

CONCEPT B: Concept Sheet for a Potential Trial Addressing an Unresolved Issue in Osteosarcoma

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| Proposers' names | Whelan, Bielack, Smeland, Sydes | | | | |
| Short title | [B] Randomised controlled trial of the optimal timing of mifamurtide (MTP) | | | | |
| Summary diagram | (See end of document) | | | | |
| Patient group (Summary only) | High grade osteosarcoma of the extremity or axial skeleton | | | | |
| Main eligibility criteria (Summary only) | <p><i>As per EURAMOS-1</i></p> <ol style="list-style-type: none"> 1. Histologically proven high grade osteosarcoma of the extremity or axial skeleton (including from second malignancies) 2. Resectable disease 3. Age up to 40 years 4. Registration within 30 days of diagnostic biopsy 5. Start chemotherapy within 30 days of diagnostic biopsy 6. Adequate neutrophils, platelets, GFR, bilirubin and cardiac function 7. Adequate performance status | | | | |
| Control treatment (Name, administration route, duration) | Neo-adjuvant chemotherapy with 36 weeks of MTP started post-operatively | | | | |
| Research treatment(s) (Name, administration route, duration) | Neo-adjuvant chemotherapy with 36 weeks of MTP started pre-operatively | | | | |
| Current knowledge (Known safety data and known activity data) | Mifamurtide has shown results in the AOST-0133 trial which warrant further investigation. The study used MTP for 36 weeks starting post-operatively. The safety data are well-reported. | | | | |
| Rationale (250 words max) | The optimal timing of mifamurtide is unknown. If mifamurtide is considered part of standard practice and the duration of treatment is fixed at 36 weeks based on the previous protocol, then consideration should be given the optimal time to commence mifamurtide. A hazard ratio of 0.80 would be targeted as a clinically relevant advantage that would justify changing to this treatment. | | | | |
| Hypothesis (50 words max) | Earlier administration of mifamurtide may lead to lower recurrence rates and improved metastatic control through a greater proportion of patients completing treatment; treatment may also be more acceptable to patients by shortening the overall duration of treatment. | | | | |
| Trial design | <table border="1" style="width: 100%;"> <tr> <td style="width: 30%;"></td> <td>Phase I</td> </tr> <tr> <td></td> <td>non-randomised Phase II, specify: _____</td> </tr> </table> | | Phase I | | non-randomised Phase II, specify: _____ |
| | Phase I | | | | |
| | non-randomised Phase II, specify: _____ | | | | |

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| | | randomised phase II, specify: _____ |
| | X | Phase III – superiority design |
| Blinding | | Single blinding possible |
| | | Double blinding possible |
| | X | No blinding possible |
| Primary outcome measure | Event-free survival (disease progression or death from any cause) | |
| Secondary outcome measures | Overall survival Toxicity Quality of life Acceptance of randomisation | |
| Control arm event rate | 67 % EFS at 3 years <i>(AOST-0133 showed 71% PFS in non-metastatic patients at 3 years)</i> | |
| Target difference | HR=0.80 is used for sample size calculations | |
| Accrual duration | 5 years | 4 years |
| Accrual rate / year | ~310 patients per year | ~530 years |
| Accrual total target | 1552 patients | 2145 patients |
| Total trial duration | 7 years | 5 years |
| Need for international collaboration | This trial could be answered in a 7-year period (5 years of accrual) if sufficient groups participate to allow recruitment of <300 patients per year or in 5-years with a high recruitment rate. | |
| Potential sub-studies | X | Biology / translation |
| | | Quality of life |
| | | Other, specify: |
| Strengths | <ul style="list-style-type: none"> • Randomisation performed before treatment starts • Arms diverge quickly after randomisation • Focuses resources on the arms showing the most promise • Might appeal to patients as would all get MTP | |
| Limitations | <ul style="list-style-type: none"> • Requires agreement on which chemo regimens to use • Does not address what is the optimal duration of MTP • Addresses only one question | |

Summary diagram

