Flaws in the trial design of IFCT-0802 by Gyawali et al.

We thank Gyawali et al. for their comments [1]. The 0802 randomized phase II–III trial [2] sought to evaluate the efficacy and safety of adding bevacizumab following induction chemotherapy (CT) in extensive-disease small-cell lung cancer (ED-SCLC). Due to the two-step study design, the whole randomly assigned population achieved a response (at least partial) at time of allocation. The chosen primary end point, i.e. disease control rate at time of fourth cycle delivery, has been calculated as the percentage of patients remaining responders at this landmark. Therefore, this end point is a given point on the progression-free survival (PFS) curve. PFS is an adequate end point in phase II study. From a methodological point of view, multitrail evaluations have previously shown that PFS is a valid surrogate end point for overall survival in first-line therapy of non-SCLC [3] and more recently in ED-SCLC [4].

The 0802 study, PFS since randomization did not significantly differ, with a median PFS of 5.5 months [95% confidence interval (CI) 4.9% to 6.0%] versus 5.3 months (95% CI 4.8% to 5.8%) in the CT alone and CT plus Bev groups, respectively (hazard ratio for CT alone: 1.1; 95% CI 0.7% to 1.7%; unadjusted P = 0.82). We concluded that administering 7.5 mg/kg Bev after induction did not improve outcome in ED-SCLC patients. Insofar as none of the tested biomarkers of neoangiogenesis has identified any specific subpopulation that could benefit from anti-angiogenesis therapy, the French Cooperative Thoracic Intergroup changed research paradigm toward other strategies (namely immunotherapy) in order to improve ED-SCLC outcome.

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MiR-29c downregulation contributes to metastatic progression in colorectal cancer

We have read with interest the recent article by Zhang et al. [1], which provides novel exciting findings about the role of miR-29c in colorectal cancer (CRC) progression and metastasis. Although little is known about the significance of this microRNA in CRC, some previous studies suggest its potential tumor suppressor role in this disease. Thus, miR-29c has been reported to be expressed at low levels in CRC [2, 3] and also to be predictive of CRC early recurrence [3]. In concordance with these data, the authors found that miR-29c was markedly downregulated in primary CRC tissues from patients with distant metastasis, and predicted worse outcome. Interestingly, miR-29c showed higher expression in liver metastatic tissues in comparison with primary tumor specimens. This observation suggests that miR-29c downregulation could be a transient relevant event in CRC progression to metastatic disease. Moreover, miR-29c reduced epithelial-to-mesenchymal transition, cell migration and invasion...
abilities of CRC cells, and metastasis development in vivo, further supporting its role in CRC metastatic development [1].

However, the precise status of miR-29c in metastatic CRC tissues is a major question to be fully investigated. Thus, we quantified miR-29c in primary and paired metastatic tissues from 17 CRC patients, 12 with liver metastasis and 5 with lung metastasis, using Taqman Low Density Arrays (TLDAs) panel A (Applied Biosystems). A pathologist reviewed the specimens to further confirm the diagnosis. All samples were taken anonymously and the ethical committee and institutional review board approved the project. Relative gene expression analysis was carried out using the 2–ΔΔCt method and U6B as internal control. We observed similar miR-29c expression between primary and metastatic tissues from those 12 CRC patients with liver metastasis. However, almost threefold increased miR-29c levels were found in the metastatic tissues of those cases with lung metastasis. We then investigated whether these differences were due to expression changes in the primary tissues or dependent on the metastatic site. Interestingly, miR-29c showed significantly lower expression in primary CRC tissues from patients with lung metastasis compared with those cases with liver metastasis (P = 0.046). No differences were observed when comparing miR-29c between liver and lung CRC metastatic tissues (P = 0.934). In summary, our results would indicate that deeper miR-29c downregulation would be required in the premetastatic CRC cell to develop lung metastasis than liver metastasis. In addition, the potential predictive value of miR-29c determining the CRC metastatic niche should be further confirmed in forthcoming studies.

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Journey to a faraway land

We have read the paper by Hartkopf et al. [1] with great interest. Returning home after a dormant phase in circulation is an interesting hypothesis which has been supported with data in literature. Returning to homeland after a period of time and resulting in locoregional recurrence was well proved with the study. However, there are some issues that can provide more additional valuable information about disseminated tumor cells (DTCs).

As mentioned in the text, 60% of the patients were treated with breast-conserving modalities. The locoregional failure data in total and subtotal mastectomized can give information about nature of DTCs and their clinical reflections. Do they cause more recurrences in a residual breast tissue? Another priceless data that can be obtained from the study is the adjuvant regimen efficacy in DTC-positive group. The group examined has been followed in a nearly 12-year period and probably with a numerous chemotherapeutic regimens with different cycles. Subgroup analysis of these regimens can provide information about efficacy of chemotherapeutics and maybe about exact length of cycles. Can more cycles of regimens provide more benefit in DTC-positive group?

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Reply to the letter to the editor ‘Journey to a faraway land’ by Alkan et al.

We thank Alkan and colleagues [1] for their interest in our article on the impact of disseminated tumor cell (DTC) detection on locoregional relapse (LR) [2]. We agree that further subgroup analyses could provide additional valuable information.

Indeed, it seems that DTCs cause more relapses in residual breast tissue. In the subgroup of patients that have been treated with breast-conserving therapy, the detection of DTCs was significantly associated with an increased risk of LR (hazard ratio (95% confidence interval) of DTC-positive versus DTC-negative