

idiopathic arthritis (www.emea.europa.eu/pdfs/human/ewp/042204en.pdf).

We agree with Taddio and Marchetti that etanercept is a valid and important treatment option for children with juvenile idiopathic arthritis. However, direct-comparison studies of the anti-TNF agents in children with juvenile idiopathic arthritis are lacking, and the available studies have not shown clear differences in efficacy or safety among the anti-TNF agents in adults with rheumatoid arthritis.²⁻⁴ Thus, we do not agree that trials of biologic treatments should be performed only in patients with juvenile idiopathic arthritis in whom treatment with etanercept has failed or that infliximab and adalimumab, as compared with etanercept, are associated with a higher risk of serious infections and malignant conditions. Testing the anti-TNF therapies in approximately similar populations of patients with juvenile idiopathic arthritis allows patients, parents, and physicians to make the decision about the use of these therapies. Our trial of adalimumab also provides information about the use or nonuse of methotrexate as background therapy in children with juvenile idiopathic arthritis.

The assay used for detection of anti-adalimumab antibodies in this trial was an enzyme-linked immunosorbent assay that has been used for more

than 11 years in the adalimumab-development program, and it has been accepted by regulatory agencies worldwide. In the study of juvenile idiopathic arthritis, serum adalimumab levels were slightly decreased if anti-adalimumab antibodies were detected; however, this patient population still showed a strong clinical response (unpublished data).

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Sorafenib in Advanced Hepatocellular Carcinoma

TO THE EDITOR: Llovet et al. (July 24 issue)¹ report that their study of sorafenib therapy in patients with hepatocellular carcinoma showed a higher overall incidence of treatment-related adverse events with sorafenib than with placebo (80% vs. 52%), although the difference was not noted to be significant. The availability of new therapies, with expected small variations in objective end points, has heightened awareness of the importance of the impact of treatment on patients' overall lives.² Besides the traditional end points (e.g., median overall survival and time to radiologic progression), quality of life has been acknowledged as an important issue in cancer clinical trials and clinical practice.^{3,4} We think that an assessment of patients' quality of life would have provided important complementary information to be evaluated in the article.

Another concern might be the low incidence

in the study of grade 3 hypertension (2% in the sorafenib group vs. <1% in the placebo group). In a recent systematic review⁵ of published clinical trials evaluating hypertension associated with sorafenib, the overall incidences of all-grade and high-grade hypertension were 23.4% and 5.7%, respectively.

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TO THE EDITOR: Llovet et al. report the results of the use of a targeted agent in a large group of patients with hepatocellular carcinoma and relatively well-preserved liver function. Despite a very limited radiologic response rate, survival was extended in the sorafenib group. As effective targeted therapies become available, the use of conventional end points in cancer clinical trials is increasingly being challenged. Furthermore, frequently coexisting liver disease in patients with hepatocellular cancer makes the assessment of clinical benefit difficult. The level of alpha-fetoprotein, a useful biomarker for measuring antitumor response or progression in hepatocellular carcinoma, may prove to be more accurate and sensitive than conventional imaging in monitoring the response to therapy in this disease.¹⁻³ Llovet et al. report that in their study, the median baseline level of alpha-fetoprotein was one of the eight prognostic indicators for survival; however, the alpha-fetoprotein response to therapy has not been provided. It would be interesting to know whether the alpha-fetoprotein response or percent alteration of serial alpha-fetoprotein values correlated with the end points of disease progression, survival, or both during treatment with sorafenib as compared with placebo.

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1. Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. *Clin Liver Dis* 2001;5:145-59.
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TO THE EDITOR: Llovet et al. report that their trial showed a survival benefit for sorafenib as compared with placebo in patients with advanced hepatocellular carcinoma, and they conclude by stating that “studies evaluating sorafenib in combination with other molecular targeted therapies” are needed. However, conventional chemotherapy should not be ignored in this context. Indeed, Raf

signaling is implicated in doxorubicin resistance in vitro, which may be reversed by Raf inhibition,^{1,2} and there is clear evidence of a benefit from the combination of chemotherapy with antiangiogenic agents in a number of other cancers.³ Furthermore, data from a randomized phase II trial investigating the addition of sorafenib to doxorubicin in patients with hepatocellular carcinoma suggest that this is an interesting combination worthy of further study,⁴ particularly in an era when one expensive drug is unattainable in many societies, let alone a combination of two.

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THE AUTHORS REPLY: Spinzi and Paggi comment on the need for a quality-of-life assessment. Our trial included patient-reported outcomes measured through the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) questionnaire, and thus, their concern has already been addressed. We did not identify differences between sorafenib and placebo in the time to the end point of symptomatic progression. Treatment-related symptoms were more frequent in the sorafenib group and appeared early during therapy, but this was counterbalanced by the appearance of tumor-related symptoms in the placebo group later on. As mentioned in our report, the FHSI8 questionnaire may be inadequate for capturing quality-of-life benefits in this setting.¹ The low incidence of arterial hypertension is probably related to the presence of underlying cirrhosis that induces peripheral arterial vasodilatation with arterial hypotension. Accordingly, it is inadequate to compare our data with data from populations with preserved liver function.

We agree with Copur that there is a need to identify biomarkers as surrogates of the efficacy

of sorafenib, and such studies are under way.² If successful, such criteria will be of major help in the design of future investigations. Nevertheless, alpha-fetoprotein levels have had limited accuracy for such purposes.^{1,2}

Finally, Palmer proposes that priority be given to combinations of sorafenib with chemotherapy. Proposals should have a scientific rationale and be based on efficacy data obtained in phase II investigations, and, optimally, the safety profile of sorafenib should be maintained. We think that priority should be given to molecular targeted therapies because of the available positive signals, whereas chemotherapy has not exhibited efficacy and has severe side effects in this study population. Obviously, as in any clinical research activity, the final answer will come from well-designed phase III trials, and fortunately, several of them have already been planned.

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THE EDITORIALIST REPLIES: Palmer makes the excellent point that molecularly targeted agents can be effectively combined with conventional chemotherapeutic agents, particularly in contexts in which there is a strong scientific rationale for enhancement of the effects of chemotherapy by the targeted agent, as is the case with the combination of doxorubicin with sorafenib.¹ As I mentioned in my editorial, “combination trials of sorafenib and similar agents with other treatment approaches and classes of agents” are eagerly anticipated.

The comment by Spinzi and Paggi highlights the importance of quality of life as an end point in clinical trials of cancer therapy and is perhaps particularly relevant in this context, since there was no significant difference between the sorafenib and placebo groups with respect to the end point of time to symptomatic progression. Regarding the overall low incidence of hypertension in both groups, it is theoretically possible that this was due to the effects of cirrhosis on the systemic circulation. Patients with cirrhosis typically have low or low-normal blood pressures because of peripheral vasodilatation and may be relatively protected from sorafenib-induced hypertension.²

Copur notes the potential value of using trends in alpha-fetoprotein levels as a marker of response to targeted therapy. This would be consistent with results shown for changes in alpha-fetoprotein levels in patients with hepatocellular carcinoma and elevated pretreatment alpha-fetoprotein levels in response to liver transplantation, surgical resection, chemoembolization, radioembolization, or ablative therapies.^{3,4}

The editorial contained an error in the price reported for sorafenib in Korea. The correct price per month in Korea is \$3,013 (U.S. dollars).

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Initial Management of Epilepsy

TO THE EDITOR: With regard to the article on the initial management of epilepsy, by French and Pedley (July 10 issue),¹ there are about 1 million women of reproductive age who have epilepsy in

the United States. Guidelines recommend highly effective contraception, since these women have a higher pregnancy-related risk than their healthy peers.² Contraceptive decision making for women