New Drug Approvals for Sarcoma in the Last 5 Years

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KEYWORDS

• Sarcoma • Connective tissue tumors • Gastrointestinal stromal tumors
• Precision medicine • Targeted treatments

KEY POINTS

- New generations of tyrosine kinase inhibitors blocking KIT and PDGFRA primary and resistance mutations are now availableImmunotherapy of sarcomas using PDL1, PD1, or CTLA-4 Ab has limited activity in unselected populations of advanced sarcoma sarcomas.
- Several histotypes, such as, ASPS, chordoma respond to ICP. New biomarkers are now identified, such as the presence of tertiary lymphoid structures.
- New tyrosine and serine threonine kinases are demonstrated active in sarcomas with somatic molecular alterations on genes encoding oncoprotein driver of specific sarcoma histotypes.

RIPRETINIB AND AVAPRITINIB IN GASTROINTESTINAL STROMAL TUMOR

During the past few years, treatment focused on primary and secondary driver mutations in *KIT*-mutated or *PDGFR*-mutated gastrointestinal stromal tumors (GISTs) have seen some advances. The main driver mutations in GIST include *KIT* (75%–80%) and platelet-derived growth factor receptor-α (*PDGFRA*; 8%–10%), with a small subset negative for *KIT* and *PDGFRA* mutations (10%–15%) that harbor other molecular alterations such as succinate dehydrogenase (SDH) deficiency (majority), *BRAF* and neurofibromatosis type 1 (*NF1)* mutations.[1] Imatinib, sunitinib, and regorafenib were the 3 approved agents in unresectable/metastatic GIST patients in first, second, and third lines, respectively, based on previous randomized studies[2,3](**Fig. 1**). Recently, the regulatory bodies granted approval to ripretinib in fourth-line GIST and to avapritinib for *PDGFR* exon 18 (D842 V)-mutated GISTs.

Resistance to imatinib can be grouped as primary or secondary resistance. The major cause of primary resistance is the D842 V *PDGFRA* mutation, which constitutes

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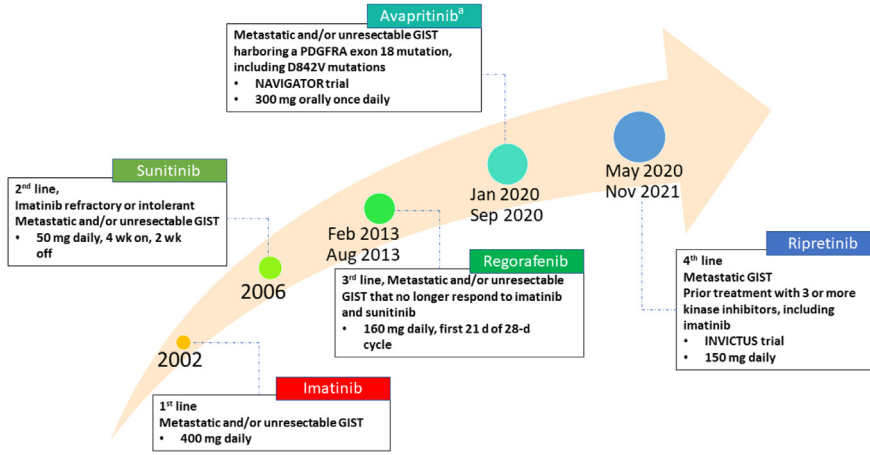
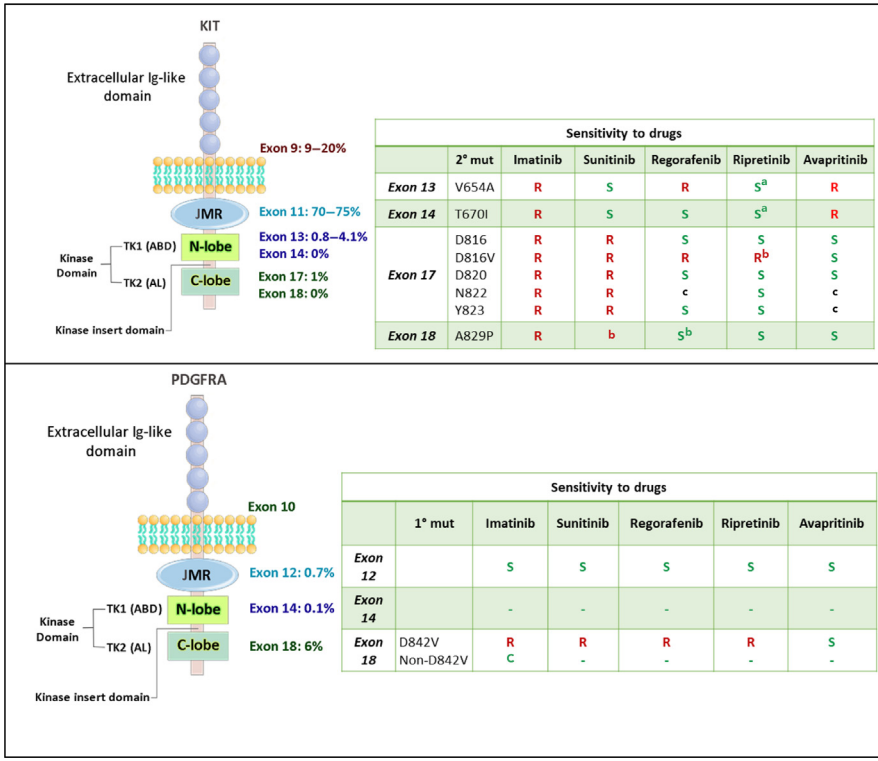


Fig. 1. The FDA and EMA approval timeline and indication(s) of drugs in metastatic GISTs. [a] Avapritinib received conditional authorization in EU in metastatic and/or unresectable GIST with a D842V PDGFRA mutation.



Sensitivity to drugs						
	2° mut	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib
Exon 13	V654A	R	S	R	S[a]	R
Exon 14	T670I	R	S	S	S[a]	R
Exon 17	D816	R	R	S	S	S
	D816V	R	R	R	R[b]	S
	D820	R	R	S	S	S
	N822	R	R	c	S	c
	Y823	R	R	S	S	c
Exon 18	A829P	R	b	S[b]	S	S

Sensitivity to drugs						
	1° mut	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib
Exon 12		S	S	S	S	S
Exon 14		-	-	-	-	-
Exon 18	D842V	R	R	R	R	S
	Non-D842V	c	-	-	-	-

Fig. 2. Distribution of KIT and PDGFRA mutations in GISTs and sensitivity to drugs. JMR, juxtamembrane region; PDGFRA, platelet-derived growth factor receptor α. [a] Decreased response. [b] Presence of conflicting data. [c] Response depend on amino acid change.

about 5% of overall GIST cases. This mutation is located in the exon 18 of *PDGFRA*, which affects the activation loop inside the C-terminal of the tyrosine kinase domain (**Fig. 2**). The modification at D842 residue interferes with the swinging movement of the activation loop, leading to conformational shift of the adenosine triphosphate (ATP)-binding pocket, thereby preventing imatinib binding.[4] Some subsets within non-*KIT* and non-*PDGFR* mutated GISTs can also confer primary resistance.

In clinic, secondary resistance is defined by progression of disease after 6 months of initial benefit on imatinib.[5] Secondary resistance usually occurs after 20 to 24 months of imatinib treatment due to secondary mutations in a subpopulation of cancer cells. The hotspots for secondary mutations are the ATP-binding pocket (exon 13, 14 of *KIT*) and the activation loop (exon 17, 18 of *KIT*) accounting for 85% to 90% of mutations.[1,6]

Sunitinib is the second-line treatment approved in metastatic GIST and has activity against secondary mutations in the ATP-binding pocket (exon 13, 14 of *KIT*), whereas regorafenib, approved in third line, has activity against activation-loop (exon 17 of *KIT*) mutations, except D816 V substitution and has poor activity against the *KIT* exon 13 V654 A mutation.[7] The efficacy of sunitinib and regorafenib in second and third lines are greatly decreased compared with first-line imatinib. This is owing to the heterogeneity of secondary KIT mutations after imatinib and emerging cross-resistant subpopulations on therapy.

RIPRETINIB

Ripretinib, similar to imatinib, sunitinib, and regorafenib, is a type 2 receptor tyrosine kinase (RTK) inhibitor. It binds the inactive form of RTKs and demonstrated broader inhibition of *KIT*/*PDGFRA* mutants than previously approved tyrosine kinase inhibitors (TKIs) in preclinical studies.[8] Ripretinib exerts its potent activity by binding to both switch pocket and activation loop preventing conformation change into active form.

In a phase 1 study, ripretinib had activity across all lines of treatment.[9] The overall response rate (ORR) in the study was 21% in second-line and third-line patients and 9% in fourth line and greater. These data led to the phase 3 double-blind study (INVICTUS) in the fourth line and beyond setting, randomizing patients to ripretinib 150 mg daily or placebo. It conferred a median progression free survival (PFS) of 6.3 months compared with only 1 month in the placebo arm (HR, 0.15; 95% CI, 0.09–0.25; $P < .0001$).[10] Furthermore, ripretinib also improved median OS from 6.6 months in the placebo arm to 15.1 months (HR, 0.36; 95% CI, 0.20–0.63; $P = .0004$) with ORR of 9.4%. Longer follow-up revealed median PFS of 6.3 months and 1.0 month in the ripretinib and placebo group, respectively, with updated ORR of 11.8% in ripretinib group.[11] Currently, ripretinib 150 mg once daily is approved for fourth and later lines of treatment in GIST based on data from this phase 3 INVICTUS trial.

The recommended dose of 150 mg oral once daily was determined by the phase 1 study.[9] No relation or interaction with food was noted. In the phase 1 dose escalation/expansion study, most of the side effects were grade 1 to 2, with grade 3 to 4 treatment emergent adverse events (TEAE) in $\geq$5% patients of asymptomatic lipase elevation (11%), anemia (7%), hypertension (6%), and abdominal pain (5%).

In the dose-expansion phase of phase 1 and the phase 3 studies, patients who progressed on ripretinib 150 mg once daily dose as determined by response evaluation criteria in solid tumors (RECIST)1.1 were given option to increase dose to 150 mg twice daily (BID).[12] PFS on ripretinib 150 mg once daily was defined as PFS1, and after dose escalation, PFS on ripretinib 150 mg BID from the date of escalation to progression or death was defined as PFS2. In the phase 1 study, PFS2 was 5.6 months for second-line therapy, 3.3 months for third-line, and 4.6 months for fourth-line or

Table 1
Treatment-related treatment-emergent adverse events on ripretinib 150 mg once daily dose (left column) and 150 mg BID dose (right column)

	Ripretinib 150 mg QD[a] (n = 85)		Ripretinib 150 mg BID[a] (n = 67)	
TEAEs, n (%)	All Grades	Grade 3/4	All Grades	Grade 3/4
Abdominal pain	-[b]	-	18 (26.9)	7 (10.4)
Anemia	3 (3)	1 (1)	15 (22.4)	4 (6.0)
Fatigue	22 (26)	2 (2)	14 (20.9)	2 (3.0)
Dyspnea	-	-	9 (13.4)	2 (3.0)
Diarrhea	18 (21)	1(1)	19 (28.4)	1 (1.5)
Headache	-	-	7 (10.4)	1 (1.5)
Peripheral edema	-	-	7 (10.4)	1 (1.5)
Decreased appetite	13 (15)	1 (1)	16 (23.9)	1 (1.5)
PPES	18 (21)	0	12 (17.9)	0
Alopecia	42 (49)	0	11 (16.4)	0
Vomiting	-	-	11 (16.4)	0
Nausea	22 (26)	1 (1)	17 (25.4)	0
Weight decreased	13 (15)	0	11 (16.4)	0
Muscle spasms	10 (12)	0	10 (14.9)	0
Myalgia	24 (28)	1 (1)	-	-
Hypertension	7(9)	3 (4)	-	-
Constipation	13 (15)	0	-	-
Blood bilirubin increased	12 (14)	0	-	-

Abbreviations: QD, once daily; BID, twice daily; PPES, Palmar-plantar erythrodysesthesia syndrome; TEAE, Treatment-related adverse events.

[a] List of TEAE with incidence greater than 10% and/or grade 3/4.

[b] Not recorded in the trial or recorded with other terms.

Data from Blay J-Y, Serrano C, Heinrich MC, et al. *The Lancet Oncology* 2020(10) and George S, Chi P, Heinrich MC, et al. *Eur J Cancer* 2021(12).

greater. The ratio of median PFS2/PFS1 was 51%, 40%, and 84% in each line, respectively. However, dose escalation led to some worsening side effects including abdominal pain, anemia, dyspnea, fatigue, peripheral edema, decrease appetite, and diarrhea. **Table 1** details side effects of standard dosing and dose escalation from the phase 1 and phase 3 studies. Rare but serious side effects included skin cancer (cutaneous squamous cell carcinoma 4.7%, melanoma 2.4%) and congestive heart failure (1.2%).

Ripretinib was also recently evaluated in a phase 3 study (INTRIGUE) in the second-line setting in comparison to sunitinib. The preliminary results were reported at the American Association for Cancer Research; ripretinib in second line failed to show superior outcomes compared with sunitinib.[13] The ORR was 21.7% and 17.6% while median PFS was 8 and 8.3 months, for ripretinib and sunitinib, respectively. This difference was not statistically significant.

AVAPRITINIB

Avapritinib is a type I inhibitor with selective inhibition of *KIT/PDGFR* activation loop mutations such as *PDGFRA* exon 18 D842 V and *KIT* D816 V.[14,15] Strong preclinical

data led to a phase 1 (NAVIGATOR) trial of Avapritinib in advanced GISTs divided into groups based on the presence or absence of a PDGFR exon 18 mutation.[16] *PDGFR* exon 18 (D842 V)-mutated GIST, previously resistant to all the available TKIs, demonstrated an ORR of 88% (49/56) with, complete response (CR) in 9% (5/56) and progression free rate of 81% at 12 months. In patients who received 300 mg starting dose, ORR was 93%. Based on this dramatic response, avapritinib 300 mg once daily was approved for patients with *PDGFR* exon 18 mutations in any line of treatment.

In non-D842 V patients in fourth or later lines, the ORR was 17% (17/103) with median PFS 3.7 months (95%CI: 2.8–4.6), whereas ORR in third or fourth line regorafenib-naïve patients was 26% (6/23). Median PFS was 8.6 months (95%CI:5.6–14.7).[17–19] No responses were seen in patients with V654 A or T670I *KIT* secondary mutations (0/25), whereas ORR in the group negative for these mutations was 26% (22/84). Following up on these results, a phase 3 (VOYAGER) study in third line or beyond was conducted randomizing unresectable/metastatic GIST patients between avapritinib and regorafenib. The study unfortunately did not meet its primary end point as the PFS for avapritinib was not superior to regorafenib (4.2 vs 5.6 months, HR 1.25, 95%CI 0.99–1.57, $P = .055$). The ORR was 17.1% and 7.2% for avapritinib and regorafenib, respectively. Around 14% of patients included on the study had a *KIT* V654 A or T670I mutation (exon 13/14) that we now know are resistant to avapritinib (see **Fig. 2**).

In the phase 1 dose escalation and expansion study, avapritinib showed a reasonable tolerability profile with only a few patients discontinuing due to side effects.[16] Most common adverse events are edema, nausea, fatigue, decreased appetite, diarrhea, constipation, hair color change, and cognitive impairment (**Table 2**). Avapritinib had less events associated with vascular endothelial growth factor receptor activation such as hypertension and hand-foot syndrome compared with sunitinib and regorafenib. Cognitive effects were seen more frequently with avapritinib and seemed as frequently as 40% (33/82) and were classified as memory impairment (30%), cognitive disorder (10%), confusion (9%), and encephalopathy (2%). Most cases were reported as grade 1 and managed with dose modifications or interruptions with treatment discontinuation reported in 2% (2/82).

The starting dose of avapritinib in the phase 1 dose-expansion was 400 mg daily but later reduced to 300 mg daily due to the concern regarding higher grade cognitive adverse events and no significant difference in ORR.[16] The approved dose is 300 mg daily with dose reduction to 200 mg or 100 mg daily recommended for side effect management. Avapritinib has to be taken on an empty stomach, 2 hours after or 1 hour before a meal.

ERIBULIN IN LIPOSARCOMA

Liposarcomas (LPS) are one of the most common soft tissue sarcomas (STS) believed to originate from an adipocytic lineage. Three main subtypes of LPS are well-differentiated/dedifferentiated (WDLPS/DDLPS), myxoid/round-cell (MRCLS), and pleomorphic (PLPS). WDLPS and DDLPS account for most LPS and have poorer response to chemotherapy compared with MRCLS. PLPS tend to have the worse prognosis but account for only about 10% of all LPS cases.[20]

Despite the poorer response, current standard systemic treatment in DDLPS is anthracycline-based chemotherapy recommended as a first-line treatment in advanced/metastatic disease based on studies in STS. No standard systemic options are available for pure WDLPS. In a pivotal phase 3, EORTC 62012 trial, combination doxorubicin–ifosfamide had superior ORR and median PFS compared with a single

Table 2
Treatment-related adverse effects of Avapritinib at different starting doses

	<300 mg (n = 30)		300 mg (n = 32)		400 mg (n = 17)	
TRAEs, n (%)	Grade1-2	Grade 3–4	Grade1-2	Grade 3–4	Grade1-2	Grade 3–4
Nausea	13(43)	1(3)	22(69)	0	12(71)	0
Fatigue	18(60)	1(3)	12(38)	1(3)	8(47)	3(18)
Diarrhea	11(37)	1(3)	13(41)	2(6)	6(35)	1(6)
Periorbital edema	15(50)	0	11(34)	1(3)	8(47)	0
Anemia	6(20)	5(17)	11(34)	7(22)	4(24)	1(6)
Decreased appetite	6(20)	1(3)	12(38)	0	5(29)	0
Vomiting	10(33)	1(3)	5(16)	0	8(47)	0
Memory impairment	7(23)	0	10(31)	0	7(41)	0
Hair color change	11(37)	0	8(25)	0	5(29)	0
Increased lacrimation	5(30)	0	7(22)	0	7(41)	0
Peripheral edema	10(33)	0	10(31)	0	4(24)	0
Blood bilirubin increased	3(10)	0	7(22)	1(3)	5(29)	1(6)
Face edema	3(10)	0	11(34)	0	3(18)	0
Dysgeusia	5(17)	0	7(22)	0	2(12)	0
Hypophosphatemia	3(10)	2(6)	3(9)	1(3)	4(24)	2(12)
Neutropenia	2(7)	1(3)	6(19)	3(9)	1(6)	1(6)
Dizziness	2(7)	0	6(19)	0	5(29)	0
Dyspepsia	6(20)	0	4(13)	0	2(12)	0
Alopecia	4(13)	0	4(13)	0	3(18)	0
Eyelid edema	3(10)	0	5(16)	0	3(18)	0
Headache	3(10)	0	4(13)	0	1(6)	0
Pleural effusion	2(7)	1(3)	3(9)	1(3)	0	1(6)
Cognitive disorder	1(3)	1(3)	4(13)	0	0	1(6)
Hypomagnesemia	2(7)	1(3)	3(9)	1(3)	0	1(6)

Abbreviation: TRAEs, Treatment related adverse events.
The table lists treatment-related adverse events occurring in 10% or more in 300 mg dose.
Data from Heinrich MC, Jones RL, von Mehren M, et al. The Lancet Oncology 2020(16).

agent doxorubicin (ORR 26% vs 14%, mPFS 7.4 vs 4.6 months, HR 0.74, 95%CI 0.60–0.90) but no significant benefit in OS (14.3 vs 12.8 months, 95%CI 10.5–14.3).[21] The study involved 14% and 11% of LPS patients in the combination and doxorubicin alone arm, respectively. Chemotherapy response specifically in WDLPS/DDLPS has been evaluated in retrospective studies revealing an ORR of 12% to 21%, varying based on WDLPS percentage and use of combination versus single agent therapy.[22,23] The commonly used second-line regimen in DDLPS is gemcitabine-docetaxel primarily based on the SARC002 study in STS.[23–25]

Options for later lines in DDLPS include trabectedin approved on the basis of a phase 3 randomized trial comparing trabectedin and dacarbazine in advanced LPS or leiomyosarcoma (LMS) after prior anthracycline and one additional systemic regimen (3rd line setting).[26] Trabectedin demonstrated a superior PFS of 4.2 months compared with 1.5 months in dacarbazine (HR 0.55, $P < .001$), though there was no difference in OS (12.4 vs 12.9 months, HR 0.87, $P = .37$). In the DDLPS subgroup, median PFS was 2.2 months with trabectedin compared with 1.9 months in dacarbazine

(95%CI 0.37–1.25, HR 0.68) but in MRCLS, the median PFS was 5.6 months with trabectedin compared with 1.5 months with dacarbazine (HR 0.41, 95%CI 0.17–0.98).[26]

Shortly thereafter, eribulin was added to the therapeutic armamentarium for previously treated advanced/metastatic LPS.

Eribulin mesylate is a derivative of Halichondrin B, a natural substance originally isolated from a rare marine Japanese sponge, *Halichondria okadai* but also present in more common sponges.[27] Eribulin belongs to the group of antitubulin drugs and has an inhibitory effect on microtubule polymerization leading to mitotic block and cell arrest in the G2–M phase of the cell cycle. Preclinical studies showed antitumor activity of eribulin against many established cancer cell lines including breast cancer, colon cancer, non-small cell lung cancer, and uterine sarcoma.

In a nonrandomized phase 2 study in progressive high-grade STS, patients who had received 1 or more prior combination chemotherapy or 2 or more prior single drugs for advanced disease were enrolled.[28] Of all STS patients, adipocytic sarcoma and LMS demonstrated a higher percentage of progression-free survival at 12 weeks (46.9% in adipocytic sarcoma and 21.6% in LMS). The promising results in LPS and LMS prompted a phase 3 randomized, open-label study comparing eribulin (1.4 mg/m^2 intravenously on days 1 and 8) and dacarbazine (850 mg/m^2, 1000 mg/m^2, or 1200 mg/m^2 depending on center and clinician, on day 1) every 21 days in advanced LPS or LMS patients who received 2 or greater prior systemic regimens including anthracycline (third-line setting).[29] Overall survival in eribulin group was significantly better compared with dacarbazine with a median OS of 13.5 months versus 11.5 months (HR 0.77, 95%CI 0.62–0.95, $P = .0169$), respectively. Median PFS was similar in eribulin and dacarbazine groups (2.6 months vs 2.6 months, HR 0.88, 95%CI 0.71–1.09, $P = .23$). The planned subgroup analysis revealed most of the survival benefit in the LPS group (HR 0.51, 95%CI 0.35–0.75) and not in LMS (HR 0.93, 95%CI 0.71–1.20). The PFS for the LPS group was 2.9 versus 1.7 months for eribulin versus dacarbazine, respectively (HR 0.521, 95%CI 0.35–0.78). Most of the LPS patients in this study were DDLPS (45.5%), followed by MRCLS (38.5%), and PLS (16.1%). Further analysis of the outcomes in this study revealed a statistically significant OS difference with eribulin compared with dacarbazine in DDLPS (HR 0.429, 95% CI 0.232–0.792) and PLPS (HR 0.182 95%CI 0.039–0.850) but not in MRCLS patients (HR 0.787, 95%CI 0.416–1.491) (**Table 3**).[30] Eribulin was granted Food and Drug

Table 3
Survival data in LS subgroups from the randomized phase 3 trial of eribulin compared with dacarbazine

Group/Subgroup (n)	Median OS (months)			Median PFS (months)		
	Eribulin	Dacarbazine	HR (95%CI)	Eribulin	Dacarbazine	HR (95%CI)
All LPSs (143)	15.6	8.4	0.511 (0.346–0.753)	2.9	1.7	0.521 (0.346–0.784)
Dedifferentiated[65]	18.0	8.1	0.429 (0.232–0.792)	2.0	2.1	0.691 (0.359–1.328)
Myxoid/round cell[55]	13.5	9.6	0.787 (0.416–1.491)	2.8	1.4	0.567 (0.289–1.113)
Pleomorphic[23]	22.2	6.7	0.182 (0.039–0.850)	4.4	1.4	0.337 (0.088–1.298)

Data from Demetri GD, Schöffski P, Grignani G, Blay J-Y, Maki RG, Van Tine BA, et al. Journal of Clinical Oncology. 2017 (30).

Administration (FDA) approval in unresectable/metastatic LPS patients who have received prior anthracycline-based therapy on January 28, 2016.[31]

Side effects of eribulin in LPS patients are consistent with previous studies and include alopecia, fatigue, neutropenia, and nausea.[30] In the randomized phase 3 study comparing eribulin and dacarbazine, grade 3 and greater adverse events were found in 62.9% of LPS patients in the eribulin arm, leading to drug interruption in 30%, dose reduction in 21.4%, and drug withdrawal in 7.1%. The recommended starting dose of eribulin is 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle, with 2 possible dose reductions to 1.1 mg/m^2 and 0.7 mg/m^2, if needed.

SELINEXOR IN DDLS

Selinexor is a selective inhibitor of XPO1, a nuclear exportin, which can recognize nuclear export signal and export many tumor suppressor proteins including p53 and p21.[32] A preclinical study in LPS cell lines with selinexor demonstrated increasing p53 and p21 expression at the protein level leading to cell cycle arrest and apoptosis.[33] Selinexor exhibited promising activity in phase 1B study in sarcoma with response noted in the DDLPS subtype. This led to the first of its kind, phase 3 randomized double-blinded placebo-controlled crossover phase 2/3 study of selinexor in advanced unresectable DDLPS (SEAL) who were progressing and were previously treated with 1 or more systemic therapies.[34] The study met its primary end point of improved PFS of selinexor compared with placebo but the incremental numerical benefit was low (2.83 mo vs 2.07 mo, HR 0.70 [95% CI 0.52–0.95], *P*-value of .0228). The median OS in the selinexor arm was not significantly different from placebo but 58% of patients from the placebo crossed over to the selinexor arm. Although some DDLPS patients derived benefit, this drug is not yet approved for use in this subtype of LPS.

The recommended phase 2 dose of selinexor was 35 mg/m^2 or 60 mg fixed dose given orally twice a week, a day apart, with dose-limiting toxicities (DLTs) of grade 3 fatigue, nausea and vomiting, hyponatremia, acute cerebellar syndrome, and anorexia.[35] In the phase 2/3 study in DDLPS, the fixed dose of selinexor (60 mg twice a week, one day apart) was administered, with dose reductions allowed for toxicity. Side effects including nausea, anorexia, and fatigue of any grade were found in more than half of the patients.[34] Grades 3 to 4 adverse events noted were hyponatremia (15%), anemia (15%), and thrombocytopenia (12%). No incidence of acute cerebellar syndrome was reported at this dosing. With early institution of supportive care measures for nausea and appetite loss, the drug seems to be well tolerated with evidence of improvement in quality of life as compared with placebo in DDLPS.[36]

TAZEMETOSTAT IN EPITHELIOID SARCOMA

Epithelioid sarcoma (ES) is a rare histotype of sarcoma with an incidence close to 0.5 new cases per million per year in nationwide registries.[37] Primary tumors are observed on any anatomic sites.[37] Median age at diagnosis is 40 years with an equal gender distribution. The loss of INI1/SMARCB1 is frequently observed in ES.[38,39] INI1 is a component of the SWI/SNF complex acting as a tumor suppressor. Loss of INI1, through genetic or epigenetic mechanisms, results in the oncogenic activation of enhancer of zeste (EZH)2, which trimethylates lysine 27 of histone H3.[40,41]

The treatment of ES follows the general rules of sarcoma management in localized phase.[42,43] In advanced phase, classic cytotoxic treatments or pazopanib of advanced sarcomas have a limited activity in this disease.[44–46] Tazemetostat is a selective inhibitor of EZH2, administered orally. It provided encouraging activity in a phase 1 study,

including patients with advanced solid tumors with loss of INI1/SMARCB1.[47] In the phase I study, 3 patients with ES were included: 2 achieved prolonged PFS.

A recently reported phase 2 basket study reported the activity of tazemetostat in patients with solid tumors harboring these alterations. Among the 62 patients with ES were enrolled in the study, 9 (15%) had an objective response. 16 (26%) patients had disease control at 32 weeks. Median time to response was 3·9 months (Interquartile Range (IQR) 1·9–7·4). Median progression-free survival was 5.5 months (95% CI 3·4–5·9), and median overall survival was 19.0 months. The treatment was overall well tolerated with grade 3 anemia in 4 (6%) and weight loss in 2 (3%) patients.

The treatment is approved by the FDA for the treatment of ES in advanced phase since January 2020, and under evaluation by the European Medicines Agency (EMA).

NEUROTROPHIN RECEPTOR TYROSINE KINASE (NTRK) INHIBITORS FOR NTRK FUSION POSITIVE SARCOMAS

The most recent WHO classification of soft tissue and bone neoplasms identifies the novel identity of *NTRK*-fusion-positive neoplasms.[48] The screening for translocation is not consistently conducted in expert sarcoma pathology laboratories. As a consequence, the exact incidence of this heterogenous entity is not precisely known. The reported incidence of infantile fibrosarcoma, fibrosarcoma, and lipofibromatosis, 3 entities where the prevalence of *NTRK*-fusion is high, is 0.04, 0.03, 0.1/10e6/year.[37] In an unpublished study screening 500 consecutive sarcomas with complex genomics, the exact incidence of *NTRK*-fusion was 1% (5/500) (personal results unreported). In GIST without canonical mutations of *KIT* or *PDGFRA*, *NTRK* fusions are also very rare.

Clinical trials have been published since 2017, demonstrating a high level of response rate with larotectinib and entrectinib in patients with any histologic subtypes, creating the concept of histoagnostic therapies of advanced cancers with different histologies but sharing similar actionable molecular alterations. In these studies, sarcomas represent close to 20% of included patients.[49–52] Infantile fibrosarcoma in relapse represent close to 40% of sarcomas treated with NTRK inhibitors in these trials. A specific analysis of the subgroup of patients with sarcoma treated with larotrectinib or entrectinib was presented at Connective Tissue Oncology Society (CTOS) 2019. With larotrectinib, this was a series of 71 patients, adults (n = 23, 32%) and children, all pretreated, with 29 infantile fibrosarcoma (41%), 4 GIST (6%), 2 bone sarcoma (3%), and 36 (51%) patients with more than 10 different other histologic types of sarcomas. Most rearrangements were on *NTRK3* (n = 42, 59%) followed by *NTRK1* (n = 26, 37%), and NTRK2 (n = 3, 5%). There were 16 (23%) CR, 45 (64%) partial responses (PR), 6 (9%) stable disease (SD), and 2 (3%) progressive disease (PD) as best response. Median duration of response was not reached. A total of 70% were still responding at the median follow-up of 16 months. Median PFS and OS were 28 and 44 months, respectively. Grade 3 and 4 side effects were limited.

With entrectinib, the series reported in CTOS 2019 included 13 adult patients, all pretreated, with 1 GIST (8%), 1 bone chondrosarcoma (8%), and 11 (84%) different other histologic subtypes of STS. Most rearrangements were on *NTRK3* (n = 8, 60%) followed by *NTRK1* (n = 5, 40%). There were 6 (48%) PR, 4 (32%) SD and 1 (8%) PD as best response. Median duration of response was 10 months. Median PFS and OS were 11 and 17 months, respectively. Grade 3 and 4 side effects were limited.

Given the rarity and heterogeneity of these tumors, it is considered very unlikely to be able to construct randomized clinical trials. For this reason, comparing patients as his/her own control to comparing previous PFS to PFS under NTRKi has been proposed by several studies.[53]

Larotrectinib was approved by the FDA for the treatment of tumors in advanced phase with translocation involving NTRK since November 26, 2018 and by the EMA since September 09, 2019. Entrectinib was approved by the FDA for the treatment of tumors in advanced phase with translocation involving NTRK since August 19, 2019 and by the EMA since July 31, 2020.

SORAFENIB AND NIROGACESTAT IN DESMOID TUMORS

Desmoid tumors (aka aggressive fibromatosis) are locally aggressive connective tissue tumors with an incidence close to 5/1000000/y, an F/M ratio close to 2, and a median age of diagnosis of 40 (ranging from pediatric to geriatric ages) in nationwide series.[37] Primary sites affected by these tumors include all anatomic sites, abdominal or trunk wall being common (>50%) and mesenteric sites being the most frequently life threatening although the overall mortality of these tumors remain rare. Desmoid tumors can be sporadic and harbor most often *CTNNB1* mutations in this case. About 10% of desmoid tumors are associated with germline *APC* mutations within the Gardner syndrome. The later are often intra-abdominal or thoracic and more frequently life threatening.

Symptoms vary considerably. Sometimes an asymptomatic mass, desmoid tumors can be painful, functionally impairing, compressive (occlusion, vital organs). Complications in young adults also include long-term opioid use, anxiety, depression, and interruption of education and employment.

Local treatments include watchful waiting, radiotherapy, and cryoablation, less frequently surgical removal.[54] A large number of agents have been reported to have activity against desmoid tumors, from non-steroidal anti-inflammatory drugs (NSAIDS), antiestrogens, cytotoxic chemotherapy, TKIs most often in uncontrolled studies resulting in difficulties in interpretation.[54]

Sorafenib

Gounder and colleagues reported recently an important randomized clinical trial comparing sorafenib 800 mg/d versus placebo in patients with desmoid tumors not amenable to a local treatment. A total of 87 patients were randomized, the 2-year PFS rate was 81% in the sorafenib group and 36% in the placebo group (hazard ratio 0.13; $P < .001$). Before crossover, the ORR was 33% in the sorafenib group and 20% in the placebo group demonstrating in a rigorous manner the unpredictable natural history of this disease.[55] The median time to response was 9.6 months in the sorafenib and 13.3 months in the placebo groups, respectively. A similar magnitude of activity was observed with pazopanib 800 mg/d in a randomized trial conducted against the methotrexate vinblastine (MV) combination (6-month PFS for pazopanib 83% vs 45% for MV), confirming the activity of this class of antiangiogenic agents in this rare entity.[56] Sorafenib is available in the United States since 2005.

Nirogacestat

Gamma secretase inhibitor nirogacestat given at a dose of 150 mg twice a day was reported in 2017 to be active in a limited series of patients with pretreated desmoid tumors. Seventeen patients were included in a phase II study, following a phase I study that had reported 5 out of 7 responses in desmoid tumors.[56] In this study, 5 of 17 patients (29%) responded to treatment, and 5 achieved SD. Median PFS is not reported, in the first publication, but was mentioned as not reached in a subsequent report.[57] All patient achieved a symptom improvement in these series.[57]

The FDA granted nirogacestat, with a breakthrough therapy designation for the treatment of adult patients with progressive, unresectable, recurrent, or refractory desmoid tumors, or deep fibromatosis in 2021.

PEXIDATINIB IN GIANT CELL TUMOR OF THE SOFT PARTS

Giant cell tumor of the soft parts (aka diffuse tenosynovial giant cell tumors [TGCT], pigmented villonodular synovitis [PVNS]) is a locally aggressive connective tissue tumor of the joints, affecting mostly young adults, with a predominance on the knee and ankle.[58,59] These tumors are characterized by a t(1;2) translocation in a minority of cells present in the tumor, resulting in a fusion gene colony-stimulating factor-1/collagen type VI alpha-3 (*CSF1/COL6A3)* whose protein product induces tumor growth and giant cell infiltrates.[60] Surgical resection is the standard treatment in first-line but local relapses are frequent. Clinical symptoms involve swelling, pain, and functional impairment that are characteristic of the disease in particular at relapse.[58,59] Surgery at relapse is rarely curative with less than 20% of patients free of relapse at 5 years.[58] Amputations may be required only very rarely in very large tumors. dTGCT are rarely multifocal and metastasize even more rarely.[58]

Before CSF1R antagonists, either TKIs or antibodies, the medical treatments for relapsing and inoperable tumors had limited efficacy.[58–61] The rationale for the use of CSF1R antagonists is based of the presence of the fusion gene involving CSF1, considered to be a driver of the tumor. CSF1R inhibitors, TKI or Ab, yielded tumor shrinkage and symptom relief in patients with inoperable diffuse type TCGT.[61–67] Imatinib exerts CSF1R inhibitory activity and was first reported as active in TGCT/PVNS in a case report in 2008.[61,62] The clinical efficacy of TKIs blocking CSF1R (imatinib, nilotinib, pexidartinib) and antibodies against CSF1R (emactuzumab, cabiralizumab) was confirmed after in retrospective studies and prospective clinical studies for imatinib,[62] emactuzumab,[63] nilotinib,[64] and pexidatinib.[65] Tap and colleagues reported in 2019 on the first randomized phase III study comparing placebo with pexidartinib orally 400 mg BID.[66] In this study involving 120 patients, tumor response was significantly higher (24/61, 39%) with pexidartinib versus placebo (0/59, 0%). Patient reported outcome and function improved during treatment with pexidartinib as compared with placebo.[66] Pexidartinib was approved for the treatment of dTGCT by the FDA on August 2, 2019 and is the only registered treatment of this disease.

MAMMALIAN TARGET OF RAPAMYCIN (mTOR) INHIBITORS IN PERIVASCULAR EPITHELIOID CELL TUMORS

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms, mostly benign[37,68–70] although malignant PEComas exist and may present as locally advanced and/or metastatic diseases.[68–71] Their incidence in the nationwide NETSARC series is 0.3/1,000,000 per year.[37] The median age at diagnosis was found to be 55, with 3.7 F/M ratio and a predominance of visceral sites (especially renal, uterine, and gastrointestinal).[37] PEComas often show loss-of-function mutations of tuberous sclerosis complex (TSC)1 or TSC2 and activation of mammalian target of rapamycin complex (mTORC)1 with phosphorylation of p70S6K and ribosomal protein S6.[72,73]

Malignant PEComa in advanced phase are treated with cytotoxic chemotherapy regimens used for sarcomas with limited response rates and PFS in retrospective series.[73]A fraction of patients with PEComas benefited from treatment with mTORC1 inhibitors (sirolimus, everolimus, temsirolimus) in retrospective analyses.[72–74] Sanfilippo and colleagues reported on a 41% ORR with mTORC1 treatment, with a median PFS

of 9 months, superior to that achieved with anthracyclins, gemcitabine, or pazopanib in this retrospective series of 40 patients.[73]

This prompted prospective studies of a new generation of mTORC1 inhibitors.[75] Nab-sirolimus was given at a dose of100 mg/m^2 IV weekly for 2 weeks every 3 weeks in a phase II study involving 34 patients. The ORR was 39% (12 of 31) with 1 CR (3%) and 36% PR, 16 (52%) SD with 7 of 12 responders still treated at a median follow-up of 2.5 years, and a median PFS of 10 months and a median OS of 40 months. 8 of 9 (89%) patient with a documented TSC2 mutation were responders versus 2 of 16 (13%) without TSC2 mutation. Nab-sirolimus was approved for the treatment of advanced PEComas by the FDA on November 22, 2021 and is the only registered treatment of this disease.

POTENTIAL OPTIONS IN THE NEAR FUTURE

Cyclin-dependent kinase (CDK) 4/6 Inhibitors in Liposarcoma

Supernumerary ring chromosomes formed by a segment of chromosome 12q13-15 are found in both WDLPS and DDLPS resulting in multiple gene amplifications, with *MDM2* (Mouse double minute 2) and *CDK4* being the most frequent genes amplified (100% and 90%, respectively).[76] MDM2 has a major function in the regulation of p53, an important tumor suppressor involved in growth arrest, senescence, and apoptosis in response to cellular damage. MDM2 regulates p53 at both the mRNA and protein level by blocking the transactivation domain and inducing degradation via E3-ubiquitin ligase activity.[77] CDK4/CDK6, together with CDK2, play a crucial role in cell cycle progression from G1 to S phase by Rb1 phosphorylation and activation of E2F.[78]

Palbociclib, a potent oral CDK4/6 inhibitor has demonstrated activity in CDK4-amplified LPS cell lines and xenografts. Data from a phase 1 study of the drug showed 2 patients with prolonged stable disease for several years prompting a phase 2 study with palbociclib 200 mg once daily for 14 out of 21 days.[79] The primary end point was met with a 12-week PFS of 66% (90% CI, 51%−100%) and a median PFS of 18 weeks. A subsequent phase 2 trial was conducted with the dose of 125 mg daily, 21 days out of a 28 day-cycle, the same dose approved in breast cancer, and revealed a compatible median PFS of 17.9 weeks (2-sided 95% CI: 11.9–24.0 weeks) with less incidence of grade 3 to 4 neutropenia (33%) and no neutropenic fever events.[80]

Another active CDK4/6 inhibitor evaluated in LPS is abemaciclib. A phase 2 study done in DDLS revealed PFS at 12 weeks of 76% (95% CI 57%–90%), median PFS of 30.4 weeks (95% CI 28.9-NE) and ORR of 3.45% (1 partial response from 29 patients).[81]

Currently, a CDK4 inhibitor is not approved in LPS treatment but palbociclib, is included as a valid category 2A option in the National Comprehensive Cancer Network (NCCN) guidelines, and there is an ongoing randomized placebo controlled study with abemaciclib in DDLPS (NCT04967521).[82]

T-cell Therapy in Synovial Sarcoma and MRCLS

Synovial sarcoma and MRCLS are rare mesenchymal tumors responsible for around 5% to 10% of STS cases.[83] Chromosomal translocation t(X;18) (p11.2;q11.2) producing SS18-SSX fusion protein is pathognomonic of synovial sarcoma and the translocation t(12;16) (q13;p11) producing fusion protein FUS-DDIT3 is pathognomonic of MRCLS.[84–86] Both these types of sarcoma are relatively more chemosensitive than other types of STS.

Synovial sarcomas and MRCLS have low mutation burden and poor response to checkpoint blockade.[87] However, 70% to 80% of these tumors express New York esophageal squamous cell carcinoma 1 (NY-ESO-1), a well-known cancer-testis

antigen (CTA), which belongs to a group of antigens that have expression restricted to certain cancers and the testis.[88,89] Although several malignancies overexpress NY-ESO-1, only MRCLS and synovial sarcoma have homogenous expression with synovial sarcoma positive in both biphasic and monophasic variants.[90] This brought about studies focused on targeting this protein through cellular immune therapy.

Adoptive cell therapy (ACT) are ways to increase immune recognition of tumors by infusing tumor cell-specific T-cells. ACT can be approached in 3 different ways; one involves harvesting, expanding, and reinfusing tumor-infiltrating lymphocytes, another uses T cell receptor (TCR) recognition of intracellular tumor proteins presented on the cell surface through major histocompatibility complex (MHC)-1, and finally, chimeric antigen receptor-modified T cells that recognize and attack tumor-cell surface receptors.[91]

A promising pilot study using autologous TCR-transduced T cells following a lympho-depleting preparative chemotherapy in human leukocyte antigen (HLA)-A*0201 (MHC class-I) patients with NY-ESO-1 positive metastatic synovial sarcoma or melanoma refractory to standard treatment was first published in 2015.[92] The study demonstrated an ORR of 61% (11/18) in synovial sarcoma patients with response lasting 3 to 18 months. Significant transient neutropenia and thrombocytopenia occurred in 100% with 1 treatment-related death. In 2018, an affinity-enhanced TCR recognizing the NY-ESO-1 derived peptide SLLMWITQC (NY-ESO-1^{c259} T cells) was tested in advanced synovial sarcoma without the use of IL-2 and was noted to be safe and feasible with a 50% (6/12) ORR.[93] This study detected circulating NY-ESO-1^{c259} T cells in all responders for at least 6 months. Although side effects from IL-2 were eliminated, adverse events caused by lympho-depleting chemotherapy were noted, with grade $\geq$3 lymphopenia (100%), neutropenia (83%), anemia (83%), thrombocytopenia (67%), and febrile neutropenia (17%). Further studies and evaluation of long-term outcome is ongoing for NY-ESO-1^{c259} T cells. In addition, an ongoing phase 2 study (NCT04044768) of afamitresgene autoleucel (previously ADP-A2M4) targeting an alternate CTA, melanoma antigen gene (MAGE) A4, with high expression in synovial sarcoma and MRCLS is showing promising results as well.

CHECKPOINT INHIBITORS IN ALVEOLAR SOFT PARTS SARCOMA

Immune-checkpoint inhibitors (CPI) have been evaluated in a few sarcoma trials. Pembrolizumab, an anti-PD-1 antibody, resulted in an ORR of 18% (7/40) in bone and STS in a phase 2 trial.[87] Among STS patients, response was noted in undifferentiated pleomorphic sarcoma (UPS) (40%), DDLS (20%), and synovial sarcoma (10%). With an expansion of the cohorts, the reported ORR dropped but remained encouraging for further study. In another study, nivolumab monotherapy resulted in an ORR of 5% (3/38) with response in alveolar soft part sarcoma (ASPS), non-uterine LMS, and an unspecified sarcoma.[94]

An open-label multicenter, phase 2 study of pembrolizumab in combination with metronomic cyclophosphamide demonstrated limited activity with an ORR of 6% in STS including LMS, UPS, other sarcomas, and GIST.[95] A combination of ipilimumab/nivolumab demonstrated an ORR of 16% (6/41) with response noted in uterine LMS, non-uterine LMS, myxofibrosarcoma, UPS, and angiosarcoma.[94] Median PFS and OS was 4.1 months and 14.3 months, respectively. Currently, the role of CPI in STS is being investigated, to try and improve outcomes, with better subtype selection, or alternate CPI combinations.

Among STS, ASPS has emerged with the highest response to anti-PD-1/PD-L1 therapy. A retrospective review of 50 advanced sarcoma patients treated with CPI

revealed an ORR of 4% (2/50), whereas it was 50% among ASPS patients (2/4), with the remaining 2/4 having stable disease.[96] A phase 2 combination study of axitinib plus pembrolizumab in STS, again revealed a higher ORR in ASPS patients of 54.5% (6/11), and a 3-month PFS of 72.7%.[97] Similarly, the ASPS cohort in a phase 2 study of durvalumab and tremelimumab in various sarcoma subtypes, experienced an ORR of 50% (5/10).[98] A single-arm multicenter phase 2 study testing atezolizumab in advanced ASPS patients is now ongoing, with interim data reporting an ORR of 37.2% (16/43) with 1 CR.[99] NCCN guidelines recommend pembrolizumab as a category 2A in ASPS[82]

The last 5 years has seen an exponential increase in the number of biomarker-specific or sarcoma subtype-specific clinical trials compared with prior years. This has led to a larger number of drugs being available for certain sarcomas and leading to incremental improvements in survival. In general, the benefit seen with biomarker-targeted therapies is of higher magnitude than seen in unselected sarcoma patients. We hope this pace of development continues, to further bridge the gap of the severe unmet need in sarcoma patients. We need less toxic and more effective systemic therapies for more than 50 different sarcoma subtypes.

CONFLICT OF INTEREST (J.-Y. BLAY, M. BRAHMI, A. DUFRESNE)

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