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GUIDELINES FOR THE CORRECT DETERMINATION OF SECOND PRIMARY MALIGNANCIES IN MYELOMA TRIALS

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As a consequence of improved treatment patients with multiple myeloma are living longer. Long-term co-morbidity may include the risk of developing a second primary malignancy (SPM). A recent meta-analysis of seven trials suggested an increased risk of SPM development in patients treated with long-term low dose oral melphalan in combination with lenalidomide. No increased risk was associated with lenalidomide in combination with other agents. These findings were in contrast to earlier studies that suggested an increased risk of MDS and AML development in patients treated with lenalidomide.

We have developed a committee led process to review all possible malignancies associated with the UK NCRI Myeloma XI study. Myeloma XI is a phase III, randomised, multi-centre, parallel-group design, open-label trial comparing thalidomide, lenalidomide and bortezomib induction combinations and lenalidomide ± vorinostat as maintenance in newly diagnosed myeloma patients (n=2737). The trial includes both transplant eligible and non-eligible pathways.

All adverse events flagged as possible SPMs are reviewed by the Myeloma XI clinical reviewer. A narrative summarising the patient journey from enrolment is written and submitted to the SPM committee formed of 5 members with a chair independent of the trial management group. Each case is discussed and according to committee determined pre-set criteria second malignancies are either confirmed as trial related or rejected (figure 1).

Eighty eight trial reported malignancies have been reviewed in 86 patients. As a consequence of the review process 21 (23.9%) cases in 20 (23.3%) patients were rejected. Sixty seven (76.1%) cases in 67 patients were confirmed as trial related SPMs. Criteria met for rejection of

the 21 cases included; evidence exists that the second malignancy was present prior to trial enrolment (57.1%), no evidence of malignancy found on further investigation (23.8%), reports related to non-malignant skin conditions (14.3%), and spontaneous resolution of cytopenia's upon cessation of treatment (4.8%). Overall trial associated SPM incidence has been 2.45%.

We have shown that careful review of trial reported second malignancies has led to the rejection of almost a quarter of cases. We believe the incorporation of such a review process and adoption of rejection criteria should form an essential component of future trials to ensure accurate assessment of the possible impact of treatment on SPM development.

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