Paediatric Strategy Forum for Medicinal Product Development of Multi-Targeted Kinase Inhibitors in Bone Sarcomas

Context: Curative treatment, with less toxicity, for bone sarcomas represents an unmet need in children, adolescents and adults. Multi-targeted kinase inhibitors (mTKI) have demonstrated biological activity against a wide range of sarcomas in vitro, in vivo and in clinical trials in adult sarcoma patients. There are many mTKIs under investigation and in clinical practice. However, their efficacy in paediatric patients with bone tumours has not been clearly demonstrated to date.

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

Meeting: The meeting was organised by ACCELERATE, in collaboration with the European Medicines Agency (EMA), with participation of the Food and Drug Administration (FDA) of the US and was held virtually on 30 November and 1 December 2021 with 180 participants: 107 international paediatric oncology experts from Europe, US, Canada and Australia; 22 representatives from 8 pharmaceutical companies in Europe and US (Allarity, Bayer, Blueprint medicines, Eisai GmbH, Exelixis, Ipsen Pharma, Hutchison Medipharma and Oncoheroes); 21 patient advocates from Europe, US and Canada (representatives from 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 Myrovolytis 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 one organiser. An overview of the existing trials of mTKIs in bone sarcomas was followed by a review on the relevant biology, and then the current plans and needs for mTKIs in osteosarcoma and Ewing sarcoma were presented 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. The Forum concluded with the patient advocate perspective and a multi-stakeholder strategic discussion.

Multi-Targeted Kinase Inhibitors products discussed: (NTRK and RET inhibitors were not included)

<table>
<thead>
<tr>
<th>Product</th>
<th>Kinases inhibited</th>
<th>Paediatric clinical development</th>
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<tbody>
<tr>
<td>Aykavit®, avapritinib, Blueprint medicines</td>
<td>KIT/PDGFRA (highly selective and potent)</td>
<td>Phase 1/2, solid tumours dependent on KIT or PDGFRA Signalling</td>
</tr>
<tr>
<td>Cabometyx®, Cometriq®, cabozantinib, Ipsen Pharma</td>
<td>VEGF, MET and AKT, RET, ROS1, TYR03, MER, KIT, TRKB, FLT3, and TIE-2</td>
<td>Monotherapy, combination and planned in front-line in osteosarcoma (COG)</td>
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<tr>
<td>Dovitinib, Oncoheroes/Allarity</td>
<td>FGFR, VEGFR, PDGFR and other RTKs.</td>
<td>Phase IB-2 osteosarcoma (DRP* biomarker-driven)</td>
</tr>
<tr>
<td>Lenvima®, Kisplyx®, lenvatinib, Eisai GmbH</td>
<td>VEGFR1, VEGFR2, VEGFR3 and FGFR1, 2, 3 and 4, PDGFRα, KIT and RET</td>
<td>Monotherapy, combination and randomised phase II (OLIE)</td>
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<tr>
<td>Nexavar®, sorafenib, Bayer</td>
<td>c-CRAF, BRAF and mutant BRAF and KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B.</td>
<td>Phase 1&amp;II - limited activity in osteosarcoma and Ewing</td>
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<tr>
<td>Surufatinib, Hutchison Medipharma</td>
<td>VEGFR-1, 2, 3, FGFR1 and CSF-1</td>
<td>Phase 1 in osteosarcoma and Ewing sarcoma with gencitabine</td>
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<tr>
<td>Stivarga®, regorafenib, Bayer</td>
<td>RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl</td>
<td>Monotherapy, combination and planned in front-line in Ewing sarcoma (INTER EWING-1)</td>
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Paediatric Investigation Plans ad Written Requests: There are currently (November 2021) 5 published PIPs agreed for mTKIs relevant to osteosarcoma and Ewing sarcoma; Votrient®, pazopanib (Novartis), Cometriq®, cabozantinib (Ipsen Pharma), avapritinib (Blueprint medicines); Kisplyx®, 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) and there are no PIPS, which include a randomised trial in front-line in bone sarcomas. Lenvatinib has a Written Request issued in 2020.

**Activity of mTKIs in bone sarcoma:** Determining the early signal of activity in bone tumours is challenging, because of the osseous nature of these malignancies and applying conventional metrics such as objective response rates may not be meaningful. The academic community has employed 4-month progression free survival (PFS) as a metric to compare activity of single agents in patients with measurable disease and 12-month PFS for those with completely resected disease.

<table>
<thead>
<tr>
<th>Product</th>
<th>N</th>
<th>PR (%)</th>
<th>4 month PFS% 95 CI</th>
<th>Median PFS (mos) 95 CI</th>
<th>Median OS (mos) 95 CI</th>
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<tbody>
<tr>
<td>Osteosarcoma</td>
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<tr>
<td>Placebo</td>
<td>20</td>
<td>0</td>
<td>10 (NA)</td>
<td>1.7 (1.2-1.8)</td>
<td>13.4 (8.5-38.1)</td>
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<tr>
<td>Sorafenib</td>
<td>35</td>
<td>9</td>
<td>46 (28-63%)</td>
<td>4 (2.5)</td>
<td>7 (7-8)</td>
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<tr>
<td>Lenvatinib</td>
<td>30</td>
<td>7.7</td>
<td>33 (17-54%)</td>
<td>3.4 (1.8-6.5)</td>
<td>NA</td>
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<tr>
<td>Regorafenib</td>
<td>26</td>
<td>7.7</td>
<td>62 (40-77%)</td>
<td>4 (2-6.5)</td>
<td>11.3 (5.9-23.9)</td>
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<tr>
<td>Regorafenib</td>
<td>22</td>
<td>14</td>
<td>44 NA</td>
<td>3.6 (2-7.6)</td>
<td>11 (4.7-26.7)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>42</td>
<td>11.9</td>
<td>71 (55-83%)</td>
<td>6.7 (5.4-7.9)</td>
<td>10.6 (7.4-12.5)</td>
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<tr>
<td>Apatinib</td>
<td>37</td>
<td>43</td>
<td>57 (39-71%)</td>
<td>4.5 (3.5-6.3)</td>
<td>9.9 (8-18.9)</td>
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<tr>
<td>Ewing Sarcoma</td>
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<td>Placebo</td>
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<td>1.7 (CI, 1.2-1.8)</td>
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<tr>
<td>Regorafenib</td>
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<td>11</td>
<td>3.6 (2.0-7.6)</td>
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<tr>
<td>Regorafenib</td>
<td>23</td>
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<td>56.6*</td>
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<td>3.8</td>
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<tr>
<td>Cabozantinib</td>
<td>10</td>
<td>26</td>
<td>4.4 (3.7-5.6)</td>
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<tr>
<td>Cabozantinib</td>
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<tr>
<td>Pazopanib</td>
<td>10</td>
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<tr>
<td>Lenvatinib†</td>
<td></td>
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* 8 weeks
† Data not available

**Monotherapy studies of relevant mTKIs in osteosarcoma and Ewing Sarcoma**

**Relevant Biology of mTKIs in Bone Sarcomas:** Although growing knowledge about the biology of specific kinases and kinase signalling pathways in osteosarcoma and Ewing sarcoma cells *ex vivo*, knowledge of the contribution of these proteins tumour progression in their *in vivo* microenvironments is more limited. In addition, we currently lack biomarkers that can be used to predict if, when, and how mTKIs will be effective in either tumour type. Tumours with kinase mutations respond well to TKIs (e.g. BCR-ABL in CML, ALK in ALCL and IMT, EGFR in lung cancer, B-RAF in low grade gliomas and LCH). Hyperactivation of a kinase/pathway can also confer sensitivity (e.g. EGFR, NTRK). However, in osteosarcoma and Ewing sarcoma there are no recurrent kinase mutations, nor evidence of kinase hyperactivation. Thus, the choice of mTKI is based on empiric studies and observations rather than specific biologic targeting. 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 single TKI through mutations and therefore resistance is less likely to quickly develop with mTKIs as these hit multiple targets simultaneously. mTKIs have a complex effect on tumour cell biology, angiogenesis and the immune microenvironment, posing further challenges in interpreting their mechanism of action. In summary there is increasing knowledge of the genetics of bone sarcomas, particularly how EWS/ETS fusion proteins in Ewing sarcoma drive tumorigenicity, but robust evidence for 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 will have value for at least some 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 tumour microenvironment.

**Challenges for Biomarkers in Bone sarcomas:** There are no mutations to target or to subsequently track with circulating DNA and isolation and study of circulating tumour cells is not feasible outside limited institutions (and still a research question). A major gap in the field, and one that continues to challenge the development of predictive biomarkers for mTKI efficacy, is that an integrated collection of serial tumour tissue has not been prospectively organised. In addition, in rare trials where tumour tissue
has been collected, organised retrospective analyses of these archived samples has not been
prioritized for study. Furthermore, clinical and technical issues complicate evaluation of
pharmacodynamic biomarkers in bone tumours that have or will be 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 importance of including prospective sample collection. Despite the
collective observation that ~10-15% of patients with Ewing sarcoma respond to IGF1R pathway
inhibition, we lack the capacity to identify in advance who will respond.

**Osteosarcoma:** The current international front-line approach to osteosarcoma is following biopsy, the
use of neo-adjuvant chemotherapy such as cisplatin, doxorubicin and high-dose methotrexate (MAP),
methotrexate-etoposide-ifosfamide (M-EI) or a doxorubicin-cisplatin-ifosfamide-based regimen (API-AI)
followed by surgery and then further adjuvant chemotherapy and potentially surgery of metastases or
radiotherapy to non-operable lesions. With this approach the overall 5-year event-free (EFS) and overall
survival (OS) is 54-56% and 71% (respectively).

The addition of mTKIs is being considered in the front-line setting throughout therapy to improve EFS.
COG is developing a front-line study (AOST2032) which will be a feasibility and randomized phase 2/3
study of cabozantinib in combination with MAP chemotherapy. In the first phase the feasibility of
combining cabozantinib with MAP will be assessed with particular regard to overlapping toxicities
(hepatotoxicity and mucositis), pharmacokinetics of cabozantinib/chemotherapy, scheduling and
maintaining chemotherapy intensity. This will then be followed by a randomization of MAP versus MAP
and cabozantinib with EFS as the primary endpoint.

In France, the ongoing REGOSTA study is randomising patients over the age of 12 years, with all sarcomas
in complete remission at the end of first line treatment to placebo or regorafenib, with no cross over.
The ongoing REGOMAIN study is randomising patients, over the age of 16 years, with bone sarcomas
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).

The prognosis for relapsed disease is poor (3-year PFS ~21%). In the relapsed setting mTKIs are being
evaluated in recurrent measurable disease and in completely resected disease. In recurrent measurable
diseases, the OLIE, 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. The primary endpoint is PFS. COG is planning a
phase 2 single arm study of adjuvant MTKI in completely resected recurrent osteosarcoma with the
primary endpoint being 12-month disease control rate compared to a historical benchmark (12-month
PFS 20%), which has been used for several studies.

**Ewing Sarcoma:** The general approach in Europe and north America for localised Ewing sarcoma is
induction chemotherapy followed by local control generally with radiotherapy or surgery with or
without radiotherapy followed by consolidation chemotherapy. With this approach the 5-year EFS is
approximately 75-80%. The approach to metastatic Ewing sarcoma includes induction followed by local
control, consolidation therapy and radiotherapy to metastatic sites. Patients with only pulmonary
metastases have a better outcome than those to other sites, including bone, but survival is still poor
(PFS~ 50%). Multi-site metastatic Ewing sarcoma has a dismal prognosis.

The addition of mTKIs is being considered in the front line setting in metastatic disease to improve EFS.
INTER EWING-1 is planning a dose confirmation study of vincristine, doxorubicin, cyclophosphamide,
ifosfamide and etoposide (VDC/IE) with regorafenib followed by a randomised evaluation (VDC/IE) with
or without regorafenib. COG is also planning a front-line study in patients with metastatic Ewing sarcoma
randomising to standard therapy with or without an mTKI.
The prognosis for relapse disease is very poor (median PFS~7 months). The combination of lenvatinib and ifosfamide is the next arm being planned in the rEECur study for relapsed Ewing Sarcoma (the previous best arm being ifosfamide alone).

**Lessons from Soft Tissue Sarcoma:** Regorafenib has been evaluated in rhabdomyosarcoma in Europe by the ITCC and EPSSG. It has been shown that regorafenib can be combined with standard dose vincristine and irinotecan in a sequential dosing schedule. 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 Ewing sarcoma (3 of 5). A combination of regorafenib, vincristine and irinotecan is being taken forward in the FaR-RMS front-line and relapsed rhabdomyosarcoma study.

COG has evaluated pazopanib in non-rhabdomyosarcoma soft tissue sarcomas (ARST1321). There was a statistically higher complete pathologic response rate in patients receiving radiation or chemo-radiation with pazopanib. Also, the combination was feasible, pazopanib did not significantly alter doxorubicin pharmacokinetics, toxicities were expected (myelotoxicity) and manageable, and wound complication rates comparable to that reported.

**Adult Perspective:** The peak incidence of patients with osteosarcoma and Ewing Sarcoma is adolescence but a significant proportion are adults, and older adults. The outcome for adults with osteosarcoma and for patients > 14 years with Ewing Sarcoma is inferior. The reasons for this are unclear and may include: i) lack of access to specialist multi-disciplinary care; ii) lack of access to clinical trials; iii) differences in histologies and sites in older patients; iv) 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 other groups of unmet need including those with inoperable and late stage disease. This would have many advantages including defining of a new standard of care and having a better understanding of biology. This could be achieved through even greater engagement across paediatric and adult sarcoma research communities across Europe and North America.

**Discussion**

**Patient Advocates’ Perspective:** The patient advocates believed that plans to detect 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 academics trials. In new trials, tissue banking should be mandatory.

As survival rates for 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 timescales and ‘fit for filing’ principles are used with active involvement of regulators. The discussion of testing mTKIs head-to-head in multi-arm trials is encouraging.

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 that are identified in this Forum. The choice of a drug to be studied in a clinical trial should hence not derive from pragmatism, but by scientific criteria. 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, which aims at building an international common database for bone sarcomas, can ease this process. The possibility of collaboration on transatlantic trials in which small numbers of potential participants could be pooled is an exciting option, as has occurred in the TITAN project in neuroblastoma 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.
General Themes

**Evaluation of mTKIs in osteosarcoma and Ewing Sarcoma:** mTKIs warrant further evaluation in bone tumours in combination with other agents and in minimal disease settings. The situation is complex as there are many products in class, lack of understanding of biology, in diseases which overlap with adults and at the same time there are already planned studies in 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. AOST2032 randomizing MAP chemotherapy with or without cabozantinib; REGOSTA/ REGOMAIN studies randomising regorafenib at the end of first line treatment; 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. Very close alignment between INTER EWING and COG will be important. Evaluating feasibility, and then undertaking a randomised trial in the same protocol accelerates drug development (AOST2032 and INTER EWING-1). Moreover, the OLIE randomised study (results expected in approximately 12 months) and rEECur will provide important data in relapsed osteosarcoma and Ewing sarcoma respectively.

**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 the 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 is formed. Furthermore, collection of serial tumour tissue prospectively in all future studies should be mandatory.

**Clinical studies:** Clinical studies should lead to regulatory approval with access for children to the medicinal products, wherever possible. Furthermore, trials should be randomised whenever possible, given the paucity of historical data and this is feasible in the context of intercontinental trials.

**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. Limited evaluation of monotherapy (one cycle or less for one cohort) could be included in the same clinical trial/protocol as a combination. This should be followed by a randomised trial in first relapse - 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. Finally, a randomised evaluation in front-line adding an mTKI to standard of care, provides pivotal evidence.

**Paediatric and adult development:** 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. The differing chemotherapy tolerance by older adults compared to children/adolescents is the major barrier to this approach. Evaluating mTKIs should be inclusive of age.

**Endpoints for trials:** 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. Acknowledging that objective response rates are not appropriate in bone tumours, data to support regulatory marketing authorisation application should principally be mature enough and therefore based on time to event endpoints, such as PFS, EFS or OS assessed in a randomised fashion.

**Formulation:** Even though most bone tumours affect adolescents, as with all innovative medicines for malignancies which occur in children, the development of oral formulations of the medicinal product that can be administered to children (suspensions or liquid formulations) is critical.

**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 in rhabdomyosarcoma, lenvatinib with ifosfamide and etoposide in osteosarcoma and pazopanib with ifosfamide and doxorubicin in ARST 1321 trial. Approaches where the feasibility of combination is determined within the same protocol as randomisations are strongly supported.

**Standard of care:** An agreed standard of care for osteosarcoma and Ewing sarcoma across to the widest age range and geography as possible would allow a more rapid evaluation of innovative drugs. Lack of an agreed standard of care for relapsed bone tumours particularly poses an issue and challenge in identifying a comparator arm.

**Optimal alignment in biological, pre-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 key. Defining which preclinical studies are necessary and what data needs to be generated is
critical. Clinical studies should be designed for scientific, regulatory and payer purposes, and to achieve this an early dialogue between academia, industry and the regulators is essential. Currently, trials for regulatory purposes of these compounds are not practice changing in first-line. For maximum efficiency and speed clinical studies undertaken by industry should be aligned with those undertaken by cooperative groups and fulfil regulatory requirements. Aligning and integrating clinical studies undertaken globally and across the Atlantic, for example through the FOSTER consortium (Fight OSteosarcoma Through European Research) and HIBiSCus are important will accelerate drug development and be of benefit to all patients with bone tumours.

**mTKIs**

With current evidence it is impossible to define the ideal characteristics for an mTKI for osteosarcoma or Ewing sarcoma. Indeed, in the absence of a validated biomarker to predict response, the choice of mTKI for clinical use will need to be largely empirical. Available preclinical and clinical evidence suggests that it is necessary to target multiple kinase pathways, however which receptor or cellular kinases are critical, either alone or in combination, is currently unknown. Preclinical studies suggest that VEGFR, RET, KIT, PDGFR and FGFRs may all play a role in bone tumour progression. Ideally, mTKIs with the greatest activity and a toxicity profile that facilitates their 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 studies, currently being planned or in progress, in front-line and relapse will inform the further development of this class of products. They should establish or not the use of mTKIs in the standard of care in bone sarcoma patients. Since all these trials in front-line are sponsored by academia, making them fit for filing in partnership with the pharmaceutical industry would warrant a full indication if approved by regulatory authorities if the results are positives.

Second or third generation products potentially could have improved activity or ability to overcome clinically relevant resistance, ability to be suitable for combination developments or evidence of less short-term or long-term toxicity. A clearly defined biomarker would also be an advantage. Relevant biological and preclinical data should be available to guide decisions.

Generally the aim should be that mTKIs are used in combination concurrently with chemotherapy at recommended dose for the backbone and mTKI. Evidence suggests a possible role at end of therapy for maintenance, which is currently being further investigated.

**Conclusions:** The development of innovative medicinal products in osteosarcoma or Ewing sarcoma is of high priority and is 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. These front-line studies, which are in planning, (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 and should be discussed with regulators.

It is mandatory that retrospective biological studies are undertaken to refine how to move forward with this class of products in bone sarcoma. In addition, prospective collection of serial tumour tissue and, where feasible, circulating nucleic acid and circulating tumour cells, should integrated into future studies. Specifically, an academia-industry biology/biomarker initiative (pooling all existing samples and streamlining future initiatives) should be established.

Furthermore, 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 landscape.