cribiform or mucinous varieties, might not be readily distinguishable from surrounding tissue with MRI.[6] The heterogeneity of the transition zone can shroud cancers in the inner prostate, a place where roughly 30% of all cases of clinically significant prostate cancer seem to reside. And although a standardised reporting system has been devised (Prostate Imaging Reporting and Data System version 2), no system of credentials has been established for radiologists to become experts in prostate MRI performance and interpretation. Inter-reader agreement of MRI scoring could therefore vary substantially; a κ score of 0·5 has been reported among experienced readers.[7] Thus, systematic sampling will probably persist as an adjunct to targeted sampling. Systematic biopsy can also have high relevance when planning focal therapies. Ideally, systematic sampling will employ template guidance, as provided in image-fusion devices.

Increased detection of clinically significant prostate cancer via the combination method described in the MRI-FIRST trial might also increase the detection of non-clinically significant or low-risk tumours. Previously, the resulting overtreatment of such tumours was often an undesirable side effect of extended biopsy—ie, over-detection led to over-treatment. Now, however, excessive treatment has been considerably mitigated by the advent of active surveillance for small, well differentiated tumours. A sharp and notable upturn in the use of active surveillance began a decade ago and is still gaining momentum.[8,9] Therefore, previous concerns about overtreatment of non-threatening tumours seems to be receding.

The MRI-FIRST trial was pragmatically designed to reflect the real-world implementation of MRI-targeted biopsy. Unlike some other contemporary trials, wherein imaging was done and interpreted at high-volume centres, in MRI-FIRST, MRI was strictly a local affair at each participating site, and radiologists did not have centralised training. As MRI-targeted biopsy is adopted in community settings, its implementation will probably have results similar to those of the MRI-FIRST trial. At the beginning of a new programme, the sensitivity of targeted biopsy alone might be less than is reported in previous clinical trials. Thus, as elegantly shown in MRI-FIRST, combined biopsy should be considered as the present standard. The decision of whether to perform biopsy in the first place will continue to be based on overall clinical suspicion, including palpable abnormalities, family history, race, prostate-specific antigen concentrations, and MRI findings (or lack thereof).

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We declare no competing interests.

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Drug development for glioma: are we repeating the same mistakes?

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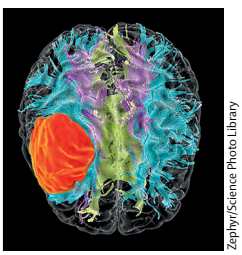
Treatment of recurrent glioma remains challenging, variable, and controversial. Despite repeated surgery, re-irradiation, and several lines of salvage chemotherapy, prognosis remains poor and most patients will die from their disease. Recent large randomised trials aiming at VEGF neutralisation with bevacizumab[1] or checkpoint inhibition with nivolumab (NCT02017717) have not shown a survival benefit.

In *The Lancet Oncology*, Giuseppe Lombardi and colleagues[2] report their findings from an Italian multicentre randomised phase 2 study (REGOMA) of treatment of glioblastoma at first recurrence. 119 patients were randomly assigned to either standard lomustine (n=60) or the multiple receptor tyrosine kinase inhibitor regorafenib (n=59). Regorafenib inhibits VEGF receptors 1–3, KIT, RET, BRAF, PDGFR, and FGFR—kinases involved in angiogenic and tumour microenvironment pathways commonly upregulated in glioblastoma. Median overall survival increased from 5·6 months (95% CI 4·7–7·3) in the lomustine group to 7·4 months (5·8–12·0) with regorafenib (hazard ratio 0·50, 95% CI 0·33–0·75; p=0·0009). Overall survival at 12 months was 38·9% (95% CI 26·6–51·1) in the regorafenib group and 15·0% (7·4–25·1) in the lomustine group. The trial has a phase 2 screening design,[3] and with the survival differences surpassing the predetermined boundaries, the investigators concluded that these results should be confirmed in a phase 3 trial. Quality-of-life analysis and in-depth biomarker evaluations are promised as separate future manuscripts; however, some top-line results of biomarker analyses would have been of great value to corroborate the clinical results.

At first glance, these results look impressive, but there are several caveats to consider before embarking on a phase 3 trial. Overall survival in both groups was less than expected, particularly in the lomustine group. Several randomised trials have used lomustine as the reference treatment, and consistently achieved median survival rates of 8–10 months,[1,4-6] whereas in the REGOMA trial, single-agent lomustine resulted in a median overall survival of only 5·6 months (table). The regorafenib group in the REGOMA trial did just as expected for an agent with no particular activity.[2] So rather than the regorafenib group doing much better, the lomustine group seems to have had a worse outcome than expected. There is no easy explanation for this fact. Indeed, the dose of lomustine was identical to other trials, toxicity was not excessive, and patient characteristics were similar between the two groups. Still, some obvious and some possible differences in patient characteristics might account for the differences. Two patients in the regorafenib group had prognostically more favourable isocitrate dehydrogenase *(IDH)*-mutated glioblastoma, whereas no *IDH* mutation was reported in the lomustine group. Still, for 37 (31%) of the 119 patients, no tissue was available for molecular testing. The absence of a central pathology and molecular review is a great limitation of this trial, excused by the authors by finite financial resources. In my opinion, central pathology review and molecular tumour characterisation need to be an integral component of any trial aiming to evaluate the efficacy of a novel treatment.

Many trials of new agents in brain tumours have not sufficiently considered drug distribution and penetration through the intact blood–brain barrier. An ideal compound would be small, lipophilic, and non-protein bound to freely diffuse across from the blood to the brain interstitium.[7] Other compounds will probably require active transport mechanisms. Whether regorafenib, a highly protein-bound molecule, sufficiently distributes into the brain remains to be established; in preclinical models, the brain distribution was low. Even the most effective anticancer agent will be unsuccessful if it cannot be delivered to the tumour in adequate concentrations. Strategies to open the blood–brain barrier are currently undergoing a revival.[8]

So far, no single agent has provided a significant or meaningful survival benefit when administered in recurrent glioblastoma. Even the approved temozolomide and tumour treating fields have shown their antitumour activity only when included in a primary multimodal treatment strategy of newly diagnosed glioblastoma.[9,10] Thus, despite the great clinical need for better treatments and strategies for patients with recurrent glioma, from a drug development point of view, integration into the first-line setting might be the more successful strategy. Patients with recurrent glioblastoma have a heterogeneous and often difficult clinical course, are likely to require concomitant high doses of steroids, and drug metabolism might be altered by frequent use



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For the **Australian Public Assessment Report for Regorafenib, 2014** see https://www.tga.gov.au/sites/default/files/auspar-regorafenib-140207.docx

	Lomustine, mg/m²	Number of patients	Median overall survival (95% CI)	1-year overall survival (95% CI)	Relative risk (95% CI)
Enzastaurin[4]	100–130	96	7·1 (6·0–8·8)	~22% (NR)	4·3% (NR)
Cediranib[5]	110	65	9·8 (NR)	40% (NR)	8·9% (NR)
BELOB[6]	110	46	8·0 (6–11)	30% (18–44)	5% (1–17)
EORTC26101[1]	110	149	8·6 (7·6–10·4)	34·1 (25·8–42·6)	13·9% (8·6–20·8)
REGOMA[2]	110	60	5·6 (4·7–7·3)	15% (7·4–25·1)	3·3% (NR)

NR=not reported.

Table: **Performance of lomustine control groups in clinical trials of recurrent glioblastoma**

of antiepileptic drugs. Exposure to the novel agent is probably too short because patients often progress within 2 months, thus not really allowing the new drug to show efficacy. In the REGOMA trial, more than half of patients in both the regorafenib group and the lomustine group had tumour progression after the first tumour assessment after 8 weeks of therapy.

The investigators are to be congratulated for choosing a randomised screening design for this study rather than adding to the many uncontrolled phase 2 trials.[3] This design has been proposed to identify potentially active new combinations or novel treatments to be taken forward into a phase 3 trial. Nevertheless, there are limitations of such a design. To reduce the number of patients required, a false-positive and a false-negative rate of 20% are to be accepted. Furthermore, the stipulated hazard ratio of less than 0·58 is also quite ambitious. Seamless phase 2–3 designs with a landmark analysis for the phase 2 portion of the trial, and, if promising, an immediate subsequent transformation into a full phase 3 comparative trial might be another option. The screening design might also be appropriate to evaluate more than one novel compound or combination against a common control group.

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I have been the principal investigator to several clinical trials in glioblastoma. I have served on advisory boards to AbbVie, Boehringer Ingelheim, Celgene, Novartis, EMD Merck, and Roche. I have received travel assistance from Novocure.

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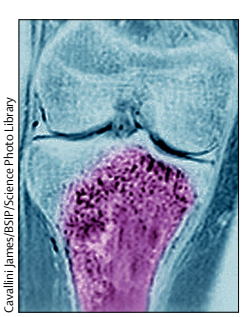
Metastatic osteosarcoma challenged by regorafenib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Osteosarcomas belong to a large family of tumour entities of mesenchymal origin which exhibit heterogeneous histological, genetic, and molecular features. Their pathogenesis can be explained by initial *TP53* or *RB1* somatic alterations, or both, leading to chromosomal instability, followed by secondary oncogenic events and the development of a polyclonal disease associated with the metastatic process. This genetic complexity has been illustrated by a recent series of patients in which investigators have identified a substantial number of point mutations and deletions in an impressive number of genes.[1] It has also stimulated the development of numerous therapeutic strategies targeting tumour cells and their microenvironment.[2] The fact that osteosarcomas are both rare forms of cancer and highly heterogeneous explains why patient survival has not improved in the past four decades, especially for metastatic and unresectable osteosarcomas. Regardless of whether or not the drugs used in the first line of chemotherapy (in neoadjuvant and/or adjuvant chemotherapy for 6–12 months) have been standardised (relatively speaking) and include doxorubicin, cisplatin, methotrexate, and ifosfamide, no consensus has been reached on either the optimum combination or the therapeutic options for patients with recurrent metastatic disease.[3]

Protein kinases are part of a large family of key enzymes that catalyse the transfer of a phosphate group from ATP to a hydroxyl group of serine or threonine. More than 50 protein kinases are receptors