reported for rectal cancer. Perhaps now might be the time for a change in practice.

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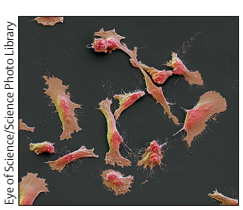
1 Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. *Colorectal Dis* 2009; **11:** 354–64.
2 MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341:** 457–60.
3 West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol* 2008; **9:** 857–65.
4 Bertelsen CA, Neuenschwander AU, Jansen JE, et al. Short-term outcomes after complete mesocolic excision compared with 'conventional' colonic cancer surgery. *Br J Surg* 2016; **103:** 581–89.
5 West NP, Kobayashi H, Takahashi K, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. *J Clin Oncol* 2012; **30:** 1763–69.
6 West NP, Sutton KM, Ingeholm P, Hagemann-Madsen RH, Hohenberger W, Quirke P. Improving the quality of colon cancer surgery through a surgical education program. *Dis Colon Rectum* 2010; **53:** 1594–603.
7 Bertelsen CA, Neuenschwander AU, Jansen JE, et al. Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol* 2015; **16:** 161–68.
8 Bertelsen CA, Neuenschwander AU, Jansen JE, et al. 5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study. *Lancet Oncol* 2019; **20:** 1556–65.

Maintenance chemotherapy in rhabdomyosarcoma: the new standard of care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In *The Lancet Oncology*, Gianni Bisogno and colleagues[1] present the results of an important frontline, phase 3 randomised study in children and adolescents with rhabdomyosarcoma. This trial was done by the European paediatric Soft tissue sarcoma Study Group (EpSSG) cooperative group, in children and adolescents with previously untreated high-risk non-metastatic rhabdomyosarcoma, and shows the benefit of six cycles of vinorelbine and oral cyclophosphamide maintenance chemotherapy in this subgroup of patients.

Although rhabdomyosarcoma is the most common soft tissue sarcoma in children, the disease is still rare, with about 400 newly diagnosed cases each year in Europe and a similar incidence in the USA. Rhabdomyosarcoma consists of two distinct molecularly defined cancers. Tumours with *PAX–FOXO1* fusions (either *PAX3* or *PAX7*) show alveolar histological features and usually do not have other somatic mutations. Fusion-negative tumours most often have embryonal histological characteristics and harbour mutations in key signalling pathways.[2] Unfortunately, at present we do not have the tools to target these alterations, nor have we found substantial differences between fusion-positive and fusion-negative tumours in their response to cytotoxic chemotherapy. As is typical for frontline rhabdomyosarcoma trials, this EpSSG study included both biological entities, which increased the heterogeneity of the study population.

Although cooperative group studies in Europe, Australia, New Zealand, and North America initially[3] made great strides in improving outcomes with the introduction of multi-agent chemotherapy, these results have plateaued in recent decades.[3] These previous studies tested many classes and combinations of chemotherapy drugs with clinical activity in rhabdomyosarcoma, including alkylating agents (cyclophosphamide, ifosfamide, melphalan, and trofosfamide), anticancer antibiotics (dactinomyin, doxorubicin, and idarubicin), vinca alkaloids (vincristine and vinorelbine), epipodophyllotoxins (etoposide), and camptothecins (topotecan and irinotecan). Before this EpSSG trial, all studies that added other active chemotherapy drugs to standard treatment (an alkylator [ifosfamide or cyclophosphamide], vincristine, and dactinomycin) did not report improved outcomes. As suggested in a commentary discussing the previous European rhabdomyosarcoma study, perhaps the issue is not that we do not have enough cards (ie, cytotoxic drugs) in our deck, but that we have not learned to play them well.[4]

This EpSSG study had some flaws. The background supporting this maintenance combination was sparse, based on two studies led by Casanova and colleagues: a single-agent vinorelbine trial (with six of 12 patients with rhabdomyoscarcoma achieving objective responses)[5] and

a follow-up vinorelbine plus cyclophosphamide study in which three of eight patients with rhabdomyosarcoma achieved a response.[6] Although the entry criteria for randomisation to maintenance therapy were well defined, assessment of completeness of response was not centrally reviewed. Rather, this important criterion was the responsibility of the individual participating institution. The study design initially projected a 6-year accrual, capturing most children and adolescents with high-risk rhabdomyosarcoma in Europe—a relatively long time even by paediatric oncology standards. The original statistical design assumed enrolment of 388 patients and 200 events to detect a 12% increase in 3-year disease-free survival; during the conduct of the trial, the study design was amended, reducing the hazard ratio (HR) to 0·5 with a new sample size of 370 patients and 79 projected events. Ultimately the study required almost a decade of patient accrual. 120 families elected not to participate. The primary outcome of the study, 5-year disease-free survival, was 77·6% (95% CI 70·6–83·2) with maintenance chemotherapy versus 69·8% (62·2–76·2) without (HR 0·68 [95% CI 0·45–1·02]; p=0·061). Although clinically significant, the improvement in disease-free survival did not quite meet the statistical parameters defined by the revised design. Only a secondary outcome, overall survival, was both clinically and statistically significant (86·5% [95% CI 80·2–90·9] with maintenance chemotherapy *vs* 73·7% [65·8–80·1] without; HR 0·52 [95% CI 0·32–0·86]; p=0·0097).

During the EpSSG study, other studies reported activity of vinorelbine in rhabdomyosarcoma. Kuttesch and colleagues reported that four of 11 patients with rhabdomyosarcoma achieved an objective response with vinorelbine monotherapy.[7] With the vinorelbine plus cyclophosphamide combination, Minard-Colin and colleagues reported 36% of patients with recurrent rhabdomyosarcoma achieving an overall response (four of 50 achieving a complete response and 14 of 50 achieving a partial response).[8] We do not know whether the improved outcome in this EpSSG study is a result of adding vinorelbine, adding metronomic continuous oral cyclophosphamide, using an active chemotherapy drug pair, or extending the total duration of therapy. Other important questions include whether the results are equally relevant for both fusion-negative and fusion-positive tumours and whether they are relevant for other rhabdomyosarcoma risk groups. However, the rarity of rhabdomyosarcoma makes it unlikely that future studies will clarify all these uncertainties.

What then is the significance of the EpSSG study? Vinorelbine plus cyclophosphamide maintenance chemotherapy cured more children and adolescents with rhabdomyosarcoma than standard treatment without maintenance chemotherapy and was generally well tolerated. Appropriately, European investigators will incorporate this therapy regimen in future clinical rhabdomyosarcoma trials. Similarly, the Children's Oncology Group (COG) investigators opted to add this maintenance chemotherapy regimen for all patients with intermediate-risk rhabdomyosarcoma in the open ARST1431 (NCT02567435) frontline therapy trial (a similar group of patients to those eligible for the EpSSG study). The results of this EpSSG study now define maintenance chemotherapy as the new standard for this group of children and adolescents with rhabdomyosarcoma—cards well played.

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1 Bisogno G, De Salvo GL, Bergeron C, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2019; **20:** 1566–75.
2 Shern JF, Chen L, Chmielecki J, et al. Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors. *Cancer Discov* 2014; **4:** 216–31.
3 Wexler LH, Skapek SX, Helman LJ. Rhabdomyosarcoma. In: Principles and practice of pediatric oncology. 7th edn. Pizzo PA, Poplack DG, eds. Wolters Philadelphia, PA: Kluwer, 2016: 815–16.
4 Meyer WH. Playing bad cards properly: challenges to improving cure rates in rhabdomyosarcoma. *J Clin Oncol* 2012; **30:** 2431–33.
5 Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. *Cancer* 2002; **94:** 3263–68.
6 Casanova M, Ferrari A, Bisogno G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. *Cancer* 2004; **101:** 1664–71.
7 Kuttesch JF Jr, Krailo MD, Madden T, Johansen M, Bleyer A. Phase II evaluation of intravenous vinorelbine (Navelbine) in recurrent or refractory pediatric malignancies: a Children's Oncology Group study. *Pediatr Blood Cancer* 2009; **53:** 590–93.
8 Minard-Colin V, Ichante JL, Nguyen L, et al. Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and young adults with a relapsed or refractory malignant solid tumour: good tolerance profile and efficacy in rhabdomyosarcoma—a report from the Societe Francaise des Cancers et leucemies de l'Enfant et de l'adolescent (SFCE). *Eur J Cancer* 2012; **48:** 2409–16.