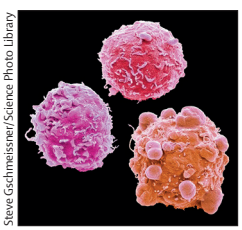
Study evidence confirms current clinical practice in refractory metastatic colorectal cancer: the ReDOS trial



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A growing number of patients with unresectable metastatic colorectal cancer can receive several lines of chemotherapy enabling maintenance of performance status and quality of life over long treatment periods. Even in the chemotherapy refractory setting (ie, after progression on fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic drugs and—if feasible in terms of *RAS* and *BRAF* status—antibodies targeting EGFR), reasonable and licensed treatment options such as regorafenib and TAS-102 are available. Regorafenib, an oral multitargeted kinase inhibitor, was shown to improve survival in the pivotal CORRECT[1] and CONCUR[2] studies in both white and Asian patients. However, its use is limited by considerable toxicities such as hypertension, hand-foot skin reaction, fatigue, diarrhoea, and liver toxicity.

It has been shown that adverse events tend to occur early in the treatment course and frequently require dose modifications and treatment delays.[3] For instance, the CONSIGN study[4] reported on 2864 patients treated with standard-dose regorafenib—ie, with a starting dose of 160 mg/day for 21 days of a 28-day cycle. Treatment modifications were required in 87% of the patients and 49% needed dose reductions. 57% of the patients initiated cycle 3. The mean daily dose was 146 mg (SD 19) and the mean percentage of planned dose was 75% (SD 20). In view of the toxicity profile and the early occurrence of toxicities, investigators have started to recommend individual initial dosing strategies and supportive measures for patients receiving regorafenib in daily practice.[5,6]

In *The Lancet Oncology*, Tanios Bekaii-Saab and colleagues report on the ReDOS study, which investigated potential measures for optimisation of regorafenib treatment.[7] Patients with chemorefractory metastatic colorectal cancer were randomly assigned to two regorafenib dosing strategies: standard dose (160 mg/day) or dose escalation starting from 80 mg/day and increasing twice by 40 mg per week to a maximum of 160 mg in case of tolerance. The primary endpoint was the percentage of evaluable patients who completed two cycles of treatment and initiated cycle 3. The study met its endpoint, with more patients starting cycle 3 in the dose-escalation group (23 [43%, 95% CI 29–56] of 54 patients) than in the standard-dose group (16 [26%, 15–37] of 62 patients; p=0·043). Progression-free survival data were comparable between groups and overall survival was numerically longer in the dose-escalation group, although not significantly different (9·8 months [95% CI 7·5–11·9] *vs* 6·0 months [4·9–10·2]; hazard ratio 0·72, 95% CI 0·47–1·10; p=0·12).

The overall adverse event profile slightly favoured the dose-escalation group, especially for grade 3 hypertension, liver toxicities, maculopapular rash, and dyspnoea. With respect to adverse events occurring during cycle 1 and 2, however, no significant differences between treatment groups were found in terms of hand-foot skin reaction, fatigue, hypertension, and diarrhoea. Although the received mean dose was lower in cycle 1 in the dose-escalation group by study design (91·8 mg [SD 33·4] *vs* 133·1 mg [34·6]), it was virtually identical in cycle 2 (121·3 mg [40·0] *vs* 117·3 mg [48·9]). The percentage of the planned dose received, however, was superior in the dose-escalation group in cycle 2 (median 100·0% [IQR 95·2–100·0] *vs* 75·0% [50·0–100·0]).

Thus, with a slightly better toxicity profile and comparable dose exposure in cycle 2, a higher percentage of patients initiated cycle 3 in the dose-escalation group, thus making ReDOS a positive trial. However, this difference was not primarily due to toxicity or patient request: it was due to a lower proportion of patients with disease progression in the dose-escalation group (20 [37%] *vs* 29 [47%]). Another important finding is that patients treated with dose escalation had a higher frequency of post-progression treatment (29 [66%] of 44 patients with information on post-progression treatment *vs* 19 [39%] of 49 patients) and numerically longer overall survival. Is there an explanation for these findings? It could be argued that tumour characteristics were more adverse in the standard-dose group, with 55% of patients with a *KRAS*-mutant tumour compared with 39% in the dose-escalation group, as well as two patients in the standard-dose group with *BRAF* mutation. However, the authors did not find *KRAS* mutations to be a significant covariate in an adjusted proportional hazard

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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R-DH has received honoraria for lectures and consulting from Amgen, Bayer, Bristol-Myers Squibb, Boehringer, Merck, Merck Sharp & Dohme, Lilly, Roche, Saladax, Sanofi, and Servier. SS has received honoraria for lectures and consulting from Amgen, Bayer, Merck, Lilly, Roche, Sanofi, Takeda, Taiho, and Merck Sharp & Dohme.

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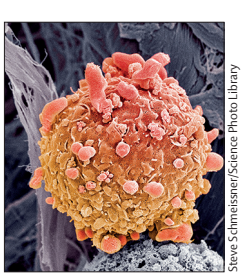
Echoes of a failure: what lessons can we learn?

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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