Intermittent vismodegib dosing to treat multiple basal-cell carcinomas

that even when treatment toxicity is quickly addressed and managed, ipilimumab has a small but relevant effect on global quality of life.

Far more important than the nuanced determinations of a threshold difference for global scores, however, is the clear clinical applicability of the HRQoL information gathered on EORTC 18071. The findings provide textured evidence about the time course of symptom effects, and the expected recovery after treatment, that is not obtained from toxicity grade reporting alone. Because most patients with melanoma want some role in decision making about their care,[6] and given the potential severe toxicities of ipilimumab versus the potential benefits of treatment, the HRQoL findings can inform patients about how treatment might affect their quality of life. Importantly, the HRQoL findings can help define treatment value, informing health policy. Moving forward, HRQoL data will undoubtedly be even more important in trials comparing active therapies.

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We declare no competing interests.

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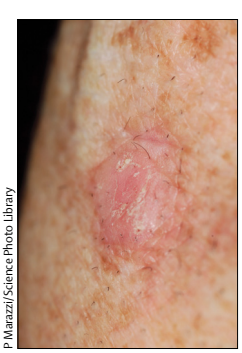

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Many basal-cell carcinomas can be treated effectively by uncomplicated surgical excision.[1] Longstanding tumours, which are often neglected or maltreated, might become inoperable. Targeted treatment with Smoothened homologue (SMO) inhibitors, such as vismodegib and sonidegib, has shown part or complete clearance.[2,3] In patients with advanced basal-cell carcinoma, however, 1 year of vismodegib treatment was associated with complete response in only 34%, and resistance seemed to be a serious problem.[2] Furthermore, in 80% of the patients who received continuous vismodegib in that study, treatment was stopped most frequently because of adverse events.[2] In contrast to advanced basal-cell carcinoma, multiple basal-cell carcinomas is a chronic condition that needs lifelong treatment. The continuous dosing schedules currently used make long-term treatment impossible, but no data supporting implementation of treatment breaks are available.

In *The Lancet Oncology*, Brigitte Dréno and colleagues[4] investigated in the MIKIE study two intermittent vismodegib dosing schedules to assess whether sufficient drug activity could be achieved to inhibit the growth of basal-cell carcinomas while improving tolerability with non-dosing periods. Adults with multiple basal-cell carcinomas amenable to surgery, including those with basal-cell nevus (Gorlin) syndrome, were randomly assigned to receive either 150 mg vismodegib per day for 12 weeks, then three rounds of 8 weeks of placebo daily followed by 12 weeks of 150 mg vismodegib daily (treatment group A) or 150 mg vismodegib per day for 24 weeks, then three rounds of 8 weeks of placebo daily followed by 8 weeks of 150 mg vismodegib daily (treatment group B). The basal-cell carcinomas treated in MIKIE differ from the advanced basal-cell carcinomas treated in previous clinical studies of SMO inhibitors. In general, advanced basal-cell carcinomas have been present and untreated for years or have recurred, are often large, might have deeply invasive structures, and are most commonly located in the head and neck region.[2] Treatment of multiple basal-cell carcinomas

is usually much less challenging. The tumours might be found anywhere on the body and surgical excision is usually done under local anaesthesia without complications. The high numbers of basal-cell carcinomas, however, cause substantial physical and psychological burdens. Patients with basal-cell nevus syndrome might have more than 1000 basal-cell carcinomas during their lives.[5] Non-invasive treatments are, therefore, very desirable in this group of patients, but none has yet been approved.

The primary endpoint of MIKIE, mean number of basal-cell carcinoma lesions at the end of treatment (week 73), was reduced from baseline in both groups: by 62·7% (95% CI 53·0–72·3) in treatment group A and 54·0% (43·6–64·4) in treatment group B. The safety profiles were similar overall in the two treatment groups.

These results provide important information about the degrees of drug activity and safety that can be achieved with intermittent dosing schedules. Furthermore, they elucidate the benefits and limitations of an SMO inhibitor in the treatment of patients with multiple basal-cell carcinomas, including those with basal-cell nevus syndrome. The sustained activity with the intermittent dosing schedules tested is promising. Given the side-effects of SMO inhibitors, the evidence might also be useful for informing the treatment of advanced basal-cell carcinoma. Remarkably, the initial 12 weeks of vismodegib in treatment group A led to tumour shrinkage that continued during the 8-week treatment break when placebo was given, and was similar to that seen in patients in treatment group B who were still receiving vismodegib as part of the first 24-week course.

The number of treatment-emergent adverse events in treatment group B was higher, adherence to treatment was lower, and treatment activity was less than in treatment group A. Additionally, tumour size was reduced more in treatment group A than in treatment group B, and more patients had at least 50% reduction in number of basal-cell carcinomas from baseline to the end of treatment. Thus, 12 weeks of vismodegib treatment followed by rounds of 8-week treatment breaks and 12 weeks of treatment seems to be the better choice of the two regimens (although this was not formally compared). However, I wonder whether even this regimen is too stringent. 108 (47%) of 229 patients discontinued treatment, mostly because of treatment-emergent adverse events. The range of adverse events seems to be similar to that seen in studies of continuous dosing,[2] although fewer were grade 3 or worse despite the median treatment duration being almost twice as long. No patient achieved 100% clearance of basal-cell carcinomas. Furthermore, new tumours will develop after treatment is stopped. Longer treatment breaks would decrease the effect of the drug even further.[6] The question needs to be posed, therefore, of whether it is worth postponing surgery for a treatment that leads to grade 3 or worse treatment-emergent adverse events in around a third of patients and serious treatment-related events in around 4% in a relatively young and healthy population. Further-extended follow-up is needed to investigate long-term effects on patients' health and how long it takes in tumour-free skin, which can still harbour histologically detectable basal-cell carcinomas, for treated tumours to recur after treatment is stopped.[6,7] Recurring tumours might not be as easy to treat as the primary tumours, and might need surgery with increased excision margins.[8] The risk of discontinuous growth, which can affect the reliability of (Mohs) surgery, is also a concern.[9]

Because the on-target side-effects of vismodegib might hamper lifelong treatment, the acceptability of systemic intermittent treatment with this drug warrants further investigation. Although so far not very successful, topical application of SMO inhibitors might be the only long-term method of administration that can be tolerated.[10]

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I have acted as a consultant for Novartis and Roche in relation to Hedgehog-pathway inhibitors.

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C/Can 2025: City Cancer Challenge, a new initiative to improve cancer care in cities

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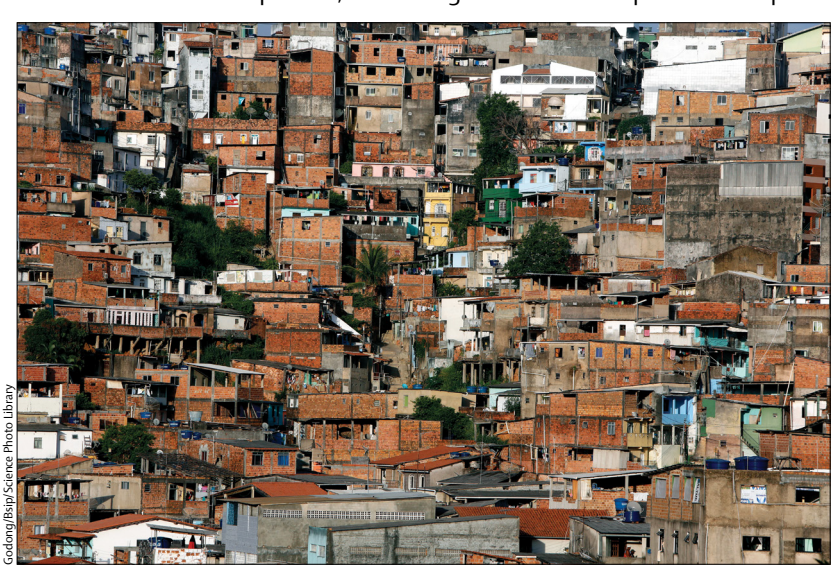
Cancer and other non-communicable diseases (NCDs) enjoy an unprecedented global profile, yet of the 4 billion people living in cities today, few of them have access to high-quality cancer treatment outside of high-income countries.

The greatest financial and human effects of cancer are felt in low-income and middle-income countries (LMICs), which are least equipped to respond to this growing burden, and where rapid urbanisation is bringing other significant developmental challenges.[1] In 2016, 1·7 billion people—23% of the world's population—lived in a city with at least 1 million inhabitants, and by 2030 this percentage is likely to increase to 27%.[2] Coordinated global efforts are urgently needed to improve cancer services to keep pace with the scale and the speed of this urbanisation process, with targeted efforts required to improve the availability of affordable cancer technologies and essential cancer medicines.



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The Union for International Cancer Control (UICC) has launched a new initiative, C/Can 2025: City Cancer Challenge, to support cities in accelerating equitable access to quality cancer services. Cities are already leading the way in cancer and NCD preventative measures through the creation of smoke-free environments, and by driving efforts to improve the quality of air for their citizens. C/Can 2025 will build on these efforts to promote health, and encourage and support cities to take the lead in the design, planning, and implementation of cancer services. Between now and 2025, the initiative will target over 200 cities to improve the health of at least 0·5 billion people worldwide. In 2017, the first three cities who have committed to C/Can 2025—Asunción (Paraguay), Cali (Colombia), and Yangon (Myanmar)—will undertake a comprehensive needs assessment to identify gaps in the delivery of cancer services, and will be supported by C/Can 2025 to develop plans for sustainable solutions that will increase the number of people with access to cancer treatment and care.

By taking an integrated health systems approach, C/Can 2025 has the potential to support improvements in cancer prevention, and help strengthen a city's capacity to deliver public health services. These efforts will help reduce the incidence of cancer and other NCDs in cities, and also ensure patients are diagnosed as early as possible. Such interventions will be crucial in LMICs where major public health challenges place increasing pressures on urban health systems and can further exacerbate inequities in access to care.