What benefit will there be to patients and their families

Children with high-risk neuroblastoma that has spread to the bone marrow have poor survival rates compared to those with localised disease, reflecting the failure of current treatments to kill neuroblastoma cells in the bone marrow. Furthermore, molecular detection of bone marrow disease in aspirates at diagnosis and after induction therapy identifies a group that are at greater risk of death or relapse, consistent with the hypothesis that some children have more aggressive bone marrow disease. However the heterogeneity and plasticity of neuroblastoma cells in the bone marrow remains unknown, highlighting the need to isolate and characterise these cells to identify those cells that do not respond to current treatment and are responsible for progression and relapse. I**mproved outcome for some children with neuroblastoma will only be realised when the drug refractory neuroblastoma cells in the bone marrow have been characterised and treatments designed to eradicate them.**

The proposed studies will increase understanding of the neuroblastoma cells in the bone marrow compartment that contribute to progression and relapse, and identify the driver pathways of the drug resistant self-renewing cells that are targets for the development of more effective treatment to kill neuroblastoma cells in the bone marrow. These studies will also generate tools (renewable cultures and *in vivo* models of neuroblastoma cells isolated from bone marrow aspirates) for the proposed and future studies on these aggressive cells, and provide **high through-put preclinical assays to assess the efficacy of novel treatment/treatment combinations** to kill these cells. We expect this approach will inform the design of **more effective treatment** for some children and may advance **personalised adaptive therapy** with the anticipated improvement in outcomes. Differences in the cells isolated from bone marrow compared to those of the primary tumour will identify abnormalities that might contribute to an **improved risk stratification** algorithm, increasing the predictive power of current strategies to select children for treatment with an anticipated **increase in cure rates and reduction in toxicity**. The results and cells will provide important tools and information towards the eradication of bone marrow disease for patient benefit. Increased understanding of neuroblastoma cells that populate the bone marrow is critical to develop effective methods to identify and kill these cells, with the **long-term goal of improved treatment and cure for children with high-risk bone marrow disease**.

These studies will complement international translational research in children with neuroblastoma that is being led by the applicant (SAB) to develop much needed biomarkers to detect disseminated and circulating tumour cells to help improve the management of children with neuroblastoma. **This provides a pipeline for the evaluation and introduction into clinical practice of new biomarkers of aggressive bone marrow disease, to select some children for more personalised treatment with the goal of improving cure rates and reducing treatment related toxicity.**

The proposed research compliments current international research in neuroblastoma led by the applicant and places Leeds in a strong position to understand the molecular heterogeneity of bone marrow disease in children with neuroblastoma and in the future design treatments to target this disease with the expectation this will improve outcomes.