IMT could mimic female genital leiomyoma and leiomyosarcoma; with the help of immunohistochemistry for Anaplastic Lymphoma Kinase (ALK) (with low threshold), authors could properly re-classify 3 of 1176 assumed leiomyomas, and 1 of 44 assumed leiomyosarcomas as IMT (Pickett et al., 2017). ALK immunohistochemistry could help recognize IMT but IMT are inconstantly ALK immune-reactive (see below).

2.1.4.2. Druggable targets: ALK rearrangements and beyond.
Approximately 50 % of IMT harbors clonal rearrangements of the ALK gene at 2p23. This gene codes for a tyrosine kinase receptor that is a member of the insulin growth factor receptor superfamily. ALK rearrangements result in constitutive expression and activation of this gene with abnormal

phosphorylation of cellular substrates. There were different reported rearrangements.

Mariño-Enríquez et al. described a sub-type of IMT characterized by both constant ALK rearrangement and aggressiveness. They described 11 cases of epithelioid inflammatory myo-fibroblastic sarcomas (EIMS) that were all immunoreactive for ALK. The tumors exhibits an epithelioid or round cell morphology. ALK fusion proteins in EIMS were detected in the nuclear membrane (or in the cytoplasm with peri-nuclear accentuation) with Ran binding protein 2 (RANBP2). EIMS associated with this fusion gene often follows an aggressive clinical behavior (Mariño-Enríquez et al., 2011).

Lovely et al. conducted a comprehensive analysis of 33 cases of IMT (immuno-histochemistry, NGS-based genomic profiling and when possible RNA-sequencing) (Lovly et al., 2014). Using immunohistochemistry (ALK01 antibody from Ventana), they found 11 ALK-negative IMT (33 %) and 22 ALK-positive IMT (67 %). Among the 11 ALK-negative IMT, 2 of them displayed *ALK* rearrangements (*EML4-ALK* and *TPM3-ALK*); furthermore 4 display actionable rearrangements: 4 cases with *ROS1* fusions and 2 cases with *PDGFRβ* fusion. Among the 22 ALK-positive IMT, 20 cases harbored *ALK* rearrangements, including *CLTC-ALK* (7 cases), *TPM3-ALK* (3 cases), *FN1-ALK* (2 cases) and *TPM4-ALK* (2 cases).

In a case series of 62 IMT, Antonescu et al. reported a comprehensive analysis which used immunohistochemistry with similar antibody, FISH, RNA sequencing and confirmatory reverse transcription polymerase chain reaction (Antonescu et al., 2015). There were 35 cases (56 %) with *ALK* rearrangement; immunoreactivity for ALK was inconstant (32/62, 52 %). There were also cases with *ROS1* rearrangement and one case with RET rearrangement. Overall, actionable rearrangements were found in 42/62 (68 %). The vast majority of IMT occurring in children harbored rearrangements (Antonescu et al., 2015). Most pulmonary IMT harbored actionable rearrangement (15/18, 83 %). On the contrary, IMT without actionable rearrangement were found mainly in patients aged ≥20 years (18/20, 90 %).

To conclude, extensive gene fusion analysis is required in to confirm IMT, especially in children patients.

2.1.4.3. *Clinical evidences.*

Since the initial case-report, there are numerous case-reports demonstrating the activity (Butrynski et al., 2010), long-term activity and repeated activity of crizotinib in ALK-positive IMT (Gaudichon et al., 2016; Alan et al., 2019; Xu et al., 2019; Michels et al., 2017; Yuan et al., 2017; Honda et al., 2019). There were two successive non-randomized phase II trials assessing activity/safety of crizotinib. In the first trial, complete response rate was observed in 5 of 14 (36 %) pediatric patients with ALK-positive IMT (Mossé et al., 2017). The rate of overall objective response was 12/14 (86 %). The median duration of treatment was 1.6 years. In the second phase II trial conducted by EORTC (Schoffski et al., 2018), 20 IMT patients were enrolled, including 19 assessable for the primary endpoint (objective response rate). ALK positivity was analyzed by both immunohistochemistry and FISH. Out of 12 patients with ALK-positive IMT, 6 experienced objective response (50 %). Out of 7 patients with ALK-negative IMT, 1 experienced objective response (14 %) (Schoffski et al., 2018).

Drug-holiday and re-challenge at progression had been described (Alan et al., 2019). Occurrence of ALK point mutation has also been described at progression (Xu et al., 2019; Michels et al., 2017). Case-reports with favorable outcome with new generation of ALK inhibitor such as ceritinib or alectinib have been published (Michels et al., 2017), including in patients with leptomeningeal progression during crizotinib treatment (Yuan et al., 2017; Honda et al., 2019).

2.1.5. *Malignant PEComa and mTOR inbitors*

2.1.5.1. *The tumor.*

The PEComa-family gathered heterogeneous clinico-pathological entities characterized by the presence of "perivascular epithelioid cells", including PEComas, angiomyolipoma (AML), clear-cell "sugar" tumor of the lung and extrapulmonary sites, lymphangioleiomyomatosis, and clear-cell myo-melanocytic tumor of the falciform ligament. PEComas are rare tumors arising in the gastrointestinal tract, retroperitoneum, uterus, or soft tissues. PEComa is a mesenchymal tumor composed of distinctive perivascular epithelioid cells (PEC). PECs are epithelioid cells with clear granular eosinophilic cytoplasm. PEC express myogenic and melanocytic

markers, such as HMB45, HMSA-1, MelanA/Mart1, micro-ophtalmia transcription factor (Mitf), actin and, less commonly, desmin (Martignoni et al., 2008).

Most PEComas are benign tumors, however there are exceptional malignant PEComas with very aggressive course leading to death. Factors associated with malignancy are tumor size > 5 cm, infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity > 1/50 HPF (Folpe et al., 2005).

2.1.5.2. *The druggable pathway.*

PEComa-family tumors usually occur sporadically, but some are related to tuberous sclerosis complex (TSC), a disorder caused by mutation of *TSC1* or *TSC2*. Both genes negatively regulate mammalian target of rapamycin complex 1 (mTORC1) (Kenerson et al., 2007). Kernerson et al. reported overexpression of phosphor-p70S6K and decrease expression of phospho-AKT in 14 out of 15 extrarenal PECOMAs, suggesting that the loss of *TSC1* or *TSC2* function led to unregulated activation of Rheb/mTOR/p70S6K cascade (Kenerson et al., 2007). Pan et al. also described overexpression of phosphor-p70S6K and decrease in phosphor-AKT expression in 11 out of 12 PEComas. Furthermore, 7 of these PEComas had loss of heterozygosity of the *TSC2* region, and one additionally showed loss of heterozygosity of *TSC1* (Pan et al., 2008). A subset of PEComas showed TFE3 rearrangement with translocation (X,1)(p11; p34) leading to the fusion gene SFPQ-TFE3 (Tanaka et al., 2009) resulting in TTFE3 immunohistochemical labeling (Argani et al., 2010). It would seem that this molecular variant does not harbor TSC mutations (Malinowska et al., 2012).

2.1.5.3. *The evidence.*

mTOR inhibitors are an appealing treatment of PEComas. In a phase 2 trial, sirolimus showed signs of activity with improvement of respiratory functional tests in patients suffering from lymphangioleiomyomatosis (McCormack et al., 2011). A large randomized phase 3 trial demonstrated that everolimus provided objective response in patients with angiomyolipoma associated with tuberous sclerosis complex or lymphangioleiomyomatosis (Bissler et al., 2013).

By analogy, mTOR inhibitors have been administered in patients with malignant PEComas. Wagner et al. reported 3 objective responses out in 3 PEComa patients treated with sirolimus (Wagner et al., 2010). Benson et al. reported the Royal Marsden experience with 10 patients treated with mTOR inhibitors; they observed 5 partial responses, 1 stable disease and 1 progressive disease among the 7 patients assessable according to RECIST (Wagner et al., 2019). More recently a non-randomized phase II trial assessing the activity of nab-sirolimus in malignant PEComa have been reported (NCT02494570; (Wagner et al., 2019)). Among the 34 enrolled patients, 31 were evaluable for response. The objective response rate was 42 %. There were 35 % stable disease and 23 % disease progression. The 6-month progression-free survival (PFS) was 66 % and the median PFS was 9 months. Objective responses were mainly seen in cases harboring T*SC2* mutations (Wagner et al., 2019).

To conclude, in retrospective studies, mTOR inhibitors provide transient objective response and stable disease in advanced malignant PEComas; new formulations such as nab-sirolimus required further clinical explorations.

2.1.6. *Epithelioid sarcoma*

2.1.6.1. *The tumor.*

Epithelioid sarcoma (ES) constitute about 1% of all soft tissue sarcoma. ES is mainly diagnosed in young adults and usually arise in the extremities. Classical ES present as subcutaneous or deep dermal mass with central necrosis in the distal extremities. The proximal variant (with larger cells, prominent nucleoli, and rhabdoid changes) is more aggressive. Surgery and radiotherapy are cornerstone of treatment. Microscopically, ES is usually multinodular with a central necrosis surrounded by bland polygonal cells with eosinophilic cytoplasm and peripheral spindling. The classic-type ES has cells with only mild atypia. They regularly express vimentin, cytokeratins, epithelial membrane antigen, and CD34 (60–70 %), whereas staining is usually negative with S100, desmin, and FLI-1 (Spillane et al., 2000; Noujaim et al., 2015).

Overall ES is regarded as an aggressive disease with high risk of local and metastatic relapses (in lung, bone, lymph nodes or brain). The 10-year overall survival is about 40 %; the risk of metastatic relapse is about 40 %

(Spillane et al., 2000). At metastatic stage, doxorubicin-based chemotherapy provides an objective response rate of 22 % and stable disease in 56 % of patients (Touati et al., 2018).

2.1.6.2. The druggable pathway. ES are characterized by the frequent loss of expression of SMARCB1; 85–90% of cases of immunoreactive for SMARCB1 (Sullivan et al., 2013). Papp et al. identified different mechanisms to explain the loss of expression of SMARCB1: 13 % of cases had biallelic deletions, 33 % showed single-allelic deletion, and 4% had point mutations (Papp et al., 2013). Inactivation of SMARCB1 led to aberrant histone methylation, oncogenic transformation, and a proliferative dependency on enhancer of zeste homolog 2 (EZH2) activity (Brenca et al., 2013).

2.1.6.3. The clinical evidences. Tazemetostat is a selective inhibitor of EZH2. In the dose-escalating phase I trial, one patient with ES experienced objective response (Italiano et al., 2018). Stachiotti et al. recently partly reported a non-randomized phase 2 trial assessing the activity of tazemetostat in 62 INI-negative ES patients (NCT02601950). There were 9/62 (15 %) with objective response (i.e., long-lasting objective response [7–103 weeks]). The median overall survival was about 20 months (Stachiotti et al., 2019).

2.2. Target NTRK in sarcoma patients

Recent outstanding clinical results have stressed the importance of identifying some fusion genes. For example, the tropomyosin-receptor kinases (TRK) include neurotrophic tyrosine receptor kinase 1, 2 and 3 (NTRK$_{1-3}$) that are activated by different ligands including: nerve growth factor, brain-derived growth factor and neurotrophin 3 or 4 (Kheder and Hong, 2018). Recently, Drilon et al. reported a basket phase 2 trial assessing the activity and safety of larotrectinib in NTRK-fusion positive cancers. Overall 55 patients were enrolled, the best response rate was 75 % objective response, including 13 % complete response; median progression-free and overall survivals were not reached at the time of this publication. Among the 55 enrolled patients, 11 suffered from soft tissue sarcomas, including myopericytoma (n = 2), malignant peripheral nerve sheath tumor (n = 2), spindle cell sarcoma (n = 3), infantile myofibromatosis (n = 1), inflammatory myofibroblastic tumor of kidney (n = 1), and sarcomas not otherwise specified (n = 2). Best responses are given for 10 cases, including 1 disease progression and 9 partial responses (Drilon et al., 2018). Other ongoing clinical trials with NTRK inhibitors include: entrectenib (NCT03375437), BAY 2,731,954/LOXO-195 (NCT03206931), and repotrectinib (NCT04094610, NCT03093116). However, less than 2 % of sarcoma display NTRK1−3 fusion, the key-question is how to better identify the subtypes of sarcomas with high rate of NTRK1−3 fusion. Immuno-reactivity to TRK could be used as first-step screening tool (Suurmeijer et al., 2019) although, the most appropriate antibodies and interpretation modalities are yet to be determined and validated.

2.3. Disappointing targets associated with some histological subtypes

2.3.1. Well-differentiated and dedifferentiated liposarcoma
2.3.1.1. The tumor. Liposarcoma is the most common group of soft tissue sarcoma. Among the different subtypes of liposarcomas, well-differentiated liposarcomas (WDLPS, also called atypical lipomatous tumor) and dedifferentiated liposarcomas (DDLPS) represent the most frequent histological subtype (about 10 cases per million of inhabitants). DDLPS arise usually in WDLPS; The dedifferentiated component is usually aggressive, rapidly growing with metastatic spreading potential. The main primaries occur in the limbs, girdles, external and internal trunk (especially retroperitoneum). Surgery and/ radiotherapy with the goal of R0 resection is the recommended treatment of localized WD/DDLPS (Cassier et al., 2014). The risk of metastatic dissemination is null in the case of WDLPS of the extremity. For all WD/DDLPS, the risk of local relapse depends of resection quality. Because achieving large en-bloc resection is more challenging in case of retroperitoneal WD/DDLP, the risk of local relapse is notably high (40–60 %) for this specific primary site (Toulmonde et al., 2014). At advanced or metastatic stage, the classical treatment is doxorubicin-based chemotherapy, with a PFS of about 4 months and objective response rate of 12 % (Italiano et al., 2012).

Most WD/DDLPS display supernumerary rings and giant chromosomes, that usually contain amplifications of 12q13−15 (Conyers et al., 2011). This amplified region contains oncogene cyclin-dependent kinase 4 (CDK4) and murine double minute-2 (MDM2; also called human double minute-2 [HDM2]) (Crago and Singer, 2011; Tap et al., 2011; Singer et al., 2007). Alteration of CDKN2A/CDKN2B/CK4/CCND1 pathway is pivotal in WD/DDLPS oncogenesis. Cell cycle is uncontrolled because of mainly CDK4 amplification or because of other alteration of the CDKN2A/CDKN2B/CK4/CCND1 pathway (Louis-Brennetot et al., 2011). In vivo, inhibition of CK4 induces growth arrest of WD/DDLPS cells (Fry et al., 2004). Furthermore, MDM2 overexpression blocks apoptosis by inhibiting p53/p21 pro-apoptotic activities (Manfredi, 2010).

2.3.1.2. WD/DDLPS and CDK4/6 inhibitors. Luke et al. reported a dose-escalating phase I trial assessing combination of doxorubicin and flavopiridol in sarcoma patients. Flavopiridol is a pan-CDK inhibitor. Out of 15 patients with WD/DDLPS enrolled in this trial, 12 were assessable according to RECIST. Out of these 12 patients, 7 experienced stable disease lasting at least 3 months. One patient received doxorubicin until maximal allowable cumulative dose and then received flavopiridol alone. The stable disease was maintained 83 weeks. The patient withdrew consent for further treatment, and 34 weeks later, there was disease progression; the patient then received flavopiridol alone again with a stable disease lasting 16 weeks (Lukes et al., 2012). Dickson et al. reported a phase 2 trial assessing palbociclib in WD/DDLPS (NCT01209598.). Sixty patients were enrolled (78 % of patients with DDLPS, 97 % of patients with intra-abdominal or retroperitoneal liposarcoma). The median PFS was 4.5 months. The PFS at 12 weeks was 57 %. There was one objective response according to RECIST: 1 complete response lasting over 2 years (Dickson et al., 2016). Other phase 2 trial assessing ribociclib (NCT03096912) or abemaciclib (NCT02846987) are ongoing. Dickson et al. partly reported the phase 2 trial assessing the activity of abemaciclib in DDLPS patients: 1 objective response was reported out of 29 assessable patients; the median PFS was 30 weeks; and the PFS at 3 months was 76 % (Dickson et al., 2019). To conclude, there are some preliminary evidence that CDK4 inhibitors provide rare objective response but clinically significant growth slowdown in DDLPS patients.

2.3.1.3. WD/DDLPS and MDM2 inhibitors. Several MDM2 inhibitors have been assessed in early-phase clinical trials in WD/DDLPS patients. Wagner et al. have reported a dose-escalating phase I trial assessing the activity of MK-8242, an inhibitor of MDM2 (NCT01463696). Overall, 9 patients with well differentiated and 17 patients with dedifferentiated liposarcomas were enrolled. In WD/DDLPS population, the objective response rate was 11 % and the median PFS was 7.8 months (without documentation of disease progression at study entry). The median PFS was 5 months in dedifferentiated liposarcomas and this was not reached in well differentiated liposarcoma (Wagner et al., 2017). De Jonge et al. reported another dose-escalating phase I trial assessing another MDM2 inhibitor (SAR405838) in patients with solid tumor and wild-type TP53 (NCT01636479). In WD/DDPLS, the best objective response was stable disease in 56 % of cases; the PFS at 3 months was 32 % (De et al., 2017). Bauer et al. partly reported a dose-escalating phase I of DS-3032b in patients with advanced tumors (NCT01877382); objective responses have been seen (Bauer et al., 2018). Ray-Coquard reported a proof-of-concept trial assessing the pharmacodynamic changes after exposure to RG7112, a MDM2 inhibitor (EudraCT 2009−05522-10). Enrolled patients had WD/DDLPS and received RG7112 as neoadjuvant treatment for 3 months after pre-treatment biopsy. The best response before surgery was disease progression (5 patients, 20 %), stable disease (14, 75 %) and partial response (1, 5%). Treatment with RG7112 was associated with increase in p53 concentration (more than 4 times compared to baseline), increase in p21 concentration (more than 3 times compared to baseline) and MDM2 mRNA expression (more than 3 times compared to baseline). There was also a decrease in Ki-67 positive cells (minus 5%). This trial suggested that RG7112 stimulated the p53 pathway. Severe hematological toxicities had been reported in 7 patients (35 %). The relative high rate of disease progression in a short-time frame is disappointing (Ray-Coquard et al., 2012). Lastly, a phase I trial assessing the combination of CDK4 inhibitor (ribociclib) and MDM2

Table 1

"Druggable" alterations by histological subtypes of sarcoma and connective tissue intermediate malignancies : synthesis of the available data.

Histological subtype	Druggable alteration	Molecular targeted therapy	Type of study	N	ORR	SD	Clinical benefit	PFS/DFS	OS	Ref
Diffuse-type tenosynovial giant-cell tumors	CSF1-R	imatinib	case-report	1	1/1	-	-	-	-	Blay et al. (2008)
		nilotinib	retrospective	29	5/27	20/27	16/22	80%(1y.)	-	Cassier et al. (2012)
		nilotinib	phase II	56	6/51	46/51	-	93%(12w.)	-	Gelderblom et al. (2018)
		emactuzumab	phase I	29	24/28	-	-	-	-	Cassier et al. (2015)
		pexidartinib	phase II	23	12/23	7/23	-	median NR	-	Tap et al. (2015)
		pexidartinib	phase III	120 (61 pex)	24/61	-	-	-	-	Tap et al. (2018)
Giant cell tumor of bone	RANK/RANKL	denosumab	phase II	37	-	-	30/35	-	-	Thomas et al. (2010)
		denosumab		532	362/510	145/510	406/510	median NR	-	Chawla et al. (2019)
		denosumab		17	15/17	2/17	14/17	-	-	Ueda et al. (2015)
		zoledronate	phase II	24	-	-	-	82% (5y.)	-	Gouin et al., (2014)
		zoledronate	phase II	14	-	-	-	62% (2y.)	-	Lipplaa et al. (2019)
Dermatofibro-sarcoma protuberans	PDGFB	imatinib	phase II	24	11/24	4/24	-	57%(1y.)	87%(1y.)	Rutkowski et al. (2010)
		imatinib	retrospective	10	8/10	1/10	-	median 11m.	-	Stacchiotti et al. (2016)
		imatinib	phase II	16	8/14	5/14	-	-	-	Ugurel et al. (2014)
		imatinib		25	9/25	-	-	-	-	Kerob et al. (2010)
		pazopanib	phase II	23	7/23	-	-	-	-	Delyon et al. (2018)
Inflammatory myofibroblastic tumor	ALK	crizotinib	case-reports	6	6/6	-	1/1	-	-	Butrynski et al. (2010), Gaudichon et al. (2016), Alan et al., (2019), Xu et al. (2019), Michels et al., (2017) and Yuan et al. (2017)
		crizotinib	phase II	14	12/14	-	-	-	-	Mossé et al. (2017)
		crizotinib	phase II	20	7/19	-	-	-	-	Schöffski et al. (2018)
		alectinib	case-reports	2	2/2	-	-	-	-	Yuan et al. (2017) and Honda et al. (2019)
		ceritinib	case-reports	2	2/2	-	1/1	-	-	Michels et al. (2017) and Yuan et al. (2017)
PEComa	mTOR	sirolimus	case-reports	3	3/3	-	-	-	-	Wagner et al. (2010)
		temsirolimus	retrospective	9	4/6	1/6	6/9	-	-	Benson et al. (2014)
		nab-sirolimus	retrospective	1	1/1	-	1/1	-	-	
Epithelioid sarcoma	EZH2	tazemetostat	phase II	34	13/31	11/31	-	median 9m.	-	Wagner et al. (2019)
		tazemetostat	phase I	1	1/1	-	-	-	-	Pannier et al. (2019)
Soft tissue sarcoma	NTRK	larotrectinib	phase II	62	9/62	-	-	-	median 20m.	Stacchiotti et al. (2019)
										Drilon et al. (2018)
Well-differentiated and dedifferentiated liposarcoma	CDK4/6	flavopiridol	phase I	11	9/10	-	-	-	-	Lukes et al. (2012)
		palbociclib	phase II	15	0/12	7/12	-	median 4.5m.	-	Gounder et al. (2017)
		abemaciclib	phase II	60	1/57	3/29	-	median 30w.	-	Dickson et al. (2019)
	MDM2	MK-8242	phase I	27 (9WD, 17DD, 1UK)	3/27	22/27	-	median 7.8m.	-	Wagner et al. (2017)
		SAR405838	phase I	40	?	56%	-	32% (3m.)	-	De et al. (2017)
		DS-3032b	phase I	20	1/20	14/20	-	-	-	Bauer et al. (2018)
		RG7112	phase II	74	3/74	36/74	-	-	-	Ray-Coquard et al. (2012)
	CDK4/6-MDM2	ribociclib and HDM201	phase I				-	-	-	Razak et al. (2018)
Sarcoma	XPO1	selinexor	phase Ib	52	0/52	30/52	-	-	-	Gounder et al. (2016)
Clear cell sarcoma	BRAF	vemurafenib	case report	1	1/1	-	-	-	-	Protsenko et al. (2015)
		vemurafenib	phase II	1	1/1	-	-	-	-	Hyman et al. (2015)
Osteosarcoma	HER2	trastuzumab + Chemotherapy	phase II	96 (34HER2+)				32% (30m.)	59% (30m.)	Ebb et al. (2012)
Rhabdomyosarcoma	ALK/MET	crizotinib	case reports	2	0/2	0/2	-	-	-	Lewin et al. (2019) and Felkai et al. (2019)
		crizotinib	phase II	20	1/20	-	-	median 1.3m.	-	Schöffski et al. (2018)

ORR : Overall response rate; SD : Stable disease; PFS : Progression-free-survival; DFS : Disease-free survival; OS : Overall survival; CSF1-R : colony-stimulating factor 1 receptor; RANK : receptor activator of nuclear factor kappa B; RANKL : receptor activator of nuclear factor kappa B ligand; PDGFB : Platelet Derived Growth Factor subunit B; ALK : anaplastic lymphoma kinase; mTOR : mammalian target of rapamycin; EZH2 : enhancer of zeste homolog 2; NTRK : neurotrophic tyrosine receptor kinase; CDK : cyclin-dependent kinase; MDM2 : murine double minute-2; XPO1 : exportin 1.

inhibitor (HDM201) in 74 liposarcoma patients have been partly reported (NCT02343172). The best objective responses reported were 3 partial responses (4%) and 36 stable disease (49 %) (Razak et al., 2018). To conclude, MDM2 inhibitor warrants further clinical investigation in WD/DDLPS.

2.3.1.4. Exportin and exportin inhibitors.

Exportin 1 (XPO1) is mediator of nuclear export that play a critical role in regulation of cytoplasm/nucleus translocation of proteins, including several tumor suppressor proteins such as p53, pRb, p21 and p27. This contributes to cell cycle control and growth arrest/apoptosis control. Selinexor is a XPO1 inhibitor. In a phase Ib trial, 52 sarcoma patients were enrolled. There was no reported objective response. Antitumor activity was particularly noted in patients with dedifferentiated LPS (DDLPS), with six (40 %) of 15 patients showing a reduction in target lesion size from baseline (partial response definition was not reached), and 7 (47 %) of 15 patients showed stable disease for 4 months or longer (Gounder et al., 2016). A dedicated phase II/III trial is ongoing (NCT02606461).

2.3.2. Clear cell sarcoma (CCS) and vemurafenib

Clear cell sarcoma (CSS) in an exceptional soft tissue sarcoma, occurring mostly in the extremities (especially in foot and ankles). CSS are diagnosed in adult aged between 20 and 30. Its behavior is very aggressive with lymph node or metastatic relapse (e.g., to the lung, bone, liver and brain). CSS is a chemoresistant malignancy. The main mimic is melanoma, that share both aggressiveness with metastatic spreading and some pathological features (presence of melanin, ultrastructural evidence of melanosomes, frequent immunoreactivity to HMB45, S100 protein or Melan A). EWSR1 rearrangement is present in more than 95 % of CSS and constantly absent in melanomas (Hocar). B-Raf V600E is the most common druggable alteration in melanoma (40–60% of melanoma). On the contrary, Hocar et al. found that B-Raf mutations are rare in CSS (1/22 cases, with another mutation with B-Raf 600E) (Hocar et al., 2012). In literature there were some intriguing cases of CSS responding to vemurafenib. In the first report, the vemurafenib-responding CSS did not harbor EWSR1/ATF1 or EWSR1/CREB1 rearrangement (Protsenko et al., 2015). In the second case, the patient had been enrolled in an agnostic-pathology phase II trial, but we did not have precise data about the confirmation of thoracic CSS diagnosis (Hyman et al., 2015). To the best of our knowledge, we did not find additional case-reports. A basket trial assessing activity/safety of vemurafenib in miscellaneous malignancies is ongoing (NCT02304809), maybe this trial will provide better evidence. To conclude, we are cautious about these observations and we think that both responding tumors could be melanoma.

2.3.3. Targeting HER-2 in osteosarcoma

Tasi et al. reported that about 25 % of osteosarcoma are immunoreactive for HER-2, however by FISH there is no positivity (Tsai et al., 2004). A phase 2 trial assessing trastuzumab in combination of chemotherapy in HER2-positive osteosarcoma selected by immunohistochemistry. Of the enrolled 96 patients 34 were HER-2-positive. The 30-month event-free and overall survival rates for patients with HER2 overexpression treated with chemotherapy and trastuzumab were 32 % and 59 %, respectively. For patients without HER2 overexpression, treated with chemotherapy alone, the 30-month event-free and overall survival rates were 32 % and 50 %, respectively ((Ebb et al., 2012); NCT00023998).

2.3.4. Targeting ALK and MET in rhabdomyosarcomas

Rhabdomyosarcomas include alveolar rhabdomyosarcoma (A-RMS), embryonal rhabdomyosarcoma (E-RMS) and pleiomorphic rhabdomyosarcoma. Both A-RMS and E-RMS could display alterations of ALK. For example, Gasparini et al. found immunoreactivity in 24/33 RMS, but without true amplification by FISH. They found recurrent copy number gain in 25 % of cases, and one case of EML4-ALK fusion (Gasparini et al., 2016). Furthermore, in vitro models suggest that MET is constitutively activated in A-RMS (Skrzypek et al., 2015). However, 2 case-reports did not find clinical activity of crizotinib, an ALK/MET inhibitor in patients with RMS (Lewin et al., 2019; Felkai et al., 2019). In a phase 2 trial, Schöffsky et al. assessed the activity of crizotinib in 20 patients with A-RMS. Only one patient experienced partial response, lasting 52 days. The overall median PFS was 1.3 month (Schöffski et al., 2018).

2.4. Use of targeted therapies in unselected sarcomas

Large clinical trials have demonstrated that the use of targeted therapies in unselected sarcomas is a disappointing strategy. For instance, use of mTOR inhibitor (ridaforolimus) as maintenance therapy did not improve outcomes of patients experiencing stable disease after classical chemotherapy (Demetri et al., 2013). Additionally, adding olaratumab (a monoclonal antibody inhibiting PDGFR-alpha) to doxorubicin did not improve outcome of patients with unselected sarcoma (Tab et al., 2020).

3. Discussion

Sarcoma is a paradigm for clinical and translational research. Development of targeted therapies follows 2 major axes (i) identification of subgroups of tumor with strong actionable drivers such as NTRK alterations (and may be FGFR alterations), and (ii) better knowledge of physiopathology for some particular entities that are best treated with targeted approaches (Table 1). Because of the extreme rarity of some clinico-pathological entities, it is of major importance to publish case-reports with precise description of the involved target, since clinical trials are not feasible for very rare clinical sarcomas. Most of available data are exploratory ones. For instance, description of the following cases could help in the management of some patients with extremely rare conditions, who are not candidates for classical clinical trials: complete response in metastatic ameloblastoma harboring B-raf mutation treated with dabrafenib and trametinib (Brunet et al., 2019), and partial response to vemurafenib in V600E B-Raf mutated histiocytic sarcoma (Idbaih et al., 2014).

Funding

Declaration of Competing Interest

None.

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