Survival Data From a Phase II, Open-Label Study of Pazopanib or Lapatinib Monotherapy in Patients With Advanced and Recurrent Cervical Cancer

TO THE EDITOR: In the August 1, 2010, issue of *Journal of Clinical Oncology*, we reported the primary end point of progression-free survival (PFS) along with immature overall survival (OS) data for pazopanib versus lapatinib in patients with metastatic recurrent cervical carcinoma.¹ At the time of publication, we reported a planned interim analysis of OS, performed at the time of the primary PFS analysis. Forty-two percent of patients in the lapatinib group and 61% of patients in the pazopanib group were still alive and were thus censored for the analysis, as shown in Figure 2B of our article.¹ Median OS at this clinical cutoff date was 11.6 weeks longer in the pazopanib arm compared with the lapatinib arm (median OS, 50.7 weeks v 39.1 weeks; hazard ratio, 0.67; 90% CI, 0.46 to 0.99; $P = .045$).

The final OS analysis was performed when 62 patients (79.5%) in the lapatinib group and 56 patients (75.7%) in the pazopanib group had died. The median OS was 44.1 weeks for patients who received lapatinib and 49.7 weeks for patients who received pazopanib (hazard ratio, 0.96; 90% CI, 0.71 to 1.30; $P = .407$; Fig 1). Importantly, the study was not powered for OS. This study met its primary end point of demonstrating an improvement in PFS with pazopanib compared with lapatinib. The updated data may be helpful to clinicians designing clinical trials of pazopanib in cervical cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Fig 1. Overall survival in patients treated with lapatinib or pazopanib. HR, hazard ratio.

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REFERENCE

1. Monk BJ, Mas Lopez L, Zarba JJ, et al: Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol* 28:3562-3569, 2010

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Idiotype Vaccination As Consolidation Therapy: Time for Integration Into Standard of Care for Follicular Lymphoma?

TO THE EDITOR: We thank Ansell and Suman¹ for their careful review of the article by Schuster et al,² which reported the outcome of the phase III trial of a heterohybridoma-derived idiotype (Id) vaccine in patients with follicular lymphoma (FL) in first remission. In the editorial, the authors¹ raised the timely concern of "where a vaccine approach fits into the therapy of newly diagnosed patients [with FL]." Furthermore, the authors speculated that, given the widespread use of maintenance rituximab after remission induction therapy, the immune recovery gap before vaccination may limit the application of

therapeutic vaccination strategies in FL. This letter addresses these two important questions and highlights the urgent and unmet need for this new class of agent for FL.

As of February 2011, the National Comprehensive Cancer Network has, for the first time, recognized consolidation therapy as a defined treatment category for FL in first remission.³ As defined by the National Comprehensive Cancer Network, current consolidation-therapy options differ from induction therapies in that they primarily seek to prolong the first remission duration by consolidating the effects of induction therapy, which is primarily used to reduce the active, bulky tumor burden. Currently recommended consolidation or extended dosing therapies include radioimmunotherapy and rituximab maintenance, both of which may cause immunosuppression.⁴ In addition, radioimmunotherapy is myelotoxic. Because the median age of FL patients at diagnosis is 60 years, the development of nontoxic approaches to consolidation

therapy is highly desirable. With regulatory approval, an Id vaccine would represent the first active, nonimmunosuppressive and non-myelotoxic class of consolidation therapy.

Ideally, the purpose of consolidation therapy should be to eradicate residual cancer cells after induction therapy with the ultimate goal of curing the patient. An ideal agent for consolidation therapy should be extremely safe, improve the duration of remission, not preclude the efficacy of future therapies in cases in which these therapies become warranted, and be complementary to induction therapy to effectively eradicate residual cancer cells that are likely to be resistant to the agents used in induction therapy. Because rituximab is used during induction therapy, it is not an ideal agent for consolidation therapy. Conceivably, one potential mechanism of action by which maintenance rituximab prolongs the remission duration may be by reinducing remission in patients with subclinical relapses rather than by eradicating residual tumor cells after induction therapy. Furthermore, maintenance rituximab can have serious adverse effects and potentially lead to rituximab resistance, which limits the efficacy of subsequent treatment options. Therefore, agents used for consolidation therapy should ideally be different from those used in induction therapy and should have a different mechanism of action because residual tumor cells may be resistant to these agents.

The current product labels for each of the approved consolidation therapies bring attention to serious potential risks associated with their use, which are highlighted as black-box warnings. These risks include the risk of severe infusion-related reactions and risks common to profound and/or extended immunosuppression, such as fatal infectious events like progressive multifocal leukoencephalopathy. The labels for radioimmunotherapy agents warn of radiation-associated risks and adverse effects.

In their editorial, Ansell and Suman¹ stated that a 6-month waiting period for vaccine production may interfere with use of maintenance-therapy approaches, particularly rituximab maintenance. The vast majority of patients who achieve a response with first-line therapy maintain this response for 6 months whether followed by rituximab maintenance or observation.^{4,5} Therefore, the 6-month waiting period intended for immune reconstitution before the administration of Id vaccine falls within a window of little risk of relapse or progression.

As expected for an autologous therapy, the BV301 trial demonstrated that Id vaccination was safe and well-tolerated, grade 3 to 4 adverse effects were rare, and there were no Id-vaccine related deaths. Furthermore, as an active immunotherapy, Id vaccination does not induce immunosuppression and spares patients from the serious potential adverse effects related to extended immunosuppression or radiation exposure. Thus, therapeutic vaccination may prolong remission duration without risks associated with currently available consolidation therapies.

In summary, Id vaccination offers a nonimmunosuppressive alternative or potentially complementary approach to rituximab maintenance or radioimmunotherapy as a consolidation therapy for FL in first remission. By its mechanism of action, Id vaccination should eliminate the risk of the development of rituximab resistance. Thus, Id vaccination represents a potentially novel option for consolidation therapy that is safe and effective, unlikely to interfere with future therapies, and potentially increases the utility

of other therapies. Because of its mode of action, safety, efficacy, and targeted nature, Id vaccination may be a nearly ideal consolidation agent for FL.

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REFERENCES

1. Ansell SM, Suman VJ: Identifying patients with follicular lymphoma who are likely to benefit from an idiotype vaccine. *J Clin Oncol* 29:2748-2749, 2011
2. Schuster SJ, Neelapu SS, Gause BL, et al: Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. *J Clin Oncol* 29:2787-2794, 2011
3. National Comprehensive Cancer Network (NCCN): NCCN clinical practice guidelines in oncology (NCCN Guidelines): Non-Hodgkin's lymphomas. Version 2.2011. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
4. Salles G, Seymour JF, Offner F, et al: Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 377:42-51, 2011
5. Rummel MJ, Niederle N, Maschmeyer G, et al: Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final Results of a randomized phase III study of the StIL (Study Group Indolent Lymphomas, Germany). 51st American Society of Hematology Annual Meeting and Exposition, New Orleans, LA, December 5-8, 2009 (abstr 405)

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