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that *KRAS* mutation status differed between people of Japanese and European origin.^{7,8} In Japanese patients, *KRAS* mutational frequency increased significantly with age, whereas no correlation was seen in patients of European origin, suggesting that some biomarkers may be specific to patients of particular ethnicities.⁸

Finally, the number of patients with T4 tumours was very high in this study¹ (between 51–57% across the different cohorts), whereas T4 tumours are normally only seen in 7–15% patients in European and American studies.^{9,10} Accordingly, Zhang and colleagues' study¹ included a fairly high rate of patients with poor prognostic features (almost 80% of patients). These clinical differences should be taken into account when applying their results to other countries. Although these points need to be addressed in future analyses, the predictive and prognostic usefulness of the six-miRNA-based classifier was successfully established, and these findings are an important step for the establishment of a better treatment strategy of stage II colon cancer.

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We declare that we have no conflicts of interest.

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Dasatinib and docetaxel in advanced prostate cancer

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In *The Lancet Oncology*, John C Araujo and colleagues¹ report the final results of the phase 3 READY trial of docetaxel with or without the Src family kinase (SFK) inhibitor dasatinib in patients with castration-resistant prostate cancer. The study is negative: dasatinib does not improve survival, or any of the typical measures of patient benefit, and now joins the long list of agents that fail to improve survival in men with castration-resistant prostate cancer when combined with docetaxel.² These results should compel the medical research community to critically reflect on the current state of affairs of cancer clinical trials. Here we retrace the steps of dasatinib's development for patients with castration-resistant prostate cancer—starting from the READY trial¹ and ending with the preclinical models—to seek insights into how to improve the rationale for development of future clinical trials.

The READY trial is one of the largest trials in castration-resistant prostate cancer, accruing more than 1500 patients. Arguably, it was statistically overpowered: a large sample size was recruited with the aim to find just a slight treatment effect. This was a high-risk, low-payoff strategy. The notion that docetaxel is easy to improve upon by using empirical oncological logic (ie, if one drug works, then two ought to work better) has proven not to be the case. Strategy should be rationalised by the proposition of smaller phase 3 trials seeking larger (more clinically relevant) treatment effects, made possible by cohort enrichment.

Clinically, the READY trial relied heavily on a small, single-arm phase 1/2 study³ to justify its design and conduct, despite the phase 2 component having only 46 patients and no prespecified primary efficacy

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endpoint. The efficacy results for the doublet were not particularly impressive, and were within the range expected with docetaxel alone. Nevertheless, these results apparently generated enough enthusiasm to proceed with a large phase 3 trial. Of note, a single-agent phase 2 trial⁴ of dasatinib in patients with castration-resistant prostate cancer concluded that dasatinib had limited activity in advanced metastatic castration-resistant prostate cancer.

The idea of combining docetaxel with dasatinib is based on the logical, albeit simplistic, notion that simultaneous targeting of the tumour cell (with docetaxel) and its microenvironment (with dasatinib) will lead to synergistic efficacy effects. However, preclinical models to support this hypothesis are somewhat scarce. In the one published study,⁵ a single-cell line (C4-2B) was used in an intratibial murine xenograft model. Although greater reduction in prostate-specific antigen (PSA) was reported with the doublet than without, the results did not clearly show that this combination improved survival, nor were these effects proven mathematically to be synergistic. Preclinical studies that included investigations of molecular signatures demonstrating SFK activation would have provided a more solid foundation for clinical trials. For example, a transcription-based androgen-receptor activity signature reported response to dasatinib only in tumours with low or absent androgen-receptor activity.⁶ Perhaps development of dasatinib in this subset of potentially responsive tumours, while refining the diagnostic assay along the way, could have resulted in a less negative outcome in the clinical setting.

SFKs have long been implicated in the development of castration-resistant prostate cancer, making them a target for drug developers.⁷ But can dasatinib meaningfully modulate this signalling process, particularly in a complex epithelial malignancy? We believe this result is unlikely, at least in unselected patients with castration-resistant prostate cancer. SFK inhibitors have only been shown to decrease cell cycle progression, not to induce substantial apoptosis.⁸ In xenograft models, SFK inhibition led to only partial decreases in PSA and tumour growth,⁹ partly due to SFKs' suppression of autophagy via mTOR. The consequent activation of autophagy and cell survival as a result of Src inhibition suggests that SFK inhibitors

might be optimally combined with autophagy modulators to produce a more robust antitumour effect.¹⁰ But this observation begs a more important question: is the Src signalling pathway a relevant target for drugs in castration-resistant prostate cancer, even though it is constitutively active? The READY trial might have been asking too much of dasatinib to improve survival in an unselected cohort when it is unknown if the proposed target is the primary driver of prostate tumour biology.

Considering all this information in retrospect, the READY trial might have been doomed to fail at its very outset. This trial is an example of the triumph of hope over science, and a reminder to all of us in the medical research community to temper our enthusiasm and heighten our scepticism before embarking on further clinical trials.

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