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Review

Paediatric Strategy Forum for medicinal product development of multi-targeted kinase inhibitors in bone sarcomas
ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration

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Abstract The eighth Paediatric Strategy Forum focused on multi-targeted kinase inhibitors (mTKIs) in osteosarcoma and Ewing sarcoma. The development of curative, innovative products in these tumours is a high priority and addresses unmet needs in children, adolescents and adults. Despite clinical and investigational use of mTKIs, efficacy in patients with bone tumours has not been definitively demonstrated.

Randomised studies, currently being planned or in progress, in front-line and relapse settings will inform the further development of this class of product. It is crucial that these are rapidly initiated to generate robust data to support international collaborative efforts. The experience to date has generally indicated that the safety profile of mTKIs as monotherapy, and in combination with chemotherapy or other targeted therapy, is consistent with that of adults and that toxicity is manageable.

Increasing understanding of relevant predictive biomarkers and tumour biology is absolutely critical to further develop this class of products. Biospecimen samples for correlative studies and biomarker development should be shared, and a joint academic-industry consortium created. This would result in an integrated collection of serial tumour tissues and a systematic retrospective and prospective analyses of these samples to ensure robust assessment of biologic effect of mTKIs.

To support access for children to benefit from these novel therapies, clinical trials should be designed with sufficient scientific rationale to support regulatory and payer requirements. To achieve this, early dialogue between academia, industry, regulators, and patient advocates is essential. Evaluating feasibility of combination strategies and then undertaking a randomised trial in the same protocol accelerates drug development. Where possible, clinical trials and development should include children, adolescents, and adults less than 40 years.

To respond to emerging science, in approximately 12 months, a multi-stakeholder group will meet and review available data to determine future directions and priorities.

1. Introduction

Multi-stakeholder involvement is crucial to optimise decision-making in anti-cancer drug development in children and adolescents. Paediatric Strategy Forums equally involve all stakeholders (patient advocates, clinical academics, scientists, pharmaceutical companies, and regulators) in dialogue on topics requiring discussion around drug development in children and adolescents with malignancy. The eighth multi-stakeholder Paediatric Strategy Forum was organised by ACCELERATE [1,2] in collaboration with the European Medicines Agency (EMA) with participation of the Food and Drug Administration (FDA) and focused on multi-targeted kinase inhibitors (mTKIs) in bone sarcomas. Previous Paediatric Strategy Forums [3–8] have shared information between all stakeholders, evaluated science and informed paediatric drug development strategies and subsequent decisions. The ultimate aim of the Forums is to prioritise innovative medicines that will improve rates of cure and reduce toxicity, and introduce them into front-line standard of care for children and adolescents with cancer.

Curative treatment for bone sarcomas represents an unmet need in children, adolescents and adults. mTKIs have demonstrated biological activity against a wide range of sarcomas *in vitro, in vivo* [9] and in clinical trials in adult sarcoma patients [10] and children and adolescents with soft tissue sarcoma [11]. There are many mTKIs under investigation and used off label in clinical practice. However, their efficacy in paediatric patients with bone tumours has not been definitively demonstrated to date.

The Paediatric Strategy Forum aimed to review current data on mTKIs and define the best strategy to evaluate their use in osteosarcoma and Ewing sarcoma. The Forum addressed the following questions: (i) Are there mTKIs of sufficient relevance (based on biology, non- and clinical evidence) in bone sarcomas that warrant further development? (ii) What should the approach be to identifying relevant biomarkers? (iii) Are there any mTKIs not relevant to bone sarcomas? (iv) When moving mTKIs into combination therapy in bone sarcomas, how should drug selection, dosing and schedule be approached in order to optimise efficacy and minimise toxicity? (v) During what stage of therapy should mTKIs be employed?

The meeting was held virtually on 30 November and 1 December 2021 with 180 participants: 107 international paediatric and adult oncology experts and scientists investigating the biology of mTKIs from Europe, USA, Canada and Australia; 22 representatives from eight pharmaceutical companies in Europe and USA (Allarity, Bayer, Blueprint Medicines, Eisai GmbH, Exelixis, Ipsen Pharma, HUTCHMED, and Oncoheroes); 21 patient advocates from Europe, USA and Canada (Andrew McDonough B+ Foundation, Ac2orn and Kindred Foundation, Childhood Cancer Canada, Children's Cancer Cause, Coalition Against Childhood Cancer, Euro Ewings Consortium, Karkinaki Awareness for Childhood and Adolescent Cancer, KIDS V CANCER, KickCancer, Imagine for Margo, MIB Agents, The Myrovlytis Trust, Osteosarcoma Institute, PORT, Solving Kids' Cancer, Solving Kids' Cancer UK, Swedish Childhood Cancer Fund, Zoé4life and Childhood Cancer International); 29 regulators from the EMA (including Paediatric Committee [PDCO]) and national competent authorities within the EU regulatory network, US FDA and Health Canada as observers and ACCELERATE as organiser. An overview of the existing trials of mTKIs in bone sarcomas was followed by a review of the relevant biology, and then a presentation of the current plans and needs for mTKIs in osteosarcoma and Ewing sarcoma by academic experts. Lessons learnt from soft tissue sarcomas and a perspective from adult oncology provided context to the discussion. Details of seven mTKIs were highlighted by industry representatives (Table 1). The Forum concluded with the patient advocate perspective and a multi-stakeholder strategic discussion.

2. Relevant biology of mTKIs in bone sarcomas

There is growing knowledge about the biology of specific kinases and kinase signalling pathways in osteosarcoma and Ewing sarcoma cells, acquired from studies of tumour models *ex vivo* [12–14] (Fig. 1). Knowledge of the contribution of these protein kinases and kinase signalling pathways to tumour initiation and progression in their *in vivo* microenvironments is limited. In addition, specific biomarkers that can be used to predict if, when and how mTKIs will be effective in either tumour type are lacking. Tumours with specific kinase mutations respond well to TKIs targeting those specific mutations in the cancer (e.g. BCR-ABL in CML [15]; ALK in ALCL and IMT [16,17], EGFR in lung cancer [18]; B-RAF in melanoma, gliomas and Langerhans cell histiocytosis [19]). Hyperactivation of a kinase/pathway can also confer sensitivity (e.g. EGFR amplification) [20]. However, in osteosarcoma and Ewing sarcoma, there are no recurrent kinase mutations, nor evidence of

Table 1
Medicinal products discussed at the Paediatric Strategy Forum.

Product	pcKinases inhibited	PIP	WR	Planned paediatric clinical development in bone sarcoma
Aykavit®, avapritinib, Blueprint medicines	KIT/PDGFRA (highly selective and potent)	+	−	Phase 1/2, solid tumours dependent on KIT or PDGFRA signalling
Cabometyx®/Cometriq®, cabozantinib, Ipsen pharma/ Exelixis	VEGFR2, MET and AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3 and TIE-2	+	−	Monotherapy, combination and planned in front-line in osteosarcoma (COG)
Dovitinib, Oncoheroes/Allarity	FGFR, VEGFR, PDGFR and other RTKs.	−	=	Phase IB-2 osteosarcoma (DRP® biomarker-driven)
Lenvima®/Kisplyx®, lenvatinib, Eisai GmbH	VEGFR1, VEGFR2, VEGFR3 and FGFR1, 2, 3 and 4, PDGFRα, KIT and RET	+	+	Monotherapy, combination (with chemotherapy and other targeted therapy) and randomised phase 2 (OLIE)
Nexavar®, sorafenib, Bayer	CRAF, BRAF and mutant BRAF and KIT, FLT-3, RET, RET/PTC, VEGFR1, VEGFR2, VEGFR3, PDGFR-β.	−	−	Phase 1 and 2 − limited activity in paediatric phase I and combinations studies which included osteosarcoma and Ewing (Completed)
Surufatinib, HUTCHMED	VEGFR1, 2, 3, FGFR1 and CSF-1	−	−	Phase 1/2 in osteosarcoma, Ewing, and soft tissue sarcoma in combination with gemcitabine
Stivarga®, regorafenib, Bayer	RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, Abl, and CSF-1	−+	−	Monotherapy, combination and planned in front-line in Ewing sarcoma (INTER EWING-1)
Votrient®, pazopanib, Novartis[a]	VEGFR1, VEGFR2, VEGFR3, PDGFRα and PDGFRβ; and c-K	+	−	Phase 2 single agent closed early due to lack of sufficient signal in Ewing and osteosarcoma [87]

PIP, Paediatric Investigation Plan; WR, Written Request.
[a] Company not present.

kinase hyperactivation, although vascular endothelial growth factor A (VEGFA) amplifications have been described in osteosarcoma [21]. Thus, the choice for an mTKI rather than a TKI selective for a single mutation/ receptor (single-targeted TKI) is based on empirical studies and clinical observations rather than specific molecular targeting or mechanistic data. Generally, the efficacy of TKIs in the clinic depends on achieving a wide therapeutic index (*vs.* off-tumour/on-target toxicity). Resistance can quickly occur to a single-targeted TKI through acquisition of de novo mutations or via alternate escape mechanisms [22]. For example, CML cells that are exposed to imatinib acquire resistance by developing de novo mutations in the ABL kinase domain [23], and this mechanism of acquired resistance can also emerge in patients who are treated with Gleevec or other approved targeted ABL inhibitors. Similarly, B-RAF V600E mutant melanoma cells that are exposed to a targeted MEK inhibitor rapidly evolve bypass mechanisms including new mutations, gene amplification, and altered splicing to restore activation of MAPK signaling [24]. Combining individual kinase inhibitors to simultaneously target bypass mechanisms and combining mTKIs with chemotherapy can diminish acquired resistance and improve outcomes [25]. The use of mTKIs rather than a single-targeted TKI can therefore be preferable given that resistance is theoretically less likely to develop quickly with mTKIs as they inhibit multiple targets simultaneously [22]. mTKIs have a complex effect on tumour cell biology, angiogenesis, and the immune microenvironment [26], which pose further challenges in interpreting which specific receptor is relevant, and if simultaneous inhibition of receptors is needed [12–14]. The complexity of bone sarcoma microenvironments poses unique challenges for preclinical evaluation of these mTKIs. The relevant targets of the agents may be expressed on tumour cells and/or on non-tumour stromal cells uniquely in the context of distinct tumour microenvironments. For example, testing novel TKIs in *in vitro* models or in non-orthotopic tumour sites such as subcutaneous xenografts does not reflect the primary tumour microenvironment of bone sarcomas in patients. As such, the ability of these assays to reliably predict response in patients with bony disease is low. Likewise, some mTKIs may be highly relevant in the context of lung metastatic microenvironments but not in the bone given that the relevant protein target(s) of the drug may be active in one but not the other anatomic site. An additional limitation in this regard is the lack of samples for biomarker analyses at initial diagnosis and relapse, given that prior treatment can also alter the tumour microenvironment. In summary, there is an increasing knowledge of the genetics of bone sarcomas, particularly how *EWSR1:ETS* fusions in Ewing sarcoma drive tumourigenicity [26,27]. However, robust evidence for the

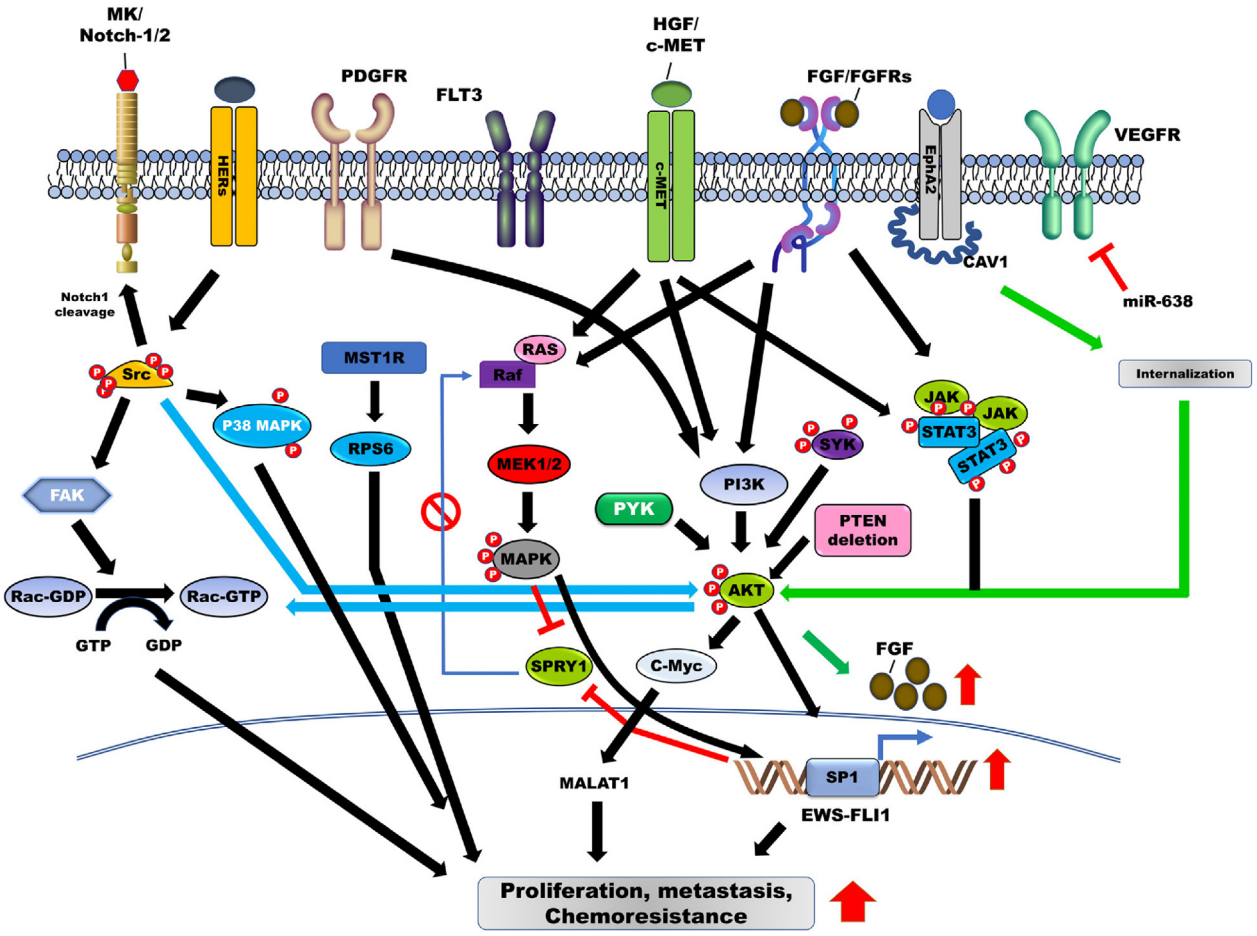

Fig. 1. Contribution of tyrosine kinases in the induction of survival, metastasis, and chemoresistance in Ewing sarcoma through the activation of downstream signalling pathways Tyrosine kinase receptors and non-receptor tyrosine kinase, including HGF/MET, EphA2, c-kit, HER2/3/4, ALK, PDGFR/PDGF, J AK/STAT, SFK, PYK22, FLT3, AXL, and SYK are involved in the pathogenesis of ES by blocking feedback inhibition of RAS/MAPK/ERK by SPRY1 and upregulation of EWS-FLI-1 through the activation of RAS/MAPK/ERK, PI3K/AKT, and JAK/STAT3 signalling pathways. Additionally, Src activation leads to cell proliferation and metastasis of Ewing sarcoma cells via induction of Rac1 activity through the activation of p38 MAPK, FAK, and PI3K/AKT signalling pathways. HGF, hepatocyte growth factor; EphA2, erythropoietin-producing hepatoma receptor A2; STAT3, signal transducer and activator of transcription-3; FAK, focal adhesion kinase; MAPK - mitogen-activated protein kinase; JAK - Janus kinase. (Reproduced from Jin W. The Role of Tyrosine Kinases as a Critical Prognostic Parameter and Its Targeted Therapies in Ewing Sarcoma. *Front Cell Dev Biol*. 2020; 8:613. https://doi.org/10.3389/fcell.2020.00613).

role of specific kinase dependencies in either osteosarcoma or Ewing sarcoma cells is lacking. Nevertheless, clinical responses to mTKIs have been observed supporting the premise that mTKI therapy may have value for at least a proportion of patients with bone tumours. Moreover, given that the exact mode of action of mTKIs in bone sarcomas remains unknown, the available evidence strongly suggests that to be effective in bone tumours, mTKIs should target signalling pathways that are active in both tumour cells and the non-tumour stroma. To enable more clinically predictive testing of mTKIs for bone sarcomas, future research should prioritise use of preclinical models that accurately reflect the complexity of bone sarcoma tumour microenvironments. These models should consider the unique biochemical and biophysical properties of the bone including non-tumour stromal cells, extracellular matrix proteins, mineralisation, pH, and hypoxia.

3. Challenges for biomarkers in bone sarcomas

There are no known recurrent kinase mutations to target or to subsequently track with circulating DNA, and studies of circulating bone tumour cells are not feasible outside limited institutions (and is still a research question). A major gap in the field, and one that has continued to challenge the development of predictive biomarkers for mTKI efficacy, is that an integrated collection of serial tumour tissues has not been prospectively organised. In addition, in trials where tumour tissue has been collected, systematic retrospective analyses of these archived

samples has not been prioritised for study. It was agreed by academics, industry, and patient advocates present that, given these limitations, a mechanism should be developed to share tissue samples. Furthermore, clinical and technical issues complicate evaluation of pharmacodynamic biomarkers in bone tumours exposed to mTKIs. Obtaining tissue is problematic as there is a need for on-treatment biopsy. In cases where such tissue can be collected, heterogeneity of signal and decalcification of bone can interfere with many assays. IGF1R inhibitor trials in Ewing sarcoma highlight the challenges of identifying biomarkers and the importance of including prospective sample collection. Despite the collective observation that ~10–15% of patients with Ewing sarcoma respond to IGF1R pathway inhibition [28], there remains no biomarker or genetic marker to identify responders in advance.

4. Activity of mTKIs as monotherapy in bone sarcoma

Determining the early signal of activity in osteosarcoma is challenging [29] because of the osseous nature of these malignancies and applying conventional metrics such as objective response rates may not be feasible. For osteosarcoma, the academic community has employed 4-month progression-free survival (PFS) as a metric to compare the activity of mTKIs in single arm trials in patients with measurable or evaluable disease and 12-month PFS for those with completely resected disease in refractory/relapsed osteosarcoma [30]. An overview of these trials is depicted in Table 2. For relapsed/refractory osteosarcoma with monotherapy, the 4-month PFS ranged from 38% to 71%. In two separate randomised evaluations, the 4-month PFS for an mTKI was 65% and 44% compared to 0% and 10% for placebo. In relapsed/refractory Ewing sarcoma, the best response was partial response in 26% and 22% of patients following an mTKI.

In summary, there is a signal of activity of mTKIs in relapsed or refractory osteosarcoma and Ewing sarcoma although the impact is modest for single agents in relapsed patients with prolongation of PFS (osteosarcoma) and a small subset of objective responders (Ewing sarcoma). The limitations of the existing data include that most of the enrolled subjects were adults and in osteosarcoma, where a sizable subset of patients with relapsed disease had no evidence of disease after resection and therefore activity could not be studied.

5. Bone sarcoma management

5.1. Osteosarcoma

The current internationally recommended approach for high-grade osteosarcoma, following biopsy, is the use of neo-adjuvant chemotherapy such as cisplatin, doxorubicin, and high-dose methotrexate (MAP) [31], methotrexate-etoposide-ifosfamide (M-EI) [32] or a doxorubicin-cisplatin-ifosfamide-based regimen (API-AI) [33]. Essential to the treatment is surgical resection of the primary tumour and metastases aiming for wide margins. Surgery is followed by further adjuvant chemotherapy. With this approach the overall 5-year EFS for resectable, non-metastatic osteosarcoma is approximately 60% and 30% for metastatic patients [31–34].

The addition of mTKIs is being considered in the front-line setting throughout therapy to improve EFS. The Children's Oncology Group (COG) is developing a front-line study (AOST2032), which will be a feasibility and randomised phase 2/3 study of cabozantinib in combination with MAP chemotherapy. In the first phase, the feasibility will be assessed with particular regard to overlapping toxicities (hepatotoxicity and mucositis), pharmacokinetics of cabozantinib/chemotherapy, effects on surgical complications and wound healing, and maintaining chemotherapy intensity. This will then be followed by a randomisation of MAP with or without cabozantinib, with EFS as the primary endpoint.

In France, the ongoing REGOSTA study (NCT04055220) is randomising patients over the age of 16 years, with osteosarcoma and other bone sarcomas (excluding Ewing sarcoma), chondrosarcoma and chordoma in complete remission at the end of first-line treatment to placebo or regorafenib, without cross over [35]. The ongoing REGOMAIN study (NCT04698785) is randomising patients, over the age of 16 years, with high-grade bone sarcomas with the same histological types as for REGOSTA who are not in complete remission at the end of first-line treatment, or relapse, to placebo or regorafenib with the possibility of cross over (open in France) [36].

The prognosis for relapsed disease is poor (3-year PFS about 21% [34,37,38]). In the relapsed setting, mTKIs are being evaluated both in measurable disease and in completely resected disease. In Europe, in the setting of recurrent measurable and evaluable (non-measurable) disease, the OLIE, Innovative Therapies for Children with Cancer (ITCC)-082 randomised study is evaluating if the combination of lenvatinib with ifosfamide and etoposide is superior to ifosfamide and etoposide alone in children, adolescents and young adults with relapsed/refractory osteosarcoma (NCT04154189) [39]. The primary endpoint is PFS, and results are expected in approximately 12 months. In the USA, there is also an ongoing academic trial of cabozantinib with cyclophosphamide and topotecan for osteosarcoma and Ewing sarcoma (NCT04661852) [40]. In addition, COG is planning a phase 2 single-arm study of adjuvant mTKI in completely resected recurrent osteosarcoma with the primary endpoint being disease control rate at 12 month compared to the historical benchmark (20% PFS at 12-months), which has been used for several studies.

Table 2
Monotherapy studies of relevant mTKIs in osteosarcoma and Ewing sarcoma -measurable disease and 12-month PFS for those with completely resected disease (Some of these studies have been conducted exclusively in adults).

Product		N/NE	Age (median/range) (years)	Responses (%:95% CI****)	4 month PFS% 95% CI	Median PFS (mos) 95% CI	Median OS (mos) 95% CI
Osteosarcoma							
Sorafenib [83]***		35	21 (15–62)	3 (8) PR 2 (6) MR 12 (34) SD	46 (28–63) – KM	4 (2–5)	7 (7–8)
Lenvatinib [84]		31	15 (9–22)	2 PR (7 [0.8–22)]) 13 SD	37.8 (20.0–55.4) – BE 29.0 (14.2–48.0) – BE	3.0 (1.8–5.4)	7.7 (5.5 – NES)
Regorafenib [85]	Regorafenib [85]	29/26	33 (22–50)	2 (8) PR 15 (58) SD	65 (47 one-sided 95% CI)[a]	4 (2–6.5)	11.3 (5.9–23.9)
	Placebo [85]	14/12	‡	0	0*	‡	‡
Regorafenib [86]#	Regorafenib [86]#	22/22	33 (18–70)	10 (26 [13–42) PR 19 (49) SD	44	3.6 (2.0–7.6)	11 0.1 (4.7–26.7)
	Placebo [86]	20/20	47 (19–76)	0	10 (‡)	1.7 (1.2–1.8)	13.4 (8.5–38.1)+
Cabozantinib [87]		45/42	34 (20–53, IQR)	5 PR (12: 4–26)	71 (55–83)	6.7 (5.4–7.9)	10.6 (7.4–12.5)
Apatinib [88]		37	23.4 (16–62)	16 PR (43)	56.76 (39.43–70.84)	44.50 (3.47–6.27)	9.87 (7.97–18.93)
Ewing Sarcoma							
Regorafenib [89]	Regorafenib [89]	23	‡	PR 5 (22) SD 11 (48)	13 (56.6: 37.5-NES)**	‡	‡
	Placebo [89]	13	‡	PR1 (8) SD 3/(23)	1 (7.7: 0.4-NES)**	‡	‡
Cabozantinib [87]		45/39	33 (IQR 24–45)	10 PR (26: 13–42)	‡	4.4 (3·7–5·6)	10.2 (8.5–18.5)
Pazopanib [90]		10	‡	0	‡	2.3	‡

* 8 weeks, ** at 12 weeks, *** Exclusively in adults, **** If available, ‡ Data not available, # Randomised, + - crossover; N - number enrolled, NE - number evaluable, NES - not estimable, PR - partial response, MR – mixed response - <30% tumour shrinkage, SD – stable disease, KM - Kaplan -Meier estimate, BE - binomial estimate.

5.2. Ewing sarcoma

The general approach in Europe and North America for localised Ewing sarcoma is induction chemotherapy with vincristine, doxorubicin, cyclophosphamide/ifosfamide, and etoposide (VDC/IE). This is followed by local control (generally with surgery with or without radiotherapy), followed by consolidation chemotherapy [34,41–47]. With this approach, the 5-year EFS is approximately 75–80% [46]. The approach to metastatic Ewing sarcoma includes induction chemotherapy followed by local control, consolidation therapy and radiotherapy to metastatic sites. Patients with isolated pulmonary metastases have a better outcome than those to other sites, including bone, but survival is still poor (3-year PFS about 50%) [48]. Multi-site metastatic Ewing sarcoma has a dismal prognosis.

The addition of mTKIs is being considered in the front-line setting in multi-metastatic disease with the aim to improve EFS. The INTER EWING-1 study is planning a dose confirmation phase of vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide (VDC/IE) with regorafenib followed by a randomised phase of VDC/IE with or without regorafenib. COG is also developing a front-line study that incorporates an mTKI for patients with metastatic Ewing sarcoma.

The prognosis for relapse disease is very poor (median PFS about 7 months) [48]. There is an ongoing academic trial of cabozantinib with cyclophosphamide and topotecan for osteosarcoma and Ewing sarcoma (NCT04661852) [39]. The combination of lenvatinib and ifosfamide is the next arm being planned in the rEECur study for relapsed Ewing sarcoma as high-dose ifosfamide alone had a favourable outcome when compared to the other treatment arms (cyclophosphamide and topotecan, irinotecan and temozolomide, gemcitabine and docetaxel) in the multi-arm randomised phase [49]. Lenvatinib is also being assessed in combination with everolimus in all solid tumours, including Ewing sarcoma (NCT03245151) [50].

6. Lessons from soft tissue sarcoma

Regorafenib has been evaluated by the ITCC as single agent and subsequently in combination with chemotherapy in paediatric patients with recurrent or refractory solid malignancies (NCT02085148) [51]. It has been shown that regorafenib can be combined with standard dose vincristine and irinotecan in a sequential dosing schedule [52,53]. Safety was manageable with dose modifications and there was no evidence of drug–drug interaction between regorafenib and irinotecan. Clinical activity was observed in patients with rhabdomyosarcoma (7 responses out of 12 patients, 1 complete response and 6 partial responses [PR]) and Ewing sarcoma (3 PR out of 5 patients). The European Paediatric Soft tissue sarcoma Study Group (EpSSG) is going to evaluate the combination of regorafenib, vincristine and irinotecan in the FaR-RMS study in relapsed rhabdomyosarcoma (NCT04625907) [54].

COG has evaluated pazopanib in non-rhabdo myosarcoma soft tissue sarcomas (ARST1321 trial) [11]. There was a statistically significant higher complete pathologic response rate in patients receiving chemo-radiation with pazopanib compared to chemo-radiation alone. Also, the combination was feasible; pazopanib did not significantly alter doxorubicin pharmacokinetics [55], toxicities were expected (myelotoxicity) and manageable, and wound complication rates comparable between arms.

7. Adult perspective

The peak incidence of patients with osteosarcoma and Ewing sarcoma is adolescence, but a significant proportion are adults and older adults [56,57]. The outcome for adults with osteosarcoma and for patients above 14 years of age with Ewing sarcoma is inferior [58,59]. The reasons for this are unclear; however, they are likely to be multifactorial and include (i) lack of access to specialist multi-disciplinary care; (ii) lack of access to clinical trials; (iii) differences in biology in some patients due to predisposing factors such as prior exposure to radiation; (iv) differences in primary sites in older patients; (iv) differences in chemotherapy tolerance and response. The lack of agreed standard of care for osteosarcoma globally hinders progress. There is a need for studies evaluating mTKIs to be inclusive of age and high risk groups including those with inoperable and late stage disease. This would have many advantages including defining a new standard of care and requiring a better understanding of the diseases at the molecular level and the role of mTKI in treating the diseases. This could be achieved through even greater engagement across paediatric and adult sarcoma research communities throughout Europe and North America.

8. Products discussed at the forum, paediatric investigation plans and written requests

Eight medicinal products (Aykavit®, avapritinib, Blueprint medicines; Cabometyx®/Cometriq®, cabozantinib; Ipsen pharma/Exelixis; Dovitinib, Oncoheroes/Allarity; Lenvima®/Kisplyx®, lenvatinib, Eisai GmbH; Nexavar®, sorafenib, Bayer; Surufatinib, HUTCHMED; Stivarga®, regorafenib, Bayer; Votrient®, pazopanib, Novartis) were discussed at the Forum (Table 1).

As of November 2021, there were five published Paediatric Investigation Plans (PIPs) agreed for mTKIs relevant to osteosarcoma and Ewing sarcoma: Votrient®, pazopanib (Novartis); Cometriq®, cabozantinib (Ipsen Pharma); Aykavit ®, avapritinib (Blueprint medicines);

Kisplyx® and Lenvima ®, lenvatinib (Eisai GmbH); and Stivarga®, regorafenib (Bayer). However, there are only two PIPs which specifically mention bone tumours as a condition or indication: Votrient®, pazopanib (Ewing sarcoma) and Kisplyx®, lenvatinib (osteosarcoma and Ewing sarcoma). There are no PIPs which include a randomised trial in front line in bone sarcomas (Table 3). The FDA issued the original Written Request for lenvatinib in 2020 for children adolescents and young adults with refractory or relapsed solid tumours including Ewing sarcoma, rhabdomyosarcoma, high-grade glioma and osteosarcoma.

9. Discussion

9.1. Patient advocates' perspective

The patient advocates highlighted that plans to discover biomarkers and tailor treatments were high priority and had not occurred in previous studies as they had expected. They strongly supported strategies for academic researchers to access and analyse retrospectively tissue obtained in industry-led, as well as academic trials and they believed there was an ethical obligation to analyse these materials. They advised that in new trials, tissue banking and analysis should be mandatory.

As survival rates for metastatic Ewing sarcoma have not significantly improved over the past 30 years and the picture is comparable for osteosarcoma, patient advocates believe that research needs to move forward urgently. It is crucial that the most relevant trials are identified and initiated, innovative methodology is employed to safely reduce timeframes and have registrational intent with active involvement of regulators.

The patient advocates stressed that the goal should be that all children and adolescents with bone sarcomas should have access to an interventional clinical trial and criteria for inclusion in trials should facilitate accrual. The patient advocates were concerned about statements such as 'we study the drugs companies are willing to give us' and call on colleagues in the pharmaceutical companies to do all they can to support those priorities identified in this Forum and to start clinical studies only when they are backed by solid data. The choice of a drug to be studied in a clinical trial should not derive from pragmatism but by scientific evidence. It is encouraging to learn of proposals for major trials in Europe and North America. Dialogue between the trial leaders to make these ventures complementary is welcome and hopefully the HIBiSCus (Harmonization International Bone Sarcoma Consortium) [60], which aims at building an international common clinical database for bone sarcomas, can ease this process. The possibility of inter-continental collaboration on trials in which small numbers of potential participants could be pooled is a promising option, as has occurred in the TITAN project in neuroblastoma [61] and GLO-BNHL for B-cell lymphoma. Patient advocates can play many roles in research, for example, championing accessing stored tissue and aiding the recruitment of trial participants. Their early engagement in study concept discussion could lead to valuable insight for industry to better understand the treatment pathway, patient community and commercialisation impact [62].

9.2. General themes

9.2.1. Evaluation of mTKIs in osteosarcoma and E. sarcoma

mTKIs warrant further evaluation in bone tumours in combination with other agents and in minimal disease settings. mTKIs could be of benefit both in overt disease (AOST2032, INTER EWING-1 and COG front-line study in patients with metastatic Ewing sarcoma) and in minimal disease (REGOSTA [35]). The results of ongoing trials in both these settings should provide clarity. The situation is complex as there are many products in class in diseases overlapping with adults, lack of understanding of disease biology, and studies in relapse and planned for front line. The need now is to generate robust data in an international/collaborative effort to quickly allow definitive conclusions on efficacy in the front-line population. For instance, AOST2032 randomising MAP chemotherapy with or without cabozantinib; REGOSTA [35]/ REGOMAIN [36] studies randomising regorafenib at the end of first-line treatment in bone sarcomas; INTER EWING-1 randomising VDC/IE with or without regorafenib in patients with metastases and the COG front-line study in patients with metastatic Ewing sarcoma will be highly informative studies. The REGOSTA [35]/ REGOMAIN [36] studies will provide data regarding role of mTKIs in maintenance therapy. Very close alignment between INTER EWING and COG will be important. Prospectively designing studies that evaluate feasibility and then undertake a randomised trial in the same protocol accelerates drug development (AOST2032 and INTER EWING-1). Moreover, the OLIE randomised study (NCT04154189) [39] (results expected in approximately 12 months) and rEECur [49] will provide important data in relapsed osteosarcoma and Ewing sarcoma, respectively.

The adjuvant use of mTKIs (sorafenib, pazopanib, axitinib and sunitinib) in non-bone adult malignancies, with adjuvant defined as use in patients who have had their disease completely resected or have had their local disease treated with curative radiation therapy, has shown limited success in randomised clinical trials in renal cell carcinoma [63–65]. Similarly in hepatocellular carcinoma, the STORM trial compared sorafenib to placebo and there was no difference in median recurrence-free survival between the two groups [66]. However, these trials are in adult malignancy and do not address the use of mTKIs given concurrently with

Table 3
Published PIPs agreed for relevant mTKIs.

Product	Votrient, pazopanib (Novartis)	Cometriq; cabozantinib (Ipsen Pharma)	Avapritinib (Blueprint medicines)	Kisplyx; Lenvatinib (Eisai GmbH)	Stivarga, regorafenib (Bayer)
PIP	EMEA-000601-PIP01-09-M06 (Decision No P/0333/2019; date 11/09/2019)	EMEA-001143-PIP01-11-M02 (Decision No P/0331/2019; date 11/09/2019)	EMEA-002358-PIP02-18-M01 (Decision No P/0007/2020; date 06/01/2020)	EMEA-001119-PIP03-19 (Decision No P/0210/2020; date 16/06/2020) EMEA-001119-PIP02,	EMEA-001178-PIP01-11-M05 (Decision No P/0141/2020; date 17/04/2020)
MoA	Including VEGF & PDGF	RET, MET, VEGFR-1,2& 3, KIT, TrkB, FLT-3, AXL, and TIE-2 pathways	PDGFRα and c-Kit, including the PDGFRα D842V mutant and various KIT exon 17 mutants	(VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)	RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl
Condition	Ewing sarcoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma	Malignant solid tumours	Malignant neoplasms (except haematopoietic/lymphoid)	Malignant neoplasms (except haematopoietic/lymphoid) Papillary thyroid cancer, follicular thyroid cancer and refractory or relapsed osteosarcoma	Malignant neoplasms (except haematopoietic/lymphoid)
PIP Indication	Ewing sarcoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma	Refractory malignant solid tumours - MET, VEGFR, and/or RET pathway activation Treatment of advanced or metastatic medullary thyroid cancer.	Relapsed/refractory solid tumour mutations in either KIT or PDGFR-α	Relapsed or refractory solid malignant tumour including Ewing/PNET, rhabdomyosarcoma & HGG	Solid malignant tumour
Waiver	Birth to less than 2 year of age	NA	Birth to 2 years of age	Birth to 2 years of age	Birth to 6 months of age
Deferral	For completion by November 2019.	For **completion by January 2023. No published compliance check yet.**	For completion by **July 2030.** No published compliance check yet.	For completion by **July 2030.** No published compliance check yet.	For completion by **December 2024.** No published compliance check yet.
Formulation	Film-coated tablet, Age-appropriate oral formulation; oral use	Film-coated tablet, Age-appropriate oral formulation; capsules oral use	Film coated tablet, Age-appropriate solid dosage form; oral use.	Only Capsule, hard	Film-coated tablet, Granules; oral use
Clinical	1 **ADVL0815** Single-agent - pharmacokinetics, pharmacodynamics and toxicity - with refractory solid tumours 2 **VEG116731/ADVL1322** - Single-agent - therapeutic activity recurrent and/or refractory soft tissue sarcoma	1 **XL184-011 -** Toxicity, tolerability, pharmacokinetics and pharmacodynamics with refractory or relapsed malignant solid tumours. 2 **XL184-005 -** Relative bioavailability (in adults 3 **XL184-208 -** Randomised, safety and efficacy in malignant solid tumours 4 **XL189 -** Safety and activity over age 2 years a relapsed or refractory solid malignant tumour	1 Safety, pharmacokinetics & activity with KIT or PDGFR-α 2 Randomised evaluate safety, pharmacokinetics & efficacy with KIT or PDGFR-α	1 Pharmacokinetics, safety & activity 2 Combination with everolimus −escalation, expansion -pharmacokinetics, safety, tolerability &activity 3 Randomised efficacy & safety single-agent/ combination	1 Pharmacokinetics 2 Pharmacokinetics, pharmacodynamics, tolerability, safety & activity 3 Randomised, combination + vincristine and irinotecan - safety & efficacy in rhabdomyosarcoma.

chemotherapy and sarcomas, and carcinoma biology is sufficiently distinct to make extrapolation of results difficult.

9.2.2. Biomarkers

Very little is understood about relevant biomarkers of response or the mechanisms of action of mTKIs in osteosarcoma and Ewing sarcoma. Increasing understanding of tumour biology is critical to the further development of this class of products. It is crucial that retrospective analyses of patient samples are performed and a consortium approach with academia and industry be formed. Furthermore, there should be a change in mind-set and collection of adequate matching, tissue samples at diagnosis and relapse becomes a priority, in contrast to the current situation where serial tumour tissue is not prospectively, routinely, collected. In addition, guidance detailing how much tissue should be obtained and stored is required. The implementation of General Data Protection Regulation (GDPR) should be simplified. Finally, there should be a comprehensive analysis involving academia and pharma, where all parties freely share biological material. In this consortium, a critical element would be that individual scientific contributions are acknowledged.

9.2.3. Clinical studies

Clinical studies should be designed and conducted with the intent for study data to support regulatory approval with age eligibility to include children wherever possible. Furthermore, trials should be randomised whenever possible, given the paucity of historical data and feasibility in the context of intercontinental trials. The randomised phase II screening trial design and the randomised phase II selection design ('pick the winner') are both relevant, depending upon the research question(s) being addressed in a clinical trial [67–69]. Novel designs (such as Bayesian or two-stage minimax Jung designs) can be used to minimise the sample size per cohort depending on the objectives and assumptions used in sample size determination. Platform trials with several parallel arms are valuable in evaluating combinations and have many advantages, including accelerating the introduction of new combination arms [70].

9.2.4. Developmental pathway for new mTKIs

An early phase clinical trial, in which results about optimal dosing, toxicity profile, pharmacodynamic biomarkers and early signals of anti-tumour activity of mTKIs as monotherapy are collected, is the first step [71]. The evaluation of feasibility, tolerability and initial activity of the combination is the next step and this could be included in the same protocol. This should be followed by a randomised trial in first relapse or metastatic disease and unfavourable prognostic factors in front-line – standard backbone versus standard backbone plus an mTKI, as has been done with lenvatinib in its phase 1/2 study and the subsequent OLIE trial. Such a trial could also provide 'pivotal' evidence of efficacy in the first-relapse setting – improved EFS in second line and signal of activity for further study. Finally, a randomised evaluation in front line adding an mTKI to standard of care aims to demonstrate whether the addition of an mTKI cures more patients.

9.2.5. Paediatric and adult development

If biology is *the same*, in the same site and same morphology, then clinical trials and development and regulatory pathways could include children and adolescents as well as adults, where possible. Studies evaluating early signals of activity should be strongly encouraged to include young adults (up to 40 years) and children. There is no objective evidence that young adults under 40 years of age tolerate chemotherapy regimens such as VDC/IE or MAP any worse than children, and in fact, toxicity has been demonstrated to be worse in children than in adults in EURO-E.W.I.N.G. 99 after VIDE [72] and following neo-adjuvant chemotherapy for osteosarcoma [73]. However, generally data comparing toxicity in adults, adolescents and children are scarce and therefore trials including patients across age ranges should systemically evaluate differences in chemotolerance. In summary, evaluating mTKIs should be inclusive of different age groups.

9.2.6. Endpoints for trials

For osteosarcoma, the academic community has used 4-month PFS as a metric to compare activity in patients with measurable and non-measurable disease in signal-seeking early phase studies to decide which mTKIs warrant further evaluation in later phase studies [30]. Acknowledging that objective response rates are not always feasible in bone tumours, data based on time to event endpoints, such as PFS, EFS or OS generated in a randomised controlled trial should principally be mature enough to support a benefit/risk assessment.

9.2.7. Formulation

Even though most osteosarcomas and Ewing sarcomas affect adolescents, as with all innovative medicines for malignancies which occur in children, the development of paediatric-appropriate oral formulations of the medicinal product that can be administered to children across all age groups (depending on comparable bioavailability and bioequivalence) is critical.

9.2.8. Toxicity in combination

Although there are concerns about potential overlapping toxicity when combining mTKIs with chemotherapy, the overall experience to date is reassuring, particularly the combination of regorafenib with vincristine and irinotecan [52], lenvatinib with ifosfamide and etoposide in osteosarcoma [74], and

pazopanib with ifosfamide and doxorubicin in non-rhabdomyosarcoma soft tissue sarcomas [11]. In the case of regorafenib, vincristine, and irinotecan, sequential dosing was determined to be more tolerable compared with concomitant [52]. A trial of pazopanib, irinotecan and temozolomide (PAZIT) was not able to identify a tolerable combination dose, highlighting the importance of careful feasibility testing [75]. Approaches where the feasibility of combination treatment is evaluated within the same protocol as a randomised trial component are strongly supported (e.g., COG AOST2032). Concurrent compared to sequential dosing should also be considered when approaching feasibility. Late toxicities, including developmental toxicities, require close monitoring, particularly cardiotoxicity in this population treated with higher doses of doxorubicin. The ACCELERATE long-term follow-up initiative proposes an international and inter-company registry of early and late adverse effects of new anti-cancer products, which will provide informative data [76].

9.2.9. Standard of care

An agreed international standard of care for osteosarcoma and Ewing sarcoma would allow a more rapid evaluation of innovative drugs. An option is to evaluate an innovative agent across different backbones, across different age ranges. Lack of an agreed standard of care for relapsed bone tumours, and paucity of data for historical controls, particularly poses an issue and challenge in identifying a comparator arm.

9.2.10. Optimal alignment in biological, non-clinical and clinical studies

This is crucial in accelerating the evaluation of mTKIs in bone tumours. A consortium approach to the collection and analysis of tumour tissue is a key. Defining which non-clinical studies are necessary and what data need to be generated are critical. Clinical studies should be designed to meet scientific, regulatory and payer requirements; early dialogue between academia, industry and the regulators is essential [2,7,29]. Currently, trials of these compounds intended for regulatory purposes are not practice-changing in the first-line setting. For maximum efficiency and speed for all clinical studies including those sponsored by industry, industry and academic cooperative groups should collaborate early to design and conduct studies that might fulfil regulatory requirements and submit these jointly [77,78,79,80]. Aligning and integrating clinical studies undertaken globally and across the Atlantic, for example, through the FOSTER consortium (Fight OSteosarcoma Through European Research), EEC (Euro-Ewings Consortium) [81] and HIBiSCus [60], are important to accelerate drug development and will be of benefit to all patients with bone tumours.

9.3. mTKIs in osteosarcoma and Ewing sarcoma

With current evidence, it is impossible to define the ideal characteristics for an mTKI for osteosarcoma or Ewing sarcoma, and therefore, prioritisation of classes of products is not possible. Indeed, in the absence of a validated biomarker to predict treatment response, the choice of mTKI for clinical use will need to be largely empirical. Available non-clinical and clinical evidence suggests that it is necessary to target multiple kinase pathways; but which receptor or cellular kinases are critical, either alone or in combination, remains unknown. Non-clinical studies suggest that VEGFR, RET, KIT, PDGFR and FGFRs may all play a role in bone tumour progression [82]. Ideally, mTKIs with the broadest activity and a tolerable toxicity profile that could be used in combination with backbone chemotherapy should be taken forward. The academic participants of the Paediatric Strategy Forum believed those mTKIs currently under investigation in front-line or first relapse studies (cabozantinib, lenvatinib and regorafenib) are very similar in these respects. The clinicians, industry participants and patient advocates concluded that further evaluation of sorafenib [83] and pazopanib [90] was not warranted based on the current data.

The studies, currently being planned or in progress, in front-line and relapse may inform the further development of this class of products. They should address the question whether mTKIs should be included in the standard of care for patients with bone sarcoma. Specifically, data from the OLIE and COG AOST2032 trial data can be used to inform the future direction of mTKIs in osteosarcoma – whether the next-generation mTKIs would be moved forward or no further evaluation is required. Since all these trials in the front-line setting are sponsored by academia, ensuring that they are adequately designed and conducted with registrational intent through partnership with the pharmaceutical industry, with input from regulators, may enable them to possibly support a marketing application to gain approval when results are positive.

Potentially new mTKI products would be of value if they had improved activity or ability to overcome clinically relevant resistance, enhanced suitability for combination development or evidence of less short-term or long-term toxicity. A clearly characterised biomarker for treatment response would be extremely beneficial to expediting clinical development. Additional biological, mechanistic and non-clinical and clinical data are important to guide decisions.

Generally, current evidence suggests that mTKIs may be used in combination with chemotherapy backbone at the recommended doses, with some exceptions highlighted earlier. Evidence also suggests a possible role for maintenance therapy following the combination therapy, which is currently being investigated.

Text box of key conclusions of the Paediatric Strategy Forum

- The development of curative, innovative products in osteosarcoma and Ewing sarcoma is high priority and addresses unmet needs in children, adolescents and adults
- Despite mTKIs being under investigation and in clinical practice, their efficacy in patients with bone tumours has not been definitively demonstrated to date.
- The studies, currently being planned or in progress, in front-line and relapse will inform the further development of this class of products, specifically, data from the OLIE and COG AOST2032 trial will inform the future direction of mTKIs in osteosarcoma and REGOSTA/REGOMAIN, INTER EWING-1 and the planed COG front-line studies in Ewing sarcoma.
- Very little is understood about relevant predictive biomarkers of response or the mechanisms of action of mTKIs in osteosarcoma and Ewing sarcoma.
- Biomarker samples should be shared and a joint academic-industry consortium created resulting in an integrated collection of serial tumour tissues and a systematic retrospective and prospective analyses of these samples.
- If biology is *the same*, in the same site and same morphology, then clinical trials and development and regulatory pathways should include children and adolescents as well as adults, where possible.
- With current evidence, it is impossible to define the ideal characteristics for an mTKI for osteosarcoma or Ewing sarcoma.
- mTKIs with the greatest activity and a tolerable toxicity profile that could be used in combination with backbone chemotherapy should be taken forward.
- Although there are concerns about potential overlapping toxicity when combining mTKIs with chemotherapy, the overall experience to date is reassuring
- Four-month PFS is the metric to compare signal-seeking activity in patients with measurable and non-measurable disease in osteosarcoma.
- Approaches where the feasibility of combination treatment is evaluated within the same protocol as a randomised trial are very strongly encouraged (e.g. COG AOST2032).
- Potentially new mTKI products would be of value if they had improved activity or ability to overcome clinically relevant resistance, enhanced suitability for combination developments or evidence of less short-term or long-term toxicity.
- Trials submitted for regulatory purposes should be aligned with those designed by academic cooperate groups to advance knowledge.
- Clinical studies should lead to regulatory approval with access for children to the medicinal products.
- Clinical studies should be designed for scientific, regulatory and payer purposes.
- An early dialogue between academia, industry and the regulators is essential.
- Patient advocates strongly urged academia and industry to jointly access and analyse retrospectively and prospectively tissue and to rapidly move forward the most relevant trials with registrational intent.
- To respond to emerging science, there is a need for 'living prioritisation' and in approximately 12 months, a multi-stakeholder group will meet and review the data, future directions and priorities.

10. Conclusions

The development of innovative medicinal products in osteosarcoma or Ewing sarcoma is of high priority and addresses an unmet need. It is crucial now to rapidly generate robust data in an international/collaborative effort to allow definitive conclusions on efficacy of mTKIs in the front-line setting in osteosarcoma and Ewing sarcoma. The results of the OLIE trial, which are due in approximately 12 months, will give an estimate of the role of mTKIs in combination with chemotherapy in relapsed/refractory osteosarcoma. Furthermore, these front-line studies, which are in the planning stages (AOST2032, INTER EWING-1 and the COG front-line study in patients with metastatic Ewing sarcoma), will be crucial to our understanding of the role of mTKIs in osteosarcoma or Ewing sarcoma.

It is critical that retrospective biological studies are undertaken to determine how to move forward with this class of products in bone sarcomas. In addition, prospective collection of serial tumour tissue and, where feasible, circulating nucleic acid and circulating tumour cells, should be integrated into current and future studies. Specifically, an academia-industry biomarker initiative (evaluating existing resources, identifying the most promising approaches to biomarker identification and enabling future biomarker studies) should be established, with the clear objective of improving knowledge and identifying new innovative and more efficacious therapeutic approaches.

Finally, to respond to emerging science, it is necessary to update the conclusions of this Paediatric Strategy Forum, and therefore, there is a need for 'living prioritisation'. In approximately 12 months, when the results of the OLIE trial will be available, a multi-stakeholder group will meet and review the data, future directions and priorities.

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