8. Assessment and Procedures

8.1. Key Timepoints

Registration	According to group practice (see Appendix B.3)
Surgery for primary tumor	Week 11
Re-starting chemotherapy after surgery	Week 12 or as soon as recovery allows
Randomization	Week 12-16 when histology available
Surgery for metastases	Week 11 to 20 (see section 9.2.2.5), preferably before non-MTX chemotherapy

8.2. Assessment before start of treatment

8.2.1. Basic patient information

1. Height, weight and surface area
2. Karnofsky or WHO performance status (patients ≥ 16 years) or Lansky play scale (patients < 16 years) (See Appendix A.2)
3. Menstrual history and pregnancy test if indicated

8.2.2. Disease assessment (primary tumor)

1. Plain radiograph in two planes
2. MRI of primary site, including, at least, entire involved bone and adjacent joints.

Other baseline investigations (dynamic bone scans, dynamic MRI, PET scans etc) may be carried out and used for pre-operative assessment of response (see Appendix B.9).

8.2.3. Disease assessment (metastases)

1. Chest X-ray
2. CT scan thorax
3. Radionuclide scan of skeleton with X-rays or MRI scans of affected areas

Definition of lung metastases: minimum criteria determined by spiral CT scanning are 3 or more lesions, which are ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. These patients will be classified as having “certain” pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as “possible” metastatic disease and may be called for central review (see Appendix B.9).

Definition of bone metastases: must include confirmation of bone scintigraphy or plain radiograph abnormalities either by MRI scan or biopsy or both.

8.2.4. Recommended baseline assessment of organ function

1. Full blood count and differential white count
2. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
3. Coagulation profile
4. Urinanalysis (dip stick) for blood, protein and glucose
5. Urine phosphate and creatinine
6. Measurement of glomerular filtration rate (GFR) either by estimation (see Appendix A.3 for suggested formulae) or direct measurement
7. Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)
8. Audiometry

Sperm storage is recommended for male patients of reproductive age.

8.3. Assessment during treatment

8.3.1. Prior to each course of chemotherapy

See section 9

8.3.2. Assessment prior to surgery

1. MRI of primary site
2. X-ray of primary tumor
3. Chest X-ray or chest CT scan
4. Appropriate imaging of known metastatic disease

8.3.3. Assessment during post-operative chemotherapy

1. Chest X-ray every 2 months
2. X-ray of primary site every 4 months

8.3.4. After last cycle of chemotherapy

1. Full blood count and differential white count
2. Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
3. Measurement of glomerular filtration rate (GFR) either by estimation (see Appendix A.3 for suggested formulae) or direct measurement (e.g. by radionuclide determination)
4. Measurement of renal tubular function (optional) e.g. Tubular phosphate reabsorption Tm_P/GFR (see Appendix A.3)
5. CT scan thorax (preferred) or chest X-ray
6. Appropriate imaging of former primary tumor site
7. Audiogram

8.4. After treatment

8.4.1. Disease-related follow-up after completion of chemotherapy

8.4.1.1. Follow-up schedule

Participating institutions will follow all patients indefinitely for relapse and survival, regardless of protocol violation. The following are minimum guidelines for timing of follow-up visits *from diagnostic biopsy* to ensure consistency in the detection of relapse or progression. The date of relapse will be defined as the date on which evidence of relapse is confirmed, whether radiologically or clinically. For the purposes of the study, patients will be followed-up for a minimum of five years after the end of the trial.

- **Clinic visits after end of chemotherapy**

Years 1-2	every 6 weeks-3 months
Years 3-4	every 2-4 months
Years 5-10	every 6 months
Thereafter	every 6-12 months according to local practice

- **Investigations at follow-up visits**

1. Physical examination at each visit
2. Chest X-ray at each visit
3. X-ray of the primary tumor site every 4 months until the end of year 4

Chest CT scan is optional, but should always be performed if chest X-ray shows metastasis or is inconclusive.

Bone scan and plain X-ray should be performed on clinical suspicion of bone metastases; if inconclusive, supplement with CT and/or MRI.

If relapse is detected at any site, a complete diagnostic investigation (chest CT scan, bone scan, imaging of primary tumor site) must be undertaken. Refer to Appendix B.9 for an overview over scheduled imaging studies.

8.4.2. Toxicity/Late – Effects Related Follow-Up

Multimodal therapy of osteosarcoma may be associated with permanent alterations of cardiac, renal, auditory, reproductive function, orthopedic problems and other late effects including secondary malignancies. Appropriate additional investigations must therefore be performed in order to ensure optimal patient care. Some of the cooperating groups recommend or require participation in national or international Late Effects Follow Up programs. Late effects of chemotherapy will be documented for EURAMOS-1, and will include cardiac toxicity, renal toxicity and ototoxicity.

For EURAMOS-1 the following investigations should be performed annually during follow-up and toxicity reported for a minimum of five years:

- Blood chemistry (creatinine, urea, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, albumin, bicarbonate, liver transaminase, bilirubin)
- Left ventricular ejection fraction or fractional shortening (echocardiogram or radionuclide scan)

8.5. Technical Guidance on Imaging studies

All imaging studies should be performed in a manner to ensure optimal quality. Refer to guidelines of competent national and international organizations for guidance. Some groups may chose to give detailed recommendations about the way in which particular imaging studies should be performed. If so, these are found in Appendix B.9. These recommendations are not mandatory parts of the protocol, but may assist to obtain optimal images.

8.6. Quality of Life

Quality of life (QL) data will be collected for all randomized patients in EURAMOS-1 via self- and parent-administered questionnaires as appropriate. The main objective of QL assessment within this clinical trial is to determine the impact on QL of the addition of IE to chemotherapy for poor responders and the addition of maintenance therapy with ifn for good responders. Describing and comparing the impact of the these regimens on QL will lead to a better understanding, from the patients' perspective, of the nature of treatment related side-effects, both short- and long-term. These data will help define future treatment options for these patients.

For patients aged 16 and over, QL will be assessed using the EORTC QLQ-C30 questionnaire (Aaronson et al, 1993; Fayers et al, 1995). For patients aged 15 and under, there is no pediatric QL measure that has been validated in all participating countries. Thus, QL for patients aged 15 and under will be assessed using either the generic PedsQL questionnaire (Varni et al, 2002), or the PEDQOL questionnaire (Calaminus et al, 2000), according to group practice.

The initial QL assessment will take place in protocol week 5, as early as the end of the second M course but before the second AP course. Assessments will then take place at 3 months after definitive surgery to primary tumor and at 18 months and 3 years after commencement of protocol therapy. If the patient doesn't complete the first quality of life form at week 5 of the protocol, he can still complete any of the other forms after that one. The quality of life forms are to be considered independent of each other and a form can be completed even if any of the previous forms have not been completed. Full details of QL administration are contained in Appendix A.8.