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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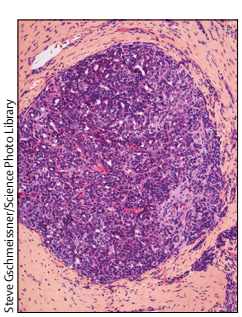
1 Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. *J Natl Cancer Inst* 2018; **110:** 354–61.
2 Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. *J Clin Oncol* 2017; **35:** 2535–41.
3 Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019; published online March 25. http://dx.doi.org/10.1016/S1470-2045(19)30020-8.
4 Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015; **372:** 621–30.
5 Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391:** 1163–73.
6 Vergote I, Teneriello M, Powell MA, et al. A phase II trial of lenvatinib in patients with advanced or recurrent endometrial cancer: angiopoietin-2 as a predictive marker for clinical outcomes. *J Clin Oncol* 2017; **31** (suppl 15)**:** 5520.
7 Kimura T, Kato Y, Ozawa Y, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. *Cancer Sci* 2018; **12:** 3993–4002.
8 Terme M, Pernot S , Marcheteau E, et al VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res* 2013: **73:** 539–49.
9 Gabrilovich D, Ishida T, Oyama T, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. *Blood* 1998; **92:** 4150–66.
10 Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functiona lmaturation of dendritic cells. *Nat Med* 1996; **2:** 1096–103.

Is it worth completely resecting hepatoblastoma at diagnosis?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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

been specified how ototoxicity in the AHEP0731 study was measured (eg, with pure tone audiometry) and how many patients were actually tested for it, which would be helpful to understand what the true proportion of ototoxicity was with this relatively small cisplatin dose.

Another interesting observation of the COG AHEP0731 trial regards the prolonged return (over 6 months) of serum α-fetoprotein concentrations to normal concentrations in a substantial proportion of patients (five [11%] of 46 patients). Only 25 (54%) patients normalised α-fetoprotein concentrations by the end of chemotherapy. It is also unclear why two additional patients never normalised α-fetoprotein concentrations, and it would be interesting to know what happened to them. For example, was this situation associated with the preresence of additional liver pathology?

A source of concern is the fact that three neoplastic events were associated either with positive PRETEXT annotation factors, such as tumour rupture, or the presence of the small-cell undifferentiated tumour histological variant.[4] Tumour rupture seems to be associated with worse prognosis, at least in the context of the CHIC analysis, and in the recent SIOPEL studies,[5,6] patients with tumour rupture were considered to be high-risk and received intense preoperative chemotherapy. It seems that, on the contrary to tumour rupture, microscopic residuum did not seem to affect the patients' outcome in this trial, which is in line with the recent SIOPEL study[7] classifying patients with post-resection microscopic residual disease that did not adversely influence the patients' outcome.

It is unusual that in this trial, as many as 20 patients had positive annotation factors (vascular involvement; or involvement of portal vein, hepatic veins, or inferior vena cava, or a combination). Seven of these patients were positive for both factors and might have been operated outside official trial recommendations. These observations call for caution about the inclusion of patients with positive PRETEXT annotation factors (vascular involvement or tumour rupture) in the low-risk hepatoblastoma group. Additionally, two patients classified as PRETEXT group III for tumour extent should have been considered ineligible for upfront resection. These observations raise the problem of insufficient adherence to surgical resection guidelines offered by the AHEP0731 study, which clearly counselled against upfront resection in patients with positive PRETEXT annotation factors. Unfortunately, in most centres worldwide, the decision on whether a tumour is initially resectable stems mostly from the experience of the surgeon and not from objective assessment, clearly showing the inherent problem of all past and upcoming new hepatoblastoma studies.

How can we standardise and determine the value of surgical intervention, either immediate or delayed, for these patients? How can we plan surgery in an objective and comparable manner? Without addressing these issues, it will be difficult to decide which patients benefit the most from immediate surgery and in which cases it should be avoided.

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1 Katzenstein H, Langham M, Malogolowkin M, et al. Minimal adjuvant chemotherapy for hepatoblastoma resected at diagnosis in children with low-risk disease (AHEP0731): a Children's Oncology Group, non-randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019; published April 8. http://dx.doi.org/10.1016/S1470-2045(18)30895-7.
2 Malogolowkin MH, Katzenstein HM, Meyers RL, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. *J Clin Oncol* 2011; **29:** 3301–06.
3 Brock PR, Maibach R, Childs M, et al. sodium thiosulfate for protection from cisplatin-induced hearing loss. *N Engl J Med* 2018; **378:** 2376–85.
4 Towbin AJ, Meyers RL, Woodley H et al. 2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT). *Pediatr Radiol* 2018; **48:** 536–54.
5 Czauderna P, Haeberle B, Hiyama E, et al. The Children's Hepatic tumors International Collaboration (CHIC): novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. *Eur J Cancer* 2016; **52:** 92–101.
6 Zsiros J, Brugieres L, Brock P, et al. Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): a prospective, single-arm, feasibility study. *Lancet Oncol* 2013; **14:** 834–42.
7 Aronson DC, Weeda VB, Maibach R, et al. Microscopically positive resection margin after hepatoblastoma resection: what is the impact on prognosis? A Childhood Liver Tumours Strategy Group (SIOPEL) report. *Eur J Cancer* 2019; **106:** 126–32.

First steps to regulate advertising of areca nut in China

The areca nut is the fruit of the areca palm (*Areca catechu*), which mainly grows in Hainan province in China. Areca nut is sometimes referred to as betel nut because betel leaves are often used to wrap it, but in China it is generally chewed without betel leaves. Although the areca nut has long been considered