Sarcoma Patients EuroNet

ASCO (American Society of Clinical Oncology) Annual Meeting 2019, Chicago:

Treatment of soft tissue sarcomas, bone sarcomas and GIST: State of the art and update from the ASCO Conference 2019

By Prof. Dr. Bernd Kasper

Prof. Dr. Bernd Kasper is an oncologist and leading sarcoma expert at the "Sarcoma Center SarcoMA" in Mannheim, Germany. He is also the current Secretary of the EORTC Soft Tissue and Bone Sarcoma Group, an appointed Board Member of Sarcoma Patients EuroNet e.V. and a future Board Member of the upcoming new German Sarcoma Foundation (Deutsche Sarkom-Stiftung).

Sarcomas and in particular soft tissue sarcomas are rare malignancies of mesenchymal origin comprising about 1 % of all adult cancers. Systemic therapies for locally advanced and metastatic disease have been restricted for decades to very few effective and approved agents such as doxorubicin and ifosfamide. However, new therapeutic strategies including new drug developments and registrations such as trabectedin, pazopanib and eribulin as well as numerous clinical trial options have recently enriched the therapeutic armamentarium in the treatment of patients with advanced soft tissue sarcomas. New therapies for the treatment benefit of sarcoma patients along with current results from this year's Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago from May 31st to June 4th 2019 will be presented in the following "ASCO Conference Report 2019 - Sarcomas/GIST".

CONTENT:

1) SOFT TISSUE SARCOMAS

1.1. BACKGROUND

Soft tissue sarcomas (STS) are a diverse group of rare tumors of mesenchymal origin comprising about 1 % of all malignancies in the adulthood. According to the 2013 updated World Health Organization (WHO) classification STS represents a highly heterogeneous tumor entity of more than 50 subtypes showing distinct histological, molecular and certainly clinical characteristics [1]. Conventional chemotherapy with doxorubicin and/or ifosfamide still represents the backbone of systemic treatment in the locally advanced and metastatic setting sequentially or in combination [2]. Since the early 1980's many trials have been investigating the addition of other chemotherapeutic drugs to doxorubicin in order to improve overall survival (OS). However, no statistically significant OS benefit could be demonstrated. Even in the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) 62012 phase III study including 455 patients treated either with single-agent doxorubicin or with a combination regimen of doxorubicin plus high-dose ifosfamide the primary endpoint, overall survival, could not be met. Although the overall response rate (ORR) was nearly doubled (27 % *vs* 14 %) and the progression-free survival (PFS) could be significantly prolonged in the combination arm (7.4 *vs* 4.6 months), the doxorubicin plus ifosfamide combination did not lead to a statistically significant improvement in OS (14.3 *vs* 12.8 months) even though showing far more toxicity than doxorubicin alone [3]. Olaratumab, a platelet-derived growth factor receptor alpha (PDGFRα) inhibitor, in combination with doxorubicin raised hope for a new first-line therapeutic option for advanced STS patients [4]; however, results of the phase III study could not confirm the initially observed OS benefit (see more details below). With the successful approval of trabectedin, pazopanib and eribulin for specific STS subtypes the treatment landscape in the clinical setting beyond first-line has been broadened and promising and well-tolerated systemic treatment options can be offered to our patients [5-8]. However, the prognosis of advanced STS patients is still unfavorable [9, 10]; median OS has increased during the last few years but is still approximately 15-18 months. Hence, there is clearly an unmet need to aim for new and innovative drugs as well as new treatment strategies in this disease [11]. Several promising agents have been investigated in recent years in large, multicentre, international registration trials. Few of them having proven efficacy were approved by the corresponding medical health authorities and reached marketing authorization. These compounds and new therapeutic agents and strategies presented at this year's ASCO Annual Meeting will be described in more detail in the following report.

1.2. COMPOUNDS AND CLINICAL STUDIES OF INTEREST FOR THE TREATMENT OF ADVANCED AND/OR METASTATIC SOFT TISSUE SARCOMA PATIENTS

Olaratumab is a recombinant human monoclonal antibody that binds to PDGFRα. PDGFRα activation by its ligand regulates cell proliferation, differentiation and survival. Olaratumab has been investigated in a phase Ib/II trial (n = 133) randomizing patients to a treatment with doxorubicin or doxorubicin combined with olaratumab. Not only PFS could be significantly prolonged by the addition of olaratumab (6.6 *vs* 4.1 months; *HR = 0.67; p = 0.0615*), an improvement in OS of 11.8 months (26.5 *vs* 14.7 months;

HR = 0.46; p = 0.0003) could be detected in favor of the combination arm for the treatment of locally advanced and metastatic STS [4]. Several limitations of the phase II trial have to be taken into account such as low patient numbers, a possible favorable selection of histologies, an unbalanced administration of olaratumab as maintenance therapy, etc. Based on the phase II results the European Medicines Agency (EMA) recommended the granting of a conditional marketing authorization for olaratumab in 2016. Unfortunately, the subsequent international, multicenter, phase III study (ANNOUNCE, NCT02451943) presented and discussed in the ASCO's 2019 Plenary Session could not confirm the initial promising phase II results. The study did not meet the primary endpoint of OS prolongation in either the overall population (20.4 *vs* 19.7 months for olaratumab plus doxorubicin *versus* doxorubicin plus placebo; *HR = 1.05; 95 % CI 0.84-1.30; p = 0.69*) or in the leiomyosarcoma sub-population (21.6 *vs* 21.9 months for olaratumab plus doxorubicin *versus* doxorubicin plus placebo; *HR = 0.95; 95 % CI 0.69-1.31; p = 0.76*). Median PFS was lower in the investigational arm in the whole population (5.4 *vs* 6.8 months; *HR = 1.23; 95 % CI 1.01-1.50; p = 0.04*) and in the subgroup of leiomyosarcoma patients (4.3 *vs* 6.9 months; *HR = 1.22; 95 % CI 0.92-1.63; p = 0.17*). The same could be detected for the ORR with a reduction in the investigational arm (14 % *vs* 18.3 %) [12]. In conclusion, ANNOUNCE did not confirm that olaratumab plus doxorubicin, followed by olaratumab monotherapy, improves OS over doxorubicin alone in patients with advanced STS. Possible reasons for the negative outcome of the study have been discussed by investigators, among them heterogeneity of the study populations within and between studies or differences in study designs. However, it was noted that patients in the doxorubicin control arm had the highest OS for doxorubicin treatment in any randomized trial in patients with STS – possibly due to a higher doxorubicin exposure.

Another drug candidate which has been evaluated in the first-line treatment of STS was **evofosfamide (TH-302)**, an investigational prodrug which is activated at low oxygen levels only. The side effect profile was expected to be lower when compared to conventional ifosfamide, which is characterized by a relevant incidence of neuro- and nephrotoxicity especially when given in high doses needed for STS treatment. The completed phase III trial (NCT01440088) was a global, randomized, open-label, multicenter, phase III study designed to assess the efficacy and safety of evofosfamide in combination with doxorubicin compared to doxorubicin alone in previously untreated patients with locally advanced, unresectable or metastatic STS. A total of 640 patients were randomized; the primary endpoint of the study was OS. As expected the response rate was better in the combination arm, 28.4 % *vs* 18.3 %, respectively. Disappointingly, no significant difference in median OS and PFS could be detected with the combination of evofosfamide plus doxorubicin when compared with doxorubicin single-agent, 18.4 *vs* 19 months (*HR = 1.06*) and 6.3 *vs* 6 months (*HR = 0.85; p = 0.099*), respectively. Interestingly, a significant improvement in OS was reported in the subgroup (n = 34) of synovial sarcomas, 22 *vs* 9 months (*HR = 0.32*), respectively, underlining the sensitivity of this STS subentity to oxazaphosphorine-based chemotherapy [13]. However, no further studies are planned.

ANNOUNCE as large negative phase III trial in advanced STS has been presented in the Plenary Session of this year's ASCO illustrating the failure of the development of olaratumab. The developmental story of both olaratumab and evofosfamide clearly shows how difficult it is to develop effective new

treatment options in first-line therapy for advanced STS patients and that a doxorubicin-based regimen continues to be the gold-standard even more than 40 years after its introduction into the STS treatment armamentarium. Please also read the discussion below.

After the registration of **trabectedin** in Europe in 2007 and **pazopanib** in 2012 for advanced STS subtypes, the results of another practice-changing trial have been published in 2016. The efficacy and safety of **eribulin**, an inhibitor of microtubule dynamics, has been evaluated in comparison with dacarbazine in an international, multicenter, phase III trial. 450 patients with pretreated, locally advanced or metastatic leiomyosarcoma or adipocytic sarcoma have been included. The inclusion of these two STS subtypes originated in a treatment benefit seen in these two strata in the previously conducted phase II trial by the EORTC / STBSG [14]. The primary endpoint OS was shown to be significantly improved by two months (13.5 *vs* 11.5 months; *HR = 0.77; p = 0.0169*) in favor of eribulin when compared to dacarbazine. In particular, subgroup analysis revealed an OS benefit in the liposarcoma cohort. Median OS was reported to be 15.6 months in the eribulin group *versus* 8.4 months in the dacarbazine treatment arm (*HR = 0.511; p = 0.0006*) [8]. Based on these results, EMA approved eribulin in 2016 for the treatment of adipocytic sarcomas in patients who received prior chemotherapy containing an anthracycline regimen.

Aldoxorubicin, a tumor-targeted doxorubicin conjugate, has been under investigation in recent years. The randomized phase II trial compared efficacy and safety parameters of aldoxorubicin *versus* doxorubicin in the first-line setting. Aldoxorubicin showed a significant prolongation of the PFS (5.6 *vs* 2.7 months; *p = 0.02*) and the 6-months PFS rate (46 % *vs* 23 %; *p = 0.02*). Notably, no cardiotoxicity was documented in the patients treated with aldoxorubicin [15] – unlike the situation with doxorubicin. The subsequent phase III study (n = 433, NCT02049905), however, investigated aldoxorubicin in the second-line setting when compared to treatment at investigator's choice (dacarbazine, pazopanib, gemcitabine plus docetaxel, doxorubicin, ifosfamide). Aldoxorubicin was not able to demonstrate a statistically significant improvement regarding PFS as the primary study endpoint (4.1 *vs* 2.9 months; *p = 0.087*) revealing a negative study for the whole study population. However, in the subcohort of L-sarcomas (leiomyosarcomas and liposarcomas, 57.5 %) aldoxorubicin could improve PFS (5.3 *vs* 2.9 months; *p = 0.007*) and the disease control rate (41.7 *vs* 27 %; *p = 0.016*). Interestingly, cardiotoxicity was less documented in the aldoxorubicin arm compared to the conventional doxorubicin arm rendering this compound an interesting alternative to conventional doxorubicin [16]. To date, it is unknown whether or not aldoxorubicin will play a role in the treatment of STS in the future.

Palbociclib, a selective CDK4/CDK6-inhibitor, and **DS-3032b**, a MDM2-inhibitor, have both been investigated for the treatment of well- and de-differentiated liposarcomas (WDLS/DDLS). Both targets act as important negative regulators of p53, a tumor suppressor gene. Several phase I and II trials have been reported and/or published so far [17-19]. Notably, palbociclib was associated with a favorable PFS rate of 66 % in patients with CDK4-amplified WDLS/DDLS who had progressive disease despite systemic therapy (NCT01209598) [18]. However, no further phase II/III development has been undertaken so far using these compounds. The newer and more potent CDK4-inhibitor **abemaciclib** presented this year in

the Sarcoma Oral Abstract Session has been evaluated in a phase II study specifically in DDLS (n = 30). The primary endpoint of the study was reached with a PFS rate at 12 weeks of 76 %; median PFS was 30.4 weeks. Grad 3/4 toxicities mainly comprised anemia (37 %), neutropenia (20 %) and thrombocytopenia (17 %) [20]. However, further development in phase III concepts is urgently needed.

Selinexor, an oral selective inhibitor of nuclear exportin protein, has been studied in STS and bone sarcomas [21]. Promising results have been published for the treatment of DDLS with selinexor in a phase I trial (NCT01896505). Although no objective responses could be demonstrated, 17 patients (33 %) showed durable (≥ 4 months) stable diseases [22]. Therefore, a seamless phase II/III trial (SEAL, NCT02606461) has been initiated which is currently recruiting patients with DDLS in the phase III portion also in Europe (n = 222).

Carotuximab (TRC105) is a monoclonal antibody targeting endoglin (CD105) which is expressed by tumor cells in angiosarcomas and up-regulated by VEGF-inhibition [23]. Hence, TRC105 is able to suppress angiogenesis and might enhance the activity of bevacizumab or pazopanib [24]. Based on this pathomechanism a phase Ib/II trial combining TRC105 with pazopanib (800 mg daily) has been conducted in STS (NCT01975519). A tumor reduction could be documented in five angiosarcoma patients; two of them had progressive disease on previous pazopanib therapy. Two patients with cutaneous angiosarcoma experienced a complete remission. Median PFS for the angiosarcoma patients was 12.9 months [25]. Unfortunately, an adaptive population enrichment phase III trial (TAPPAS, NCT02979899 [26]) investigating the combination of carotuximab and standard dose pazopanib compared to single-agent pazopanib 800 mg daily in patients with advanced angiosarcomas was stopped prematurely after the recruitment of 120 patients due to non-superiority of the combination arm compared to pazopanib single-agent. Once more, TAPPAS is an example of a negative phase III trial in STS in most recent years.

The revival of the therapeutic affectation of the immune system has revolutionized patients' outcome in many solid tumors in the last few years, in particular in melanoma [27]. This **Immunotherapy** approach is currently also being evaluated in sarcomas, even though with limited success. The largest published clinical phase II study has been performed by the Sarcoma Alliance for Research through Collaboration (SARC) study group. In total, 80 patients with STS and bone sarcomas from 12 participating centers have been treated with the PD1-inhibitor **pembrolizumab**. The primary endpoint was the response rate. An overall response rate of 18 % was reported for the 40 included STS patients. The heterogeneity of STS in terms of biology and response to systemic treatment could be confirmed once again by showing different response rates depending on sarcoma subtypes. A promising response rate of 40 % was reported for the undifferentiated, pleomorphic sarcoma cohort and 20 % for the liposarcoma cohort [28]. Enrolling an additional 30 patients in each of these two cohorts led to an overall response rate in the undifferentiated, pleomorphic sarcoma cohort of 23 % (9/40) and 10 % (4/39) in the liposarcoma cohort, respectively. Median PFS for the undifferentiated, pleomorphic sarcoma cohort was 3 months and for the liposarcoma cohort 2 months, respectively [29]. No doubt, further work has to be done in order to clarify the role of immunotherapy in STS. In particular, investigating potential

predictive markers on a molecular level for suggested differences in treatment sensitivity and evaluating the optimal treatment combinations of checkpoint inhibitors with chemotherapy, radiotherapy or targeted treatment options would be of major interest. Therefore, combination treatment strategies such as nivolumab plus sunitinib (IMMUNOSARC [30]) or doxorubicin plus pembrolizumab [31] are currently being investigated. While this study investigating doxorubicin plus pembrolizumab failed to meet its primary endpoint "response rate", a highly significant improvement in PFS was observed compared with historical controls. This is consistent with findings in other cancers, where improved clinical outcomes were observed without significant increase in response rate by RECIST. A randomized trial of this combination therapy will carefully be considered in light of recent negative trials in STS.

With STS being a highly heterogeneous tumor entity of more than 50 subtypes with distinct histological, molecular and certainly clinical characteristics, research more and more focuses on specific subtypes or cancer characterized by certain biomarkers.
At ASCO 2019, results of phase II study in epithelioid sarcoma (ES) were presented. ES is a rare soft tissue sarcoma that metastasizes in approximately 30% to 50% of cases. More than 90% of ES tumors lack expression of INI1, which allows EZH2, an epigenetic modifier, to become an oncogenic driver in tumor cells. **Tazemetostat** is a selective, oral inhibitor of EZH2. In the largest prospective clinical trial of ES to date, 62 INI1-negative ES pts were enrolled and treated with tazemetostat 800 mg twice daily (BID). Tazemetostat achieved disease control in 26% of patients with advanced ES, 15% of patients achieved partial responses (PRs). Durable clinical response of the drug was documented as well as a favorable safety profile. In May, tazemetostat was submitted for marketing approval at the US. Food and Drug Administration (FDA) for the treatment of patients with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery.[32]
Malignant PEComa - perivascular epithelioid cell tumors – is another rare sarcoma. It is aggressive, with no approved treatment. The AMPECT phase II trial is the first prospective study in malignant PEComa, which investigates **ABI-009 (nab-sirolimus)**, an albumin-bound mTOR inhibitor. Study participants received ABI-009 until progression or unacceptable toxicity. Overall response rate was 42%, median progression-free survival was 8.4 months. In summary, preliminary outcomes showed that ABI-009 treatment of PEComa resulted in substantial and durable responses with manageable toxicities. [33]

1.3. NEOADJUVANT TREATMENT STRATEGIES FOR PATIENTS WITH LOCALIZED SOFT TISSUE SARCOMAS

One of the basic questions regarding neoadjuvant treatment strategies in retroperitoneal STS is the question if the addition of a preoperative radiotherapy can improve the prognosis of this patient group. In this regard the EORTC / Soft Tissue and Bone Sarcoma Group (STBSG) initiated in cooperation with the EORTC / Radiation Oncology Group (ROG) a randomized phase III study (STRASS, EORTC 62092-22092) evaluating preoperative radiotherapy in addition to surgical intervention compared to surgery only in 266 patients with primary operable retroperitoneal STS. The treatment consisted of the preoperative radiotherapy starting eight weeks after randomization (28 fractions each 1.8 Gy to a total dose of 50.4 Gy) followed by a multivisceral, en-bloc resection of the tumor with potential curative intent (R0) within 4-8 weeks post radiotherapy. 266 patients from Europe, USA and Canada were randomized between January 2012 and April 2017; 198 patients (75 %) had liposarcomas. The primary endpoint is the abdominal recurrence-free survival (ARFS) defined by local relapse after complete resection, peritoneal sarcomatosis, R2 surgery, progressive disease during radiotherapy or unresectable disease.

The IDMC recommended a sensitivity analysis in which local progression on radiotherapy is not regarded as an event for patients who subsequently achieved complete surgical resection. The 3-year ARFS was 60.4 % and 58.7 % (*HR = 1.01; 95 % CI 0.71-1.44; p = 0.954*) in the radiotherapy / surgery *versus* surgery alone groups. In the sensitivity analysis, the 3-year ARFS was 66 % and 58.7 % in the radiotherapy / surgery *versus* surgery alone arms (*HR = 0.84; 95 % CI 0.58-1.21; p = 0.340*). In the liposarcoma subgroup, the 3-year ARFS (sensitivity analysis) was 71.6 % and 60.4 % in the radiotherapy / surgery *versus* surgery alone groups (*HR = 0.64; 95 % CI 0.40-1.01; p = 0.049*) reaching statistical significance. In summary, STRASS failed to demonstrate a benefit of preoperative radiotherapy for retroperitoneal STS patients. Interestingly, in the exploratory analysis, preoperative radiotherapy may at least benefit the liposarcoma subgroup [34].

A randomized trial from the Italian Sarcoma Group on five cycles of adjuvant **epirubicin** plus ifosfamide *versus* no chemotherapy suggested an OS benefit in localized high-risk STS. A subsequent trial showed no difference between three *versus* five cycles of the same neoadjuvant regimen. The aim of the current trial (ISG-STS 1001, NCT01710176) was to compare three cycles of epirubicin (120 mg/m²) plus ifosfamide (9 g/m²) chemotherapy *versus* a histology-tailored neoadjuvant regimen in selected localized high-risk STS subtypes: gemcitabine + docetaxel in undifferentiated pleomorphic sarcoma (n = 97), trabectedin in high-grade myxoid liposarcoma (n = 65), high-dose prolonged-infusion ifosfamide in synovial sarcoma (n = 70), etoposide + ifosfamide in malignant peripheral nerve sheath tumors (n = 27) and gemcitabine + dacarbazine in leiomyosarcoma (n = 28). From May 2011 to May 2016, 287 patients were randomized. Patients had localized high-risk (grade = 3; size ≥ 5 cm) STS of the extremities or trunk wall. The primary endpoint was the disease-free survival. The median follow-up was 52 months for the patients alive. The disease-free and OS probability at 5 years were 0.47 and 0.55 (*HR = 1.232; 95 % CI 0.875-1.733; p = 0.323*) and 0.66 and 0.76 (*HR = 1.766; 95 % CI 1.101-2.831; p = 0.018*), in the histology-tailored neoadjuvant regimen *versus* epirubicin plus ifosfamide arm, respectively. In conclusion, the final analysis showed a non-statistically significant disease-free survival difference in favor of the standard chemotherapy arm with a larger and statistically significant OS difference. Therefore, epirubicin plus ifosfamide should remain the regimen of choice when neoadjuvant chemotherapy is used in high-risk localized STS. However, this trial cannot be used as a formal proof of efficacy of (neo)adjuvant chemotherapy per se [35]. Therefore, EORTC / STBSG is currently setting up a worldwide, randomized phase III study (n = 250) to evaluate the role of neoadjuvant chemotherapy *versus* no treatment in retroperitoneal liposarcomas and leiomyosarcomas which is planned to start recruitment at the beginning of 2020 (EORTC 1809, STRASS 2).

2) BONE SARCOMAS

One oral presentation of interest on recurrent and primary refractory Ewing sarcomas has been presented at this year's ASCO in the Sarcoma Oral Abstract Session and is, therefore, included in this summary report. The 5-year OS for this patient group of Ewing sarcomas is about 15 %. Several chemotherapy regimens are used, however, lacking any robust evidence. The first randomized controlled trial in this setting (EORTC 1403, rEECur) is aiming to define a standard of care balancing efficacy and toxicity. Patients aged 4-50 years with recurrent and primary refractory Ewing sarcoma and

fit to receive chemotherapy were randomized between four different chemotherapeutic regimens: topotecan plus cyclophosphamide (TC), irinotecan plus temolozomide (IT), gemcitabine plus docetaxel (GD) or high-dose ifosfamide (IFOS). Primary outcome measure was the objective response after four therapy cycles. The first interim assessment to determine which arm should be closed occurred when 50 evaluable patients had been recruited to three arms and evaluated for the primary outcome measure. 242 patients recruited between December 2014 and June 2018 were randomized to TC (n = 75), IT (n = 71), GD (n = 66) and IFOS (n = 30). Median age was 21 years (range 4 to 49). Median follow up was 11.3 months. Outcomes in the gemcitabine plus docetaxel (GD) arm were: response rate 11.5 %, median PFS 3.0 months and median OS 13.7 months. For objective response and PFS, all comparisons favored the other three chemotherapy arms. However, there were fewer grade 3/4 adverse events with gemcitabine plus docetaxel than with the other arms (58 *vs* 74 %). In summary, rEECur could demonstrate that gemcitabine plus docetaxel is a less effective treatment than the other three tested regimens in reducing tumour burden or prolonging PFS in recurrent and primary refractory Ewing sarcoma patients. Recruitment continues to the remaining arms of the rEECur study [36].

3) GASTROINTESTINAL STROMAL TUMORS (GIST)

GIST is the most common mesenchymal malignancy of the gastrointestinal tract. Advanced GIST is commonly treated with tyrosine kinase inhibitors; however, most patients develop resistance over time. The most interesting GIST trial presented at this year's ASCO was the EORTC 1317 study (CaboGIST, NCT02216578) assessing the safety and activity of **cabozantinib** in GIST patients who had progressed on imatinib and sunitinib. In this multi-center, open-label, single-arm phase II study eligible metastatic GIST patients received 60 mg cabozantinib per os daily. The primary endpoint was the PFS rate at week 12. If at least 21 of 41 eligible and evaluable patients were progression-free at week 12, the activity of cabozantinib was sufficient to warrant further exploration. 50 patients were eligible and started treatment between 02/2017 and 08/2018, with one third still continuing cabozantinib at the database cut-off in January 2019. Among the first 41 eligible and evaluable patients, 24 were progression-free at week 12, satisfying the study decision rule. Among all 50 included patients, 30 (60 %) were progression-free at week 12. Seven patients achieved a confirmed partial response (14 %) and 33 had stable disease (66 %). Progression was seen in nine patients only (18 %), one was not evaluable. Hence, disease control was achieved in 40 patients (80 %). The median PFS was 6.0 months. The most common cabozantinib-related grade ≥ 3 adverse events were diarrhea (74 %), hand-foot syndrome (58 %), fatigue (46 %), hypertension (46 %), weight loss (38 %) and oral mucositis (28 %), with two thirds of patients requiring dose reductions. Taken together, EORTC 1317 met its primary endpoint, with 24/41 patients (58.5 %) being progression-free at week 12. The results of this trial confirm preclinical data and warrant further exploration of cabozantinib in GIST patients in a possible phase III study [37].

Updated results from the phase I study (NAVIGATOR, NCT02508532) of **avapritinib** in patients with advanced GIST were also presented in the Poster Discussion Session. The 4th line+ (n = 111) overall response rate for avapritinib was 22 % and in addition 52 stable diseases with a median duration of response of 10.2 months were observed. In the 62 patients with PDGFRα Exon 18 mutation (56 patients with D842V, 6 patients with non-D842V) the response rate was 86 % and five patients with stable

disease. The overall response rate and duration of response for avapritinib in 4th line+ clearly exceeds that of approved 2nd and 3rd line therapies and shows unprecedented activity in D842V and other Exon 18 mutant PDGFRα GIST. These results suggest that avapritinib has the potential to change the treatment paradigm of patients with advanced GIST in the near future [38].

4) SUMMARY AND DISCUSSION

Since the early 1970s systemic therapies for locally advanced and metastatic STS patients have been restricted to very few effective and approved agents such as doxorubicin and ifosfamide - and that hasn't substantially changed until today. In 2007, trabectedin has been granted approval only in Europe and later in 2015 worldwide; it has turned out to be an effective compound especially for liposarcoma and leiomyosarcoma patients with the ability to stabilize the disease for long time periods. The next two registrations for STS, pazopanib and eribulin, have both been developed systematically in the phase II within the EORTC / STBSG. Activity has been studied in four different strata - leiomyosarcoma, liposarcoma, synovial sarcoma and other subtypes - and further development of the drug has only been undertaken in those strata where predefined EORTC activity criteria have been met. For example, for pazopanib no activity could be demonstrated for the adipocytic stratum. Hence, liposarcoma patients were not included in the subsequent phase III study (PALETTE) and, consequently, they are excluded from the registration label [7]. For eribulin, activity could only be demonstrated in the liposarcoma and leiomyosarcoma strata. Hence, the subsequent phase III registration trial comparing eribulin to dacarbazine only included these two histologies [8]. This approach at least takes into account the perspective of disease groups and different histologies. In contrast, a number of large phase III trials in the last few years eventually failed (ridaforolimus, palifosfamide, evofosfamide and most recently olaratumab); exactly because disease subgroups were not taken into account and all histologies were lumped together in one trial. The Plenary Session of this year's ASCO including the presentation and discussion of the latest large phase III sarcoma trial (ANNOUNCE) being surprisingly negative clearly illustrates the complexity to develop new drug candidates especially in the first-line setting for this heterogeneous tumor entity of advanced STS patients. More and more upcoming clinical trials address specific subtypes such as SEAL evaluating selinexor in liposarcomas and are hopefully leading to a more "personalization of sarcoma treatment".

What new actions can we take from these lessons? What should we not do? We should only develop drugs with a clear scientific rationale and with clearly documented preclinical and early clinical activity. Empirical use of new drugs in different entities as it currently appears to be done in the immune-oncology field should be avoided. We should restrain from lumping together all histological subtypes in one trial. Rather to ensure that reimbursement follows licensing approvals, we should aim for meaningful treatment effects outweighing possible toxicities and drug costs and including patient reported outcome measures. We are definitely at a current breakpoint from classical drug development to more personalized strategies taking into account sequencing techniques with the possibility to identify patients for targeted therapies. However, we are still far away from designing a kind of personalized therapy for each of our patients. But with the number of registered drugs and the possibility to sequence them one after the other - even though we do not know which sequence is the

best - we have been able to significantly prolong the OS for our advanced STS patients in most recent years aiming to reach a two years median OS time [39].

5) TAKE-HOME-MESSAGES

- Patients suffering from sarcoma should be admitted to sarcoma centers early in their disease course. Sarcoma treatment should be concentrated in designated institutions with a high expertise in sarcoma diagnostics and therapy. The European Reference Network (ERN) for rare adult solid cancers (EURACAN) will certainly play a central role in this respect in the near future.
- Doxorubicin-based chemotherapy remains as the gold-standard treatment for locally advanced and metastatic STS patients in the first-line setting.
- Trabectedin, pazopanib and eribulin represent efficacious and well-tolerated treatment options beyond first-line therapy in several STS subtypes.
- Promising new drug compounds (palbociclib, abemaciclib, selinexor as well as tazemetosatat or nab-sirolimus etc.) and new therapeutic avenues such as immunotherapy are currently studied within ongoing clinical trials.
- The addition of preoperative radiotherapy to definitive surgical resection in retroperitoneal STS could not demonstrate a significant benefit for the whole study cohort; however, the liposarcoma subgroup may benefit.
- An anthracycline plus ifosfamide should remain the regimen of choice when neoadjuvant chemotherapy is administered in high-risk localized STS.
- Cabozantinib and avapritinib may enrich the therapeutic armamentarium for advanced GIST patients in the near future.
- Patients should preferably be treated within clinical trials, if available. International collaboration should be promoted in this matter.

Sarcoma Patients EuroNet

6) REFERENCES

1 Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone (IARC WHO Classification of Tumours), 4th edition, 2013.

2 Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Supplement 4): iv268-iv269.

3 Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014; 15: 415-23.

4 Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388: 488-97.

5 Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009; 27: 4188-96.

6 Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group (EORTC Study 62043). J Clin Oncol 2009; 27: 3126-32.

7 Van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379: 1879-86.

8 Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016; 387: 1629-37.

9 Clark MA, Fisher C, Judson I, et al. Soft-tissue sarcomas in adults. N Engl J Med 2005; 353: 701-11.

10 Blay JY, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003; 39: 64-9.

11 Nagar SP, Mytelka DS, Candrilli SD, et al. Treatment Patterns and Survival among Adult Patients with Advanced Soft Tissue Sarcoma: A Retrospective Medical Record Review in the United Kingdom, Spain, Germany, and France. Sarcoma. 2018: 5467057.

12 Tap WD, Wagner AJ, Papai Z, et al. ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). J Clin Oncol 2019; 37 (suppl; abstr LBA3).

13 Tap WD, Papai Z, Van Tine B, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2017; 18: 1089-103.

14 Schöffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011; 12: 1045-52.

15 Chawla SP, Papai Z, Mukhametshina G, et al. First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized Clinical Trial. JAMA Oncol 2015; 1: 1272-80.

16 Chawla SP, Ganjoo KN, Schuetze S, et al. Phase III study of aldoxorubicin vs investigators' choice as treatment for relapsed/refractory soft tissue sarcomas. J Clin Oncol 2017; 35 (Suppl; abstr 11000).

17 Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 2013; 31: 2024-28.

18 Dickson MA, Schwartz GK, Keohan ML, et al. Progression-Free Survival Among Patients With Well-Differentiated or Dedifferentiated Liposarcoma Treated With CDK4 Inhibitor Palbociclib: A Phase 2 Clinical Trial. JAMA Oncol 2016; 2: 937-40.

19 Gounder MM, Bauer TM, Schwartz GK et al. A phase 1 study of the MDM2 inhibitor DS-3032b in patients (pts) with advanced solid tumors and lymphomas. J Clin Oncol 2016; 34 (Suppl; abstr 2581).

20 Dickson MA, Koff A, D'Angelo SP, et al. Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma. J Clin Oncol 2019; 37 (suppl; abstr 11004).

21 Nakayama R, Zhang YX, Czaplinski JT et al. Preclinical activity of selinexor, an inhibitor of XPO1, in sarcoma Oncotarget 2016; 7: 16581-92.

22 Gounder MM, Zer A, Tap WD, et al. Phase IB Study of Selinexor, a First-in-Class Inhibitor of Nuclear Export, in Patients with Advanced Refractory Bone or Soft Tissue Sarcoma. J Clin Oncol 2016; 34: 3166-74.

23 Seon BK, Haba A, Matsuno F et al. Endoglin-Targeted Cancer Therapy. Curr Drug Deliv 2011; 8: 135-43.

24 Rosen LS, Gordon MS, Robert F, Matei DE. Endoglin for targeted cancer treatment. Curr Oncol Rep 2014; 16: 365.

25 Sankhala KK, Attia S, Barve MA et al. TRC105 (Endoglin antibody) in combination with pazopanib in patients with advanced angiosarcoma, CTOS annual meeting, poster #110.

26 Mehta CR, Liu L, Theuer C. An adaptive population enrichment phase III trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (TAPPAS trial). Ann Oncol 2019; 30: 103-8.

27 Nanda V, Peng W, Hwu P et al. Melanoma and immunotherapy bridge 2015. J Transl Med 2016; 14 (Suppl 1): 65.

28 Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017; 18: 1493-501.

29 Burgess MA, Bolejack V, Schuetze S, et al. Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. J Clin Oncol 2019; 37 (suppl; abstr 11015).

30 Martin Broto J, Hindi N, Redondo A, et al. IMMUNOSARC: A collaborative Spanish (GEIS) and Italian (ISG) Sarcoma Groups phase I/II trial of sunitinib plus nivolumab in selected bone and soft tissue sarcoma subtypes - results of the phase I part. J Clin Oncol 2018; 36 (suppl; abstr 11515).

31 Pollack S, Redman MW, Wagner M, et al. A phase I/II study of pembrolizumab (Pem) and doxorubicin (Dox) in treating patients with metastatic/unresectable sarcoma. J Clin Oncol 2019; 37 (suppl; abstr 11009).

32 Stacchiotti S, Schoffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). J Clin Oncol 37, 2019 (suppl; abstr 11003).

33 Wagner A, Ravi V, Ganjoo KN, et al. ABI-009 (nab-sirolimus) in advanced malignant perivascular epithelioid cell tumors (PEComa): Preliminary efficacy, safety, and mutational status from AMPECT, an open label phase II registration trial. J Clin Oncol 37, 2019 (suppl; abstr 11005).

34 Bonvalot S, Gronchi A, Le Pechoux C, et al. STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. J Clin Oncol 2019; 37 (suppl; abstr 11001).

35 Gronchi A, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: Final results of a randomized clinical trial from the Italian Sarcoma Group, the Spanish Sarcoma Group (GEIS), the French Sarcoma Group (FSG), and the Polish Sarcoma Group (PSG). J Clin Oncol 2019; 37 (suppl; abstr 11000).

36 McCabe M, Moroz V, Khan M, et al. Results of the first interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma. J Clin Oncol 2019; 37 (suppl; abstr 11007).

37 Schöffski P, Mir O, Kasper B, et al. Activity and safety of cabozantinib in patients with gastrointestinal stromal tumor after failure of imatinib and sunitinib: EORTC phase II trial 1317 CaboGIST. J Clin Oncol 2019; 37 (suppl; abstr 11006).

38 Heinrich MC, Jones RL, von Mehren M, et al. Clinical activity of avapritinib in ≥ fourth-line (4L+) and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). J Clin Oncol 2019; 37 (suppl; abstr 11022).

39 Kasper B. The challenge of finding new therapeutic avenues in soft tissue sarcomas. Clin Sarcoma Res 2019; 9: 5.