immune checkpoint blockade, provocative findings regarding long-term benefit in the setting of a pCR need to be validated. The hypothesis that treatment with neoadjuvant therapy in patients provides an advantage over adjuvant therapy alone also needs to be tested. Translational data in patients from earlier clinical trials suggests enhanced antitumour immune responses in patients given neoadjuvant compared with adjuvant checkpoint blockade,[8] although this outcome needs to be evaluated carefully in larger clinical trials. Additionally, a subset of patients clearly benefit from anti-PD-1 monotherapy in the neoadjuvant setting[7,9] and could be spared the potential toxicity of combined immune checkpoint blockade. However, a subset of patients will not benefit from monotherapy;[7] thus better pretreatment biomarkers are needed to identify these cohorts. Similarly, better understanding of toxicity of these regimens and identification of biomarkers and strategies to mitigate treatment-related adverse events is needed because toxicity is higher in these patients with earlier stage disease and might affect perioperative management. Furthermore, analysis of on-treatment or surgical samples might help to guide the choice of adjuvant therapy long-term. Finally, additional combination strategies should be taken into consideration; however, these combinations need to have a sound scientific basis and potential added toxicity must be taken into account.

Is neoadjuvant therapy for melanoma ready for prime time? It is certainly time to embrace this concept in melanoma (and for other cancers) in light of the tremendous advances in management of systemic disease; although the adoption of neoadjuvant therapy needs to be done in the context of carefully planned clinical trials (ideally in collaboration with cooperative groups and the INMC). Through such studies and through engagement with regulatory bodies and other key stakeholders, the full potential of this approach will be realised and we will continue to transform cancer care for patients.

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Quantifying survival disparities among children diagnosed with cancer on a global scale

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The remarkable increase in 5-year net survival for children diagnosed with cancer from nearly 0% to 80% over the past six decades highlights notable success in cancer treatment and research.[1] These improvements have been the most striking in high-income countries such as the UK. Although it is largely accepted that

low-income and middle-income countries have not achieved these gains, the magnitude of the overall survival gap is difficult to ascertain, largely due to the absence of population-based cancer registries in many of these countries. Thus far, the best available global data were available from the CONCORD programme, which across three studies[2-4] (or cycles) compiled individual records from more than 300 population-based registries in over 70 countries. In fact, CONCORD-3[2] covered almost 1 billion people worldwide. However, this massive effort only published survival estimates for a subset of childhood cancers: acute lymphoblastic leukaemia, acute myeloid leukaemia, lymphomas (as a group), and brain tumours.[2] Although these diseases are the three most common childhood cancers, overall, they comprise approximately 60% of diagnoses.[1] Therefore, data from the CONCORD programme is insufficient to make inferences about survival for a notable proportion of other childhood cancers.

This important deficit in our knowledge of survival disparities among children diagnosed with cancer led Zachary Ward and colleagues[5] to develop a simulation model, published in *The Lancet Oncology*, which synthesises clinical, epidemiological, and health-system data to estimate country-specific childhood cancer survival. Specifically, the Global Childhood Cancer (GCC) microsimulation model was developed to estimate survival for 200 countries or territories across 48 cancer subtypes included as part of the International Classification of Childhood Cancer (third edition). Importantly, the survival module of the GCC model was calibrated with data from the CONCORD programme[2-4] to ensure simulation estimates were consistent with population-based estimates obtained from analysing individual records. The authors found that for children diagnosed in 2015, 5-year net survival for all cancers combined was 37·4% (95% uncertainty interval [UI] 34·7–39·8). As expected, there was a great deal of variability by region, ranging from 8·1% (4·4–13·7) in eastern Africa to 83·0% (81·6–84·4) in North America. Additionally, there was variability by specific cancer diagnosis, with differences of over 80% for cancers such as Hodgkin lymphoma and retinoblastoma, which have high survival in North America, but poor survival in Africa.

Another important and notable aspect of the Article by Ward and colleagues[5] is that, aside from the simulated estimates of survival, the authors evaluated the effect of a range of policy interventions on survival disparities. These interventions included individual policy interventions (eg, increase the availability of chemotherapy to mean of high-income countries) and packages of policy interventions. Although the authors noted that increasing the availability of all treatments to that of high-income countries resulted in substantial improvements, those improvements were quite modest on global 5-year net survival (54·1%, 95% UI 50·1–58·5). This observation was also true for improving service delivery (50·2%, 47·3–53·0). However, by implementing all potential interventions, it was estimated that global 5-year net survival could increase to 80·8% (79·5–82·1).

Although this study[5] is an important step in characterising global survival disparities among children diagnosed with cancer, it is hoped this information could not only inform policy-making and health-investment decisions, but also guide the next-generation of genomic studies of childhood cancer and drug-development strategies. Specifically, there is emerging evidence that differences in the incidence and outcome of childhood cancer could be due to differences in germline genetic susceptibility, tumour biology, and treatment response across populations.[6-9] For instance, one assessment[10] indicated that Latino children with acute myeloid leukaemia have poorer outcomes than non-Latino, white children, even when treated in the same hospital and on identical protocols.

Additionally, by interrogating genome-wide germline genetic variants in a large cohort of children with acute lymphoblastic leukaemia, Yang and colleagues[7] showed that that genomic variation that co-segregated with Native American ancestry was associated with risk of relapse even after adjusting for known prognostic factors. Notably, these ancestry-related differences in relapse risk were reduced by the inclusion of an additional phase of chemotherapy, indicating that modifications to therapy can mitigate the ancestry-related risk of relapse.

This landmark Article by Ward and colleagues[5] is the first to systematically characterise global survival disparities among children diagnosed with cancer. It is hoped that assessments such as this one, and other descriptive epidemiological assessments, will inform not only policy makers and clinicians for priority-setting, but also future genomic and drug-development studies in children diagnosed with cancer.

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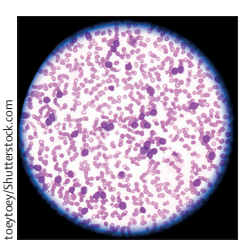
Oral targeted agent versus chemotherapy in acute myeloid leukaemia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In *The Lancet Oncology*, Jorge E Cortes and colleagues[1] present the results of the QuANTUM-R trial, a randomised comparison between the second-generation tyrosine kinase inhibitor quizartinib and standard of care chemotherapy in patients with relapsed or refractory acute myeloid leukaemia carrying an *FLT3* internal tandem duplication (*FLT3*-ITD) mutation. In this difficult clinical situation, patients treated with quizartinib survived for longer than those who received standard chemotherapy. Although the improvement in median survival across all enrolled patients was moderate (6·2 months for quizartinib *vs* 4·7 months for chemotherapy), the results are a substantial step forward in the treatment of acute myeloid leukaemia, since they represent the first published (with the exception of meeting abstracts) randomised evidence that tyrosine kinase inhibition by a single agent can be more efficacious than standard chemotherapy.

Although potentially curable, less than a third of patients with newly diagnosed acute myeloid leukaemia survive the disease. Although a morphological first remission can be achieved in most patients who are treated intensively, the high proportion of patients who relapse is a clinical challenge and the greatest obstacle to a cure.[2] The presence of an ITD mutation in the gene coding region for *FLT3* tyrosine kinase can drive haemopoietic cells towards leukaemia and lead to increased proliferation and resistance to apoptosis in myeloid blasts, corresponding to a high incidence of relapse and poor long-term survival.[3,4] It was hypothesised that small molecules inhibiting *FLT3* signalling could improve the course of disease.[5] First-generation tyrosine kinase inhibitors target several cellular kinases and have restricted single-agent activity. In combination with intensive chemotherapy, sorafenib and midostaurin have shown clinical activity in randomised placebo-controlled trials.[6,7] A significant overall survival benefit in the RATIFY trial[7] led to the approval of midostaurin for first-line treatment of *FLT3*-mutated acute myeloid leukaemia. Quizartinib belongs to a second generation of tyrosine kinase inhibitors that are more specific for *FLT3* and inhibit fewer additional kinases.[5] In early clinical trials enrolling patients with relapsed or refractory *FLT3*-ITD acute myeloid leukaemia, quizartinib has shown significant single-agent activity, with 24–47% of patients achieving remission.[8] QuANTUM-R shows that this single-agent activity is more efficacious than a standard chemotherapy-based approach in patients with primary refractory disease or early relapse. Indicated by a median survival of 4·7–6·2 months, the medical need in this subgroup of acute myeloid leukaemia is particularly high and the prognosis is unsatisfying even when quizartinib is used. However, it is remarkable