Report from the Medical Oncology and Radiotherapy Subcommittee

SSG Working Group Meeting January 22nd and 23rd 2018

Local treatment in Ewing sarcoma (common session with orthopedic surgeons).
Asle Hesla introduced the topic and showed data on secondary cancers after treatment for Ewing sarcoma in Sweden. The cumulative risk was 10% at 30 years which was in accordance with two other large-scale studies from Britain and North America. These studies have shown late relapse (local and metastatic) to be the main cause of death for up to 35 years of follow up, thereafter non-tumor related causes, of which secondary malignancies constitute the most significant cause, surpassing late relapse as the major cause of death. The main priority when treating ES should therefore be to prevent late progression and distant relapse rather than preventing secondary cancers. Kjetil Boye reported from a meeting in London in June 2017 about local therapy in Ewing Sarcoma. Finally, Antroula Papakonstantinou suggested establishing Scandinavian multidisciplinary team meetings for difficult cases. In Sweden, national MDT meetings for Ewing sarcoma are planned, and we decided to await the implementation of this before discussing the Scandinavian perspective.

Adjuvant chemotherapy in localized soft tissue sarcoma.
The results from the SSGXX study, other relevant studies on adjuvant chemotherapy in soft tissue sarcoma (STS) of the extremities and trunk wall and new SSG recommendations were discussed in detail.

The most important trial in addition to SSGXX is the randomized histotype-tailored study coordinated by the Italian Sarcoma Group (Gronchi *et al*, Lancet Oncol 2017;18(6):812-22), where 3 cycles of preoperative epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 were given as the standard arm. The histotype-tailored chemotherapy group had inferior outcome compared to the control group, suggesting that the standard chemotherapy regimen is beneficial for patients with high-risk localized STS, although the study was not designed to demonstrate the superiority of the standard regimen. Even though the two trials cannot be directly compared due to different inclusion criteria and different chemotherapy regimens, it is interesting to note that metastasis-free survival in the SSGXX study and in the control group of the histotype-tailored study is similar.

After a detailed discussion, **we concluded that adjuvant chemotherapy is recommended for patients with high-risk localized soft tissue sarcoma of the extremities and trunk wall.** A combination regimen consisting of an anthracycline and ifosfamide should be chosen. The optimal regimen is still undefined, and both the regimen in the SSGXX study (6 cycles of doxorubicin 60 mg/m^2 and ifosfamide 6 g/m^2) and the standard arm in the histotype-tailored study (3 cycles of epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2) are valid options. For SSG centers that have participated in the SSGXX study, the most reasonable would likely be to continue with the SSGXX regimen.

We further discussed criteria for selection of patients for adjuvant chemotherapy. The SSGXX study included patients with high-grade (i.e. FNCLCC grade 2 or 3) STS of the extremity and trunk wall, and in addition the presence of at least one the following factors on histopathological examination of the surgical specimen was required: (i) vascular invasion or (ii) at least two of the following: size $\geq$8.0 cm, infiltrating growth pattern or necrosis. The histotype-tailored trial included patients with deep-seated STS $\geq$5.0 cm in the extremities and trunk wall. The tumors had to be FNCLCC grade 3 or FNCLCC grade 2 with >50% necrosis present at baseline radiology. In the SSGXX study, 124 patients had deep-seated tumors, of

which 113 were ≥5.0 cm (91.1%). Kjetil Boye presented real-world data from Oslo on 205 consecutive patients with deep-seated tumors. For 182 of these (88.7%), the decision on adjuvant chemotherapy would be the same using the criteria in SSGXX and in the histotype-tailored study (170 patients would be recommended chemotherapy and 12 not). Thus, for the vast majority of patients with high-grade, deep-seated tumors, it seems that the criteria used in the two trials would imply the same therapeutic decision. One possible implication is that participation in a new clinical study using the criteria in the histotype-tailored study is not in conflict with clinical practice according to the SSGXX protocol, which until now has been our recommendation. Another implication is that preoperative radiotherapy, which could hinder the histopathological evaluation of risk criteria, would not exclude patients to be considered for adjuvant chemotherapy. The optimal risk classification criteria for deep-seated tumors are still undefined. Since the criteria in the SSGXX protocol are incorporated in most centers, it seems reasonable to continue with this approach. For superficial tumors, there are no other well-established risk factors, and we recommend using the criteria from the SSGXX study.

ESMO guidelines. The revision of the guidelines was presented in the plenary session, and we had a short follow-up discussion on specific oncology matters. The use of olaratumab was discussed. The opinion was different between centers, possibly related to the use of combination regimens in the metastatic setting. Still, the impression was that most centers in Sweden and Denmark use olaratumab in combination with doxorubicin, whereas the authorities in Norway has not yet decided whether olaratumab will be reimbursed.

Radiotherapy and immunotherapy: synergism, abscopal effects and clinical trials in sarcoma. Ana Carneiro held an inspiring lecture on the topic, which was followed by a discussion led by Jacob Engellau. Even though the results of PD-1 inhibitors in sarcoma are generally disappointing, it seems promising to test combination regimens and combinations with radiotherapy. Studies on this topic initiated from SSG centers are encouraged!

Possible SSG studies on the prognostic and predictive value of serum biomarkers in sarcoma. Akmal Safwat presented the results from a project in Aarhus on serum biomarkers in bone and soft tissue sarcoma. The aim is to expand this work, and SSG centers were invited to collaborate. There was a positive attitude, and we decided that Safwat will write a synopsis and circulate it within the SSG.

What´s new? Novel therapies in sarcoma.
The drugs olaratumab and eribulin were covered in the discussion on ESMO guidelines. Kjetil Boye briefly presented data on the tropomysion receptor kinase (TRK) inhibitor larotrectinib, which has shown promising results in tumors with TRK fusions. The majority of patients responded, and many of the responses were durable. TRK fusions are rare, but 35% of the included patients had sarcoma, indicating that it might be more common in sarcomas than other cancer types. The company is planning a New Drug Application to the FDA early 2018.

Study updates
rEECur: The relapse protocol for Ewing sarcoma is open in Denmark, Norway and Finland. Denmark has included 6 patients, Norway 3 and Finland nil. Sweden has not yet had the approval from Legemiddelvärket. A contract between the centers and Skane län must be in

place before patients can be included. About 200 patients have been included so far. One treatment arm will soon close and be replaced by an arm with an experimental drug which has not yet been decided. Multi arm multi stage design (MAMS) is used. Each center will get 150€ for covering the pharmacy expenses and 150€ for each patient included. SSG has a delegated sponsor responsibility with the University of Birmingham as the head sponsor of the study.

DOREMY: Nina Jebsen reported status of the inclusion in the study of reduced preoperative radiotherapy dose in myxoid liposarcomas, in which Oslo has recruited 4 patients and Bergen 1. Application for regulatory approval is in progress in Denmark and Sweden, and centres in Toronto and Houston are planning to participate.

EuroJosss: A joint pediatric and adult synovial sarcoma study has been discussed since 2014. Kjetil Boye reported from a meeting in Milan in November 2017, where it was decided that further development of this protocol will not take place. The main reason is the lack of a sufficiently good scientific question. All participating pediatric and adult groups were interested in continuing the discussions about developing common protocols.

March 5th
Nina Jebsen and Kjetil Boye