Editorial

# Raising the bar for enthusiasm when looking at results of randomized phase II trials—the case of sunitinib in small-cell lung cancer

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**Abstract:** With the advent of targeted agents, randomized phase II trials designed with explicit comparative intent, to allow a better interpretation of the results obtained with experimental treatment, have become a common approach for anti-cancer drug development. In the Cancer and Leukemia Group B (CALGB) 30504 randomized phase II trial, patients with extensive-stage small-cell lung cancer (SCLC), without progression after four to six cycles of standard chemotherapy with cisplatin or carboplatin plus etoposide, were randomized to sunitinib or placebo, until disease progression. Primary endpoint of the study was progression-free survival (PFS), and the results were formally positive [hazard ratio (HR) 0.62; one-sided P=0.02]. However, the prognosis of patients with extensive-stage SCLC is particularly bad, and even a relevant relative benefit (i.e., an encouraging HR) will likely correspond to a debatable absolute benefit: the difference in median PFS between patients treated with sunitinib and patients assigned to control arm was slightly higher than 1.5 months. Is this difference in median PFS big enough to predict a clinically relevant benefit in overall survival? Unfortunately, we do not know. From a "clinical" point of view, is this small absolute improvement in PFS relevant enough to further invest in the strategy? Probably not, also considering the absence of known predictive factors. If the results of the phase II trial had been really promising, the subsequent phase III study should have been promptly conducted, but this was not the case. It seems that, this time, the bar for enthusiasm was already raised in the phase II setting.

**Keywords:** Sunitinib; small-cell lung cancer (SCLC); randomized trial

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While non-small-cell lung cancer has been recently characterized by a number of advances in terms of molecular characterization and availability of new therapeutic approaches, patients affected by small-cell lung cancer (SCLC) are currently treated with the same old cytotoxic drugs that became standard treatment several decades ago (1). This stalemate situation is particularly disappointing, if we consider the bad prognosis of these patients: in this setting, the identification of active agents remains an unmet need.

In the recently published Cancer and Leukemia Group B (CALGB) 30504 randomized phase II trial, patients with extensive-stage SCLC, without progression after four to six cycles of standard chemotherapy with cisplatin or carboplatin plus etoposide, were randomized to sunitinib (37.5 mg daily) or placebo, until disease progression (2). The primary endpoint of this study was progression-free survival (PFS), and the CALGB investigators applied the so-called "relaxed" statistical criteria [one-sided log-rank test with alpha =0.15 and 89% power to detect a hazard ratio (HR) of 0.60], allowing a small sample size (80 patients needed) despite the randomized design. Differently from the concomitant administration of sunitinib and chemotherapy initially planned, the maintenance schedule finally used in the CALGB study proved to be feasible. However, even if the daily dose used in this trial was lower compared to the full dose of sunitinib (50 mg) used in clinical practice for patients with renal cell cancer, toxicity was not negligible: nearly half of patients assigned to experimental arm required dose reduction, and incidence of severe fatigue was nearly doubled compared to placebo. As for activity, median PFS

from randomization was 2.1 months for patients assigned to placebo and 3.7 months for patients assigned to sunitinib (HR for sunitinib *vs*. placebo, 0.62; 70% confidence interval 0.48-0.79; one-sided P=0.02). The study report published in the *Journal of Clinical Oncology* (*JCO*) describes also overall survival results. Overall survival was a secondary endpoint of the study that was not powered to exclude potentially relevant differences between the arms. Median overall survival from random assignment was 6.9 months for patients assigned to placebo and 9.0 months for patients assigned to sunitinib (HR 0.78; 95% confidence interval, 0.48–1.27; one-sided P=0.16).

This was not the first study to test the activity of a maintenance strategy in patients with SCLC. In principle, maintenance appears a good strategy to test a new drug, because patients do not lose the chance of receiving established first-line chemotherapy (that is associated with quite high response rates) and, at the same time, they will receive the new drug as single agent, without the problems of tolerability related to concomitant administration with chemotherapy. Unfortunately, previous efforts of testing other drugs as maintenance options in these patients were negative (3). Adverse events observed with sunitinib emphasize that a favorable balance between efficacy and toxicity of treatment, that is relevant for all anticancer treatments, is particularly critical in the maintenance setting. According to the framework recently proposed by American Society of Clinical Oncology (ASCO) for the definition of value of anticancer treatments (4), treatment-free interval is one of the factors determining a higher score. At least in principle, together with the burden of toxicity, this could penalize maintenance approach, given that patients are treated until progression, without a treatment-free period. Of course, if the drug used as maintenance treatment shows an improvement in patients' outcome and the benefit in efficacy overcome the issues related to toxicity, the overall evaluation will be in favor of treatment.

Within a "stop or go" approach for drug development, phase II trials of anticancer treatments should be designed to allow selection of promising treatments for further clinical trials. In this early phase setting, the real challenge of clinical trial design is to be enough sensitive to avoid discarding a good treatment: in a disease where effective treatments, able to improve the modest results obtained with standard chemotherapy, are lacking, there is no doubt that a false negative result would be particularly disappointing. However, at the same time, these trials should be specific enough to avoid a positive result if the treatment is not good enough to deserve further consideration. Subsequent phase III trials imply a great investment in terms of number of patients and in terms of costs: ideally, only really effective treatments should pass the "phase II" filter. Several years ago, most phase II trials in oncology were single-arm studies, typically designed to test the activity of experimental treatments in terms of objective response. With the advent of targeted agents, randomized phase II trials designed with explicit comparative intent in order to allow a better interpretation of the results obtained with experimental treatment, have become a common approach for anti-cancer drug development (5). Sunitinib was tested as maintenance treatment for patients with advanced SCLC in another phase II trial, designed as a single-arm study, with proportion of patients alive at 1 year as primary endpoint (6). The result obtained was promising, because 54% of patients were alive after 1 year, but the authors themselves recognized that the single-arm design did not allow excluding selection bias in the interpretation of the outcome, and they called for a randomized trial.

In the recent *JCO* paper, Ready and colleagues commented their results stating that maintenance sunitinib was safe and able to improve PFS. This synthesis is technically true, but what next? Following this positive study, if the results are convincing and the benefit/risk ratio is judged acceptable, the next step should be the conduction of a phase III trial, to formally test the efficacy of the experimental drug. However, in the conclusions of the article, CALGB investigators call for the conduction of another phase II trial, claiming that an appropriate next step would be a randomized phase II trial, with overall survival as the primary endpoint. In other words, the results obtained are not considered "fully" positive by the authors themselves. Given those results, technically positive but clinically not exciting, the question is: why calling for another, preliminary trial? More generally, the results of the CALGB 30504, and the uncertainty about the future development of sunitinib in this setting despite the formally positive results of the study, deserve some considerations about the criteria to design, and to interpret, a phase II trial.

First issue: if the demonstration of a benefit in PFS is not considered enough for proceeding to phase III setting, that endpoint should probably be considered not adequate for a phase II trial. When individual patient data from 870 patients with extensive stage SCLC participating in six single-arm (274 patients) and three randomized trials (596 patients) have been pooled, PFS was strongly associated with overall survival, both at the patient-level and trial-level (7). Based on these data, PFS could be considered a better surrogate endpoint for overall survival, compared to response rate. The real problem is that the prognosis of patients with extensive-stage SCLC is particularly bad, and even a relevant relative benefit (i.e., an encouraging HR) will likely correspond to a debatable absolute benefit. For instance, in the CALGB trial the difference in median PFS between patients treated with

 

sunitinib and patients assigned to control arm was slightly higher than 1.5 months. From a methodological point of view, is this difference in median PFS big enough to predict a clinically relevant overall survival benefit? Unfortunately, we do not know. From a "clinical" point of view, is this small absolute improvement in PFS relevant enough to further invest in the strategy? Probably not. Furthermore, is a surrogate endpoint really needed instead of overall survival, given the very bad prognosis of these patients, characterized by a short life expectancy, and the limited impact of treatment administered after disease progression?

Second issue: no useful information is available about predictive factors of efficacy of sunitinib in this setting. This is not surprising, if we consider that the same drug has been previously developed and approved for clinical practice in other solid tumors, but the study of biomarkers and predictive factors was unfruitful. Despite the prognostic selection bias inherent in maintenance trials, where randomization selects patients who are free from progression at the completion of first-line chemotherapy, in the CALGB trial nearly half of the patients had already stopped maintenance treatment after 3 months. It is quite obvious that a predictive factor of efficacy could greatly improve the proportion of patients obtaining clinical benefit, avoiding the treatment to those who will likely receive only side effects. If we hypothesize that the experimental drug works in all patients, with a modest activity, there is no way to improve the results obtained (at least with that specific schedule of administration). On the other hand, if the drug works well in a limited subpopulation of patients, the availability of a predictive factor would be crucial for the performance of the treatment.

As of June 2015, at least in the U.S. National Institutes of Health ClinicalTrials.gov database, there is no active phase III trial testing sunitinib as maintenance treatment after platinum-based chemotherapy in patients with extensive-stage SCLC. A long time has passed since the completion of the randomized phase II trial, whose accrual was completed in December 2011, and data were locked in October 2013. If the results of the phase II trial had been really promising, the phase III study should now be open, but this was not the case. It seems that, this time, the bar for enthusiasm was already raised in the phase II setting.

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## Footnote

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