model for survival. Nevertheless, better post-progression treatment options potentially influencing survival data might have been in place for patients with *RAS* wild-type tumors (eg, re-challenge of anti-EGFR drugs).

Although survival in the standard-dose group compares adequately with the CORRECT study[1] (median of 6·0 in ReDOS *vs* 6·4 months in CORRECT), only 26% of patients in the standard-dose group initiated cycle 3. This percentage is low compared with both the CORRECT[1] (assumed proportion of 45% of patients initiating cycle 3) and CONSIGN[4] studies (57% of patients). Moreover, it is—as is often the case with clinical trials including patients in the refractory treatment setting—questionable whether the study results obtained in ReDOS are transferable to most patients treated under routine clinical conditions. ReDOS took almost 25 months to achieve its recruitment goal of 116 evaluable patients in 39 centres, an average of 1·4 patients per centre per year. Thus, an obviously small subset of all patients was included in the ReDOS study that might not represent the majority of patients treated with regorafenib.

Nevertheless, after years of individual dosing approaches based on expert opinion, Bekaii-Saab and colleagues should be commended for effectively conducting a first randomised trial on the question of optimal dosing of regorafenib. Further studies are clearly needed, but the results from ReDOS will certainly prompt those who have not yet become accustomed to using individual dosing approaches thus far to change their regorafenib treatment algorithms.

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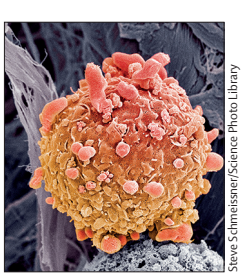
Echoes of a failure: what lessons can we learn?

There were high expectations for combining the IDO1 inhibitor epacadostat with pembrolizumab, an anti-PD-1 antibody, based on promising data from a phase 1 trial,[1] which involved just 22 patients with melanoma (12 of whom responded) treated with various doses of epacadostat. The placebo-controlled phase 3 ECHO-301/KEYNOTE-252 trial done by Georgina V Long and colleagues,[2] published in *The Lancet Oncology*, involving 706 patients with melanoma, was launched to assess if the combination of epacadostat 100 mg orally twice per day with pembrolizumab 200 mg intravenously every 3 weeks was better than pembrolizumab alone. This study was the first phase 3 trial to report results from among a myriad looking for combination regimens that could surpass anti-PD-1 monotherapy in patients with treatment-naive or treatment-refractory melanoma.

After a median follow-up of 12·4 months, no significant differences were found between the treatment groups for progression-free survival (median 4·7 months, 95% CI 2·9–6·8, for pembrolizumab plus epacadostat *vs* 4·9 months, 2·9–6·8, for pembrolizumab plus placebo; hazard ratio [HR] 1·00, 95% CI 0·83–1·21; one-sided p=0·52) or overall survival (HR 1·13, 0·86–1·49; one-sided p=0·81). These results were an epic failure and led to the cancellation of other trials testing IDO1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inhibition in melanoma. However, it is worth pointing out that, so far, no phase 3 trial of any combination therapy in melanoma has shown a significant survival benefit compared with that of anti-PD-1 alone. So, what lessons can we learn from this failure to ensure that future phase 3 trials have the greatest chance of success, while minimising the number of patients subjected to ineffective and potentially toxic drugs?

We can reasonably expect that a phase 3 trial should use a dose and schedule of drugs optimal for assessment. Unlike cytotoxic agents administered at or near the maximum tolerated dose, doses for immunotherapy agents are rarely conclusively determined. It is fair to ask whether the epacadostat 100 mg orally twice daily dose used in ECHO-301/KEYNOTE-252 was optimal for combination with pembrolizumab. A well defined dose, preferably with strong evidence assessment of target engagement in humans, would seem a reasonable prerequisite for phase 3 testing. Preclinical evidence of the importance of the target and of supra-additive or synergistic combination activity should likewise be considered prerequisites. But dosing schedule should not be neglected: concurrent use of immunotherapy agents in phase 3 trials should be based on confidence that the beneficial effects of a combination do not require a specific sequence of administration. Until now, epacadostat monotherapy has not been documented to have antitumour activity in melanoma, and it remains an unproven hypothesis that drugs without single-agent activity can improve any meaningful efficacy endpoint when combined with checkpoint blockade. When considering future phase 3 trials of combination immunotherapy, the rationale for including inactive drugs should be closely scrutinised. Demonstrated antitumour activity of the combination in patients clearly refractory to the active drug would be a viable surrogate, recognising that some patients who did not respond to checkpoint blockade initially respond later to the exact same drug at the same dose and schedule. If the putative partner is intended to manipulate a target that does not itself lead to tumour response, but strong laboratory evidence suggests that it could augment antitumour immunity, we should consider showing that the relevant biological activity occurs in a neoadjuvant approach with the proposed phase 3 dose. The existence of candidate biomarkers to select patients who are most likely to respond further strengthens the rationale for phase 3 testing but, in general, such studies should assess the combination in all patients, perhaps with coprimary endpoints for the biomarker-positive subset.

A randomised phase 2 trial showing superiority of the combination over single-agent immunotherapy would provide the strongest rationale for a phase 3 trial, but is it really a necessary precondition? These trials have limited power to detect a small difference and, therefore, have a distinct risk of abandoning a potentially effective combination,[3] a risk that admittedly exists even in large, well conducted phase 3 trials such as ECHO-301/KEYNOTE-252. Additionally, positive randomised phase 2 trials do not guarantee positive phase 3 trials.[4] Therefore, if a phase 3 trial goes forward on the basis of exciting preclinical science combined with highly promising phase 1 clinical trial data, how do we best protect trial participants if the experimental intervention proves to be unhelpful? Options include incorporating futility analyses or using a phase 2–3 design.[5,6] Futility analyses allow for early stopping of a trial without interrupting accrual, whereas phase 2–3 designs usually involve mandatory accrual holds. The treatment landscape might already have changed by the time accrual is resumed, jeopardising the success of a potentially positive phase 3 trial. There is clearly not just one right answer, but this epic failure should remind us all of the importance of every detail in trial design. The lesson might have been a costly one, but failure to heed the implications would be costlier still.

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Improving selection of individuals into lung cancer screening programmes

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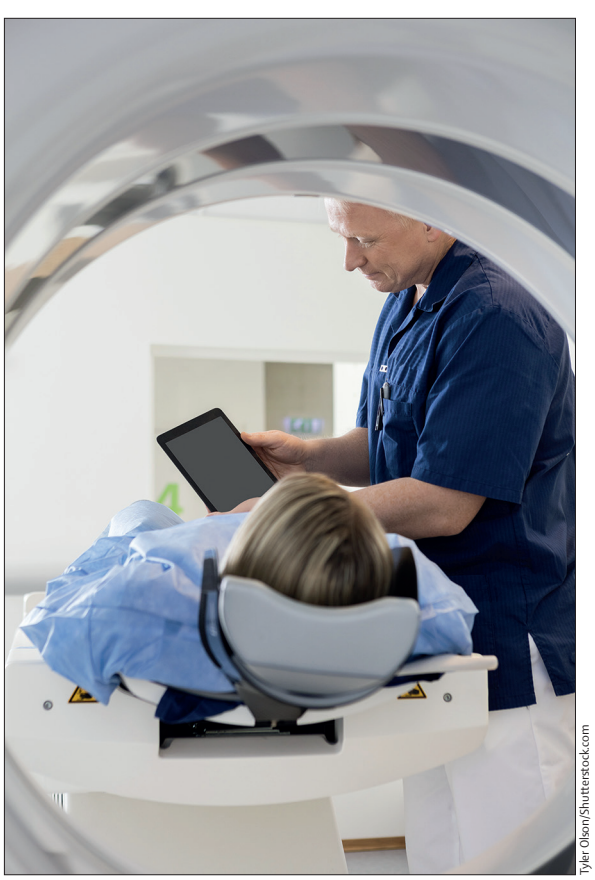
The results of the National Lung Screening Trial (NLST), first announced in November, 2010, showed a 20% decline in mortality with three rounds of screening.[1] The NELSON study was presented at the International Association for the Study of Lung Cancer meeting and confirmed the benefit of screening.[2] Work by James Hanley and colleagues[3] utilised the NLST data and showed that continued annual screening could potentially lower mortality by as much as 30%. Current screening guidelines by the US Preventive Services Task Force (USPSTF), Centers for Medicare and Medicaid Services, and many major US medical organisations follow entry criteria similar to that used for the NLST:[4] age 55–80 years, 30 pack-years of smoking, and, for former smokers, those who quit within the past 15 years. The USPSTF guidelines were based on microsimulation modelling from the Cancer Intervention Surveillance Network and a point on their efficacy frontier that resembled the NLST entry criteria but extended the age cutoff to 80 years.[5] Uptake of lung cancer screening is low according to data from the American College of Radiology.[6]

Many lung cancers in the USA arise in individuals who do not meet current USPSTF entry criteria.[7] The frequency of lung cancer diagnoses varies across the USA because of different demographics such as smoking intensity and socioeconomic and racial diversity. Some of the major medical organisations in the USA, including the National Comprehensive Cancer Network, the American College of Chest Physicians, and the American Association of Thoracic Surgery, call for screening of individuals who do not meet current criteria because of these discrepancies.[4]

In *The Lancet Oncology*, Yung-Hung Luo and colleagues[8] provide comparative information about overall survival in three different subgroups of patients with lung cancer, using prospectively collected long-term data on lung cancer cases at the Mayo Clinic and in Olmstead County, MN, USA. The authors assessed data from patients diagnosed between Jan 1, 1997, to Dec 31, 2017. Although the NLST results were announced in November, 2010, only approximately 1% of patients with lung cancer in the current study had undergone screening. In previous work, this group had shown that in a defined population, aged 50–80 years, with a smoking history of 30 pack-years or more, the most common high-risk



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