quality of life. The EQ-5D-3L assessment questions health status at the time of completion of the instrument and the EORTC QLQ-30 questions health status during the previous week. If the event does not occur at that time of assessment, it will not be recorded. An example in the COMBI-AD study is the common severe event of pyrexia. In patients who had pyrexia, 209 (72%) of 292 patients had two or more episodes, with the pyrexia lasting a median of 3 days (range 2–7).[2] The timing of the completion of the questionnaire will have affected the ability to capture these adverse events, such that the patients who stopped receiving therapy because of adverse effects might have recovered to equivalence with the less toxic group. The frequency of discontinuation and reversibility of adverse events is likely to be a reason for the apparent lack of effect on the average health-related quality-of-life score when the whole cohort is analysed.[1] The high frequency of discontinuation in the two adjuvant immunotherapy trials could have affected reporting of health-related quality of life.[4,6] These adjuvant trials were powered to assess survival and recurrence endpoints, not health-related quality of life. As designed, there would need to be several severe adverse events with long-term consequences before one would see a substantial effect on the comparison of health-related quality of life between groups, particularly in the two placebo-controlled trials.

Clinicians might have affected the health-related quality-of-life assessment because of early recognition and management of adverse events, including withdrawal of therapy, which could affect results, dependent on the timing of completion of the questionnaire. Patients' assessments might be influenced by being motivated and feeling optimistic about agreeing to participate in the trial. Patients might also perceive drug-induced toxicity as being indicative of potential benefit, or could believe they are receiving active treatment; as such, a true assessment of the effect of drug toxicity on quality of life is not recorded.[7]

In the COMBI-AD trial, for an individual who does not have known metastatic melanoma, the overall conclusion—that treatment with dabrafenib plus trametinib has the same health-related quality-of-life outcome as placebo—does not tell the full story. However, the patient can be reassured that if they have an adverse event or have ceased therapy that they are likely to return to a satisfactory functioning level. In COMBI-AD, the absence of a detrimental effect on longer term health-related quality of life, if the disease does not recur, is also reassuring. For immunotherapy trials, patients can be offered similar counselling related to recovery after adverse events and at the end of the treatment, although in these trials, the longer term impact on health-related quality of life is awaited.

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I declare no competing interests.

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Inhibition of PD-1 and VEGF in microsatellite-stable endometrial cancer

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A 2018 study[1] showed that the incidence of endometrial cancer increased over the past 25 years in several countries, especially those undergoing rapid socioeconomic transitions. Although early-stage endometrial cancer is treatable with surgery and adjuvant therapy, long-term outcomes for patients with advanced disease are

poor, and the activity of chemotherapy or hormonal therapy in this setting is very low. The US Food and Drug Administration's approval of the tumour-site-agnostic PD-1 inhibitor pembrolizumab for patients with high microsatellite instability solid tumours has given patients with high microsatellite instability endometrial cancer an effective new treatment option. However, only 20–30% of endometrial cancers have microsatellite instability, and PD-1 inhibition is much less efficacious in patients with microsatellite-stable disease.[2]

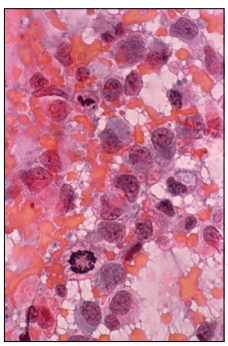
In *The Lancet Oncology*, Vicky Makker and colleagues report interim results of a phase 2 study[3] in which they assessed the activity of the multikinase inhibitor lenvatinib in combination with pembrolizumab in unselected patients with advanced endometrial cancer. 45 (85%) of the 53 patients in the per-protocol population had microsatellite-stable tumours. According to independent review, 25 (47%) of 53 patients had objective responses—a high proportion compared with those reported for standard-of-care chemotherapy regimens or endocrine therapy.

However, the combination of lenvatinib and pembrolizumab was associated with considerable toxicity. Hypertension, fatigue, and diarrhoea were each reported in more than 50% of patients, and grade 3 treatment-related adverse events occurred in 36 (68%) patients. Nonetheless, most adverse effects were managed with dose interruptions (39 [74%] patients) or reductions (28 [53%] patients). Only five (9%) patients discontinued treatment because of treatment related adverse events. It is unclear whether the treatment-related adverse events that were reported were produced synergistically by the combination of lenvatinib and pembrolizumab, or whether they were simply the addition of non-overlapping toxic effects common in patients who receive monotherapy with either drug. The frequencies of hypertension and proteinuria (which are associated with the use of multikinase inhibitors that block VEGFR) reported by Makker and colleagues were similar to those reported in previous studies[4,5] of lenvatinib monotherapy in advanced hepatocellular and thyroid cancer. Likewise, the immune-mediated side-effects were similar in type and frequency to those reported among patients given pembrolizumab monotherapy, although the proportion of patients with hypothyroidism was higher in Makker and colleagues' study.

The proportion of patients with objective responses in this interim analysis seems higher than that reported with pembrolizumab (13% [95% CI 2·8–33·6%]) or lenvatinib (14·3%) monotherapy in patients with advanced endometrial cancer.[2,6] Although non-randomised phase 2 studies that do not have an unbiased treatment comparator group consisting of patients from the same population are at risk of bias because of their small sample size and patient selection (ie, unintentional enrolment of patients with favourable characteristics), the activity of lenvatinib and pembrolizumab in microsatellite-stable endometrial cancer is promising enough that the combination clearly warrants further assessment in randomised phase 3 studies. Another caveat is that Makker and colleagues report interim findings. Although some might believe that longer-term findings would provide a stronger basis for a phase 3 trial, the fact that a phase 3 trial (NCT03517449) is already underway suggests that these interim findings were judged to be sufficient.

Notably, in mouse models, the combination of lenvatinib with a monoclonal antibody with activity against PD-1 resulted in greater anti-tumour activity than either agent alone.[7] Furthermore, co-inhibition of VEGF and PD-1 signalling could be an effective strategy to improve immunotherapy because VEGF modulates anti-tumour immunity by inducing proliferation of suppressive regulatory T cells, and VEGF inhibition in turn can decrease the number of regulatory T cells.[8] VEGF can also promote the expansion of myeloid-derived suppressor cells[9] and limit the maturation of dendritic cells capable of presenting tumour antigens and inducing a T-cell response.[10] Modulation of a VEGF-mediated immune suppressive state in the tumour microenvironment through inhibition of angiogenesis could be an effective strategy to improve the clinical activity of PD-1 inhibition in endometrial cancer, irrespective of the tumour's microsatellite status. In this respect, the combination of lenvatinib and pembrolizumab could also be of interest in other oncological specialties, because it will probably be a potential treatment option for other cancers with low tumour mutational burden or microsatellite stability against which single-agent immunotherapy has had poor efficacy. However, further clinical validation is required to establish whether use of a multikinase inhibitor such as lenvatinib truly affects the tumour environment, resulting in increased sensitivity to immune checkpoint inhibitors.

On the basis of the interim activity and safety data reported by Makker and colleagues, the Food



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See **Articles** page 711

and Drug Administration has granted breakthrough therapy designation to lenvatinib in combination with pembrolizumab for the potential treatment of patients with advanced microsatellite-stable endometrial cancer that has progressed after treatment with at least one previous systemic therapy. This designation will expedite development and review of the combination. The phase 3 study that is underway should help to clarify whether the promising results noted in this interim phase 2 analysis will translate to meaningful improvements in outcomes with an acceptable safety profile when compared with the standard chemotherapy available for patients with advanced microsatellite-stable endometrial cancer.

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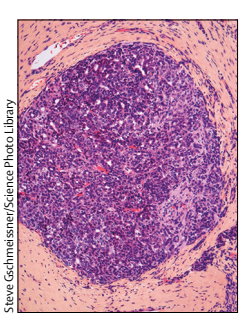
Is it worth completely resecting hepatoblastoma at diagnosis?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See Articles page 719

Until recently, the value of complete resection at the time of hepatoblastoma diagnosis was unclear. However, two key study from the American Children's Oncology Group (COG) and the European Childhood Liver Tumors Strategy Group (SIOPEL) achieved similar outcomes in patients with localised hepatoblastoma who underwent resection using two different approaches: upfront resection in selected cases (COG AHEP0731) and delayed resection after preoperative chemotherapy in every case (all prevoius SIOPEL studies).

In *The Lancet Oncology*, Howard Katzenstein and colleagues[1] report their findings on complete resection at diagnosis, in one of the groups of the COG AHEP0731 trial. Patients in this study showed good overall survival with shorter postoperative chemotherapy than normally used. Previously, COG reported good 5-year overall survival and event-free survival for children who had complete resection at diagnosis,[2] corroborating the firm role of primary surgery with curative intent in selected cases of hepatoplastoma, allowing for further de-intensification or even complete omittance of postoperative chemotherapy.

Nevertheless, some controversies persist regarding optimal patient selection that might partly be resolved by a new Pediatric Hepatic Malignancy International Therapeutic Trial (PHITT), organised jointly by COG, SIOPEL, and the Japanese Pediatric Liver Tumors group comparing two versus four courses of preoperative chemotherapy in patients with standard-risk hepatoblastoma (EudraCT number 2016-002828-85).

The question also remains whether use of cisplatin is superior to multi-drug therapy. The European SIOPEL 3 and SIOPEL 6 studies used cisplatin monotherapy, while the American COG approach used in AHEP0731 relied on a combination of multiple drugs (cisplatin, fluorouracil, and vincristine). For this reason, the comparison of toxicity and side-effects remains difficult. Long-term hearing loss (grade 1 or worse) was quite common and occurred in 29 (63%) of 46 patients in the cisplatin monotherapy group of SIOPEL 6.[3] Although ototoxicity in the COG study was infrequent (n=1 [2%]), vincristine-associated neurotoxicity (two cases of neuropathy that resulted in deviation from protocol-defined therapy) and febrile neutropenia (seven [14%] cases) were observed. It has not