

Adjuvant bevacizumab for resected non-small cell lung cancer: the end of an era?

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Comment on: Wakelee HA, Dahlberg SE, Keller SM, *et al.* Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2017;18:1610-23.

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The field of adjuvant therapy for surgically resected non-small cell lung cancer (NSCLC) has remained practically unchanged for the last 10–15 years, since the results of several large randomized clinical trials evaluating the benefit of platinum-based chemotherapy after surgery were published (1-4). Taken together, these data suggested that the addition of platinum-based chemotherapy, usually with vinorelbine, to surgery in stage IB–IIIA (AJCC 6th edition) NSCLC provided a modest survival benefit of approximately 4% in 5-year, whereas there was absolutely no benefit in stage IA (T1NO) disease (4). Based on these data, four to six cycles of adjuvant platinum-based chemotherapy has become the standard of care for patients with surgically resected stage IB–IIIA NSCLC, although relapse rates remained unacceptably high in those patients, ranging from approximately 15% in stage IB to 40% in stage IIIA (1-4). Especially for stage IB disease, the CALGB-9633 trial suggested that not all patients diagnosed at this stage benefit from adjuvant chemotherapy and proposed that only patients whose tumors are more than 4 cm in greatest diameter at diagnosis might benefit from platinum-based chemotherapy (5). Since then, no biological agent has been able to show convincingly that it can improve this modest survival benefit when added to adjuvant platinum-based chemotherapy.

Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF), has been the anti-angiogenic agent most extensively studied in advanced

NSCLC. It has been thought to exert antineoplastic activity by both depriving the tumor from its necessary oxygenation and also by targeting the tumor microenvironment, exhibiting antineoplastic and immunomodulatory activity against tumor cells (6). Two landmark randomized phase III trials, one in the US (7) and one in Europe (8), have established the role of a bevacizumab in advanced NSCLC, by showing an overall survival (OS) benefit in the former and a progression-free survival (PFS) in the latter, when added to standard platinum-based chemotherapy. These two studies lead to regulatory approvals of bevacizumab for the treatment of advanced non-squamous NSCLC in both the US and in Europe, achieving an OS exceeding the landmark of 12 months for the first time (7,8). A series of other studies established the role of bevacizumab in the maintenance setting, either as monotherapy, or combined with chemotherapeutics such as pemetrexed (9) or with targeted agents like erlotinib (10). All these trials consistently showed an additional PFS benefit when another agent was added to bevacizumab in the maintenance setting.

Based on the aforementioned data, the E1505 trial was the largest ever conducted trial to test the benefit of bevacizumab in the adjuvant setting of early-stage NSCLC, when added to chemotherapy (11). The trial followed a prolonged accrual period (from 2007 to 2013) to recruit 1,501 patients with stage IB (>4 cm) to IIIA NSCLC and randomized them to either standard platinum-based chemotherapy or chemotherapy plus bevacizumab

concurrently with chemotherapy and as maintenance treatment thereafter, for 1 year. Of note, the chemotherapy regimen for each patient was selected before randomization and consisted of one of the following regimens: four 21-day cycles of cisplatin (75 mg/m² on day 1 in all regimens) in combination with investigator's choice of vinorelbine (30 mg/m² on days 1 and 8), docetaxel (75 mg/m² on day 1), gemcitabine (1,200 mg/m² on days 1 and 8), or pemetrexed (500 mg/m² on day 1). Patients in the bevacizumab group received bevacizumab 15 mg/kg intravenously every 21 days starting with cycle 1 of chemotherapy and continuing for 1 year. It should be noted that the pemetrexed arm was added later on during patient enrolment following a protocol amendment (11). Patients were stratified by chemotherapy regimen, stage of disease, histology, and sex. The primary endpoint of the study was overall survival, requiring thus a large number of patients and a long period of follow-up.

In the final results of the E1505 trial reported recently in *Lancet Oncology* by Wakelee *et al.* (11), the scientific community was notified that the study did not meet its primary endpoint of overall survival; After the sixth planned interim analysis occurring at 60.9% of information, the independent Data Safety and Monitoring Committee recommended release of the study results because the repeated CI (0.77–1.33) barely included the alternative of interest (0.79) and the trial was stopped for futility. At a median follow-up of 50.3 [interquartile range (IQR), 32.9–68.0] months, the estimated median overall survival in group A (chemotherapy group) has not been reached, and in group B (chemotherapy plus bevacizumab) was 85.8 (95% CI, 74.9 to not reached) months; hazard ratio (HR; group B *vs.* group A) =0.99; (95% CI, 0.82–1.19; P=0.90). Results were similar for DFS: The estimated median disease-free survival was 42.9 (95% CI, 36.7–57.0) months in group A and 40.6 (35.5–49.5) months in group B, giving an estimated disease-free survival HR for group B versus group A of 0.99 (95% CI, 0.86–1.15; P=0.95). Moreover, patients assigned to the bevacizumab plus chemotherapy arm suffered from additive toxicity as compared to the control arm, including overall worst grade [i.e., all grade 3–5 toxicities; 496 (67%) of 738 in group A *vs.* 610 (83%) of 735 in group B], hypertension [60 (8%) *vs.* 219 (30%)], and neutropenia [241 (33%) *vs.* 275 (37%)]. The clear conclusion of the authors was that bevacizumab does not have a role in this setting and should not be considered as an adjuvant therapy for patients with resected early-stage NSCLC.

The E1505 trial was a very well designed and conducted clinical trial, created to address a very specific scientific

question. The statistical design was robust, including a large number of patients allowing thus stratification for important confounders, such as disease stage, age, sex and treatment regimen. The authors selected very carefully the target population, excluding patients that had been previously shown not to benefit from adjuvant chemotherapy [namely patients with stage IA and IB (<4 cm) disease]. However, it should be noted that there was a high number of non-eligible patients (234 out of 1,501, 16%), included in the intention-to-treat-analysis, that the accrual period was long (6 years) and that a fourth chemotherapy regimen was added later in the trial following publication results of the cisplatin-pemetrexed as compared to the cisplatin-gemcitabine combination (12). It should be emphasized that, apart from the cisplatin-vinorelbine combination, all other three partners of cisplatin used in the E1505 trial (namely docetaxel, gemcitabine and pemetrexed) do not have solid scientific evidence for use in the adjuvant setting, but their use is rather based on extrapolation from the experience with these agents in the metastatic setting of NSCLC (1–4). Nevertheless, all of the above combinations are widely used in everyday clinical practice both in the US and in Europe and their use in the comparator arm of E1505 is thus justified. Another potential drawback of the design of the study, is the duration of bevacizumab use in the experimental arm: the choice of administration for 1 year is somewhat arbitrary and certainly not based on solid preclinical evidence; it follows the general strategy of administering bevacizumab for 1 year in the post-operative setting, in a way similar to the design of adjuvant bevacizumab in resected colorectal (13), breast (14) and ovarian (15) cancer. Of note, in many of these trials, as well as in E1505, the analysis of DFS curves shows that in the first 12–15 months of follow-up, the addition of bevacizumab to standard chemotherapy seems to confer a DFS benefit, by reducing the number of relapses, for as long as it is administered; In the E1505 trial, in particular, the chemotherapy plus bevacizumab arm seems to fare better in the first 24 months of the study (11); Nevertheless, after bevacizumab discontinuation, there is a cumulative rate of relapses in the experimental arm, resulting in an inferior performance as compared to the control arm. These observations are suggestive of the fact that bevacizumab may “delay” disease recurrence for as long as it is administered, but does not have the capacity to abolish the recurrence, reinforcing thus the hypothesis of the arbitrary choice of 1 year for bevacizumab administration. Could prolonged bevacizumab administration beyond 1 year maximize the

clinical benefit in levels of statistical significance? Presently, we do not know.

Another intriguing finding of the study is that the control arm performed notably well, and certainly much better than the corresponding arm of the ANITA trial, which evaluated the benefit of adjuvant platinum-based chemotherapy in a similar population (1). As the authors of E1505 comment themselves, the survival difference between E1505 and ANITA is nearly 20 months despite the fact that bevacizumab was not additive, and that patients received no other therapeutic intervention beyond that given in ANITA. This favorable performance of the control group has certainly contributed to the negative results of E1505; however, it should be noted that the two trials are largely not comparable: ANITA used only vinorelbine as a partner of cisplatin (pemetrexed and docetaxel were not available at that time), fewer supportive agents for treatment side-effects and certainly the diagnostic imaging techniques used at the time of the ANITA trial were not as efficient in detecting oligometastatic or micrometastatic disease as today, resulting in an overestimation of patients considered as fully resected. On the other hand, the patients in the E1505 trial were adequately staged as fully resected, resulting in a more selected population with a higher likelihood of favorable prognosis and longer overall survival.

Another point that merits to be discussed, is the finding from the exploratory analysis that in the subgroup of patients receiving cisplatin plus pemetrexed, there was a statistically significant favorable effect of the addition of bevacizumab in both DFS and OS (11). It should be underlined that the E1505 was not designed to compare chemotherapy regimens, and at this point no clear differences between the four chemotherapy regimens used have emerged. As the authors state in the discussion of their manuscript (11), follow-up is limited, especially for the cisplatin plus pemetrexed group because this regimen was added later in the trial and longer follow-up accounting for potential imbalances in prognostic factors between treatment groups are needed before any conclusions of an effect of chemotherapy choice on outcomes can be made.

Conclusively, the results of the E1505 trial, albeit negative, come of no surprise to the scientific oncology community. They come to add to the body of evidence suggesting that bevacizumab has no role in the adjuvant setting of completely resected malignancy. In colorectal cancer, bevacizumab is beneficial in the metastatic, but not in the adjuvant setting (13); the same is true for breast cancer (14) and for melanoma (16). In ovarian cancer,

bevacizumab increases survival after sub-optimal debulking (i.e., residual disease of more than 1 cm) (15), but not after optimal debulking, further suggesting that bevacizumab is active in the metastatic setting, or when residual disease is present, but not in the “truly adjuvant” setting. Where is this difference attributed? It has been hypothesized that in gross residual disease after surgery, bevacizumab acts as a “normalizer” of the chaotic tumor vasculature, enabling thus better penetration of cytotoxic agents inside the tumor and therefore better efficacy; On the contrary, the role of bevacizumab in the tumor microenvironment is less clear (6). It would be reasonable to say that after many negative trials of bevacizumab in the adjuvant setting of a variety of malignancies, the drug has no role in the pure adjuvant setting, it should not be used with that indication and that future clinical trials evaluating bevacizumab in the adjuvant setting are not likely to show clinical benefit and should therefore be strongly discouraged. It is fair to state that E1505 sets the end of the era of bevacizumab trials in the purely adjuvant setting. Future trials should definitely focus on the identification of predictive biomarkers for bevacizumab activity, which are desperately lacking currently. It is hoped that the development of such biomarkers, will enable the personalized administration of bevacizumab, in patients that are more likely to benefit from such a treatment.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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