The PARAMOUNT trial in NSCLC: is the amount of benefit clinically meaningful?

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Abstract: The PARAMOUNT study recently updated for survival analysis, showed that continuous maintenance with pemetrexed (P) lead to a 3 months overall survival (OS) benefit in non-small cell lung cancer (NSCLC) patients not progressing after P-based induction chemotherapy. The conclusion are that, continuing P alone up to progression of disease, is better that stop chemotherapy after 4 cycles of cisplatinum/P doublet, at the expense of a slightly worst toxicity compared to placebo arm, and no worsening of quality of life. If the benefit in this population of performance status 0-1 (and nonsquamous histology) subjects, would have been the same with reintroduction of P (or with any active second line available) at the progression of disease, is a matter of debate. Appropriate randomized trials are ongoing and will answer to this question.

Keywords: Pemetrexed; maintenance therapy; non-small cell lung cancer (NSCLC); PARAMOUNT

The PARAMOUNT trial (1), recently published in the Journal of Clinical Oncology with update survival results, shows that continuation maintenance with pemetrexed (P), after an induction course of 4 cycles of chemotherapy with cisplatin + P in patients with stable or responding disease, offers a survival benefit of about 3 months [hazard ratio (HR) 0.78; P=0.0195] compared to placebo. Also, a progression-free survival (PFS) gain of 1.6 months was observed. The study enrolled patients with advanced nonsquamous non-small cell lung cancer (NSCLC) with performance status 0-1. The addition of further cycles of P maintenance increased haematological, and not, toxicity, that was however low in frequence and increased the risk of neutropenia in particular for those patients treated with more than six cycles of P. Overall there was no worsening of quality of life that was discussed in a separate previous publication.

A recent meta-analysis of randomized trials concluded that only switch maintenance is able to find an overall survival (OS) benefit, and only in adenocarcinomas, where hazard ratio (HR) is significant (2).

The question that arises from this study is the value of continuous maintenance therapy in (fit) patients, not progressing after platinum/P-based chemotherapy, and the weight of this benefit into the current strategy of treatment of NSCLC adenocarcinoma. The data show that in all subjects (not progressing after 4 cycles of platinum-based chemotherapy) maintenance therapy is an acceptable treatment that can be discussed and proposed to patients.

A second point of discussion is the value of second and further lines of therapy, and their impact on OS of patients. There are no doubts that in this well selected population of nonsquamous carcinomas, OS is among the highest observed with a first line doublet [Scagliotti trial showed 12.6 months of OS with cisplatinn/P (3)]. It is well known however the influence of post progression survival (PPS) also in lung cancer (4), other than breast and colorectal cancer. In fact in NSCLC, PFS is not well correlated with OS due to crossover to second line treatment. In PARAMOUNT trials PPS is about 10 months (60% of the overall amount.
of survival) and this is likely related to salvage second line treatments (about 70% of patients did it). If we observe the median OS of second line P in performance status 0-1 patients in the Hanna registrative trial (P vs. docetaxel), this value is 9.4 months, comparable to PPS of Paz Ares study (5). This data highlight the importance of selection of patients suitable for a maintenance treatment. Can we hypothesize that if we treat fit patients (with performance status 0-1) with second line chemotherapy, we can offer a similar OS than with maintenance? Obviously this hypothesis may be confirmed with a properly randomized trial. Fidias did not showed a significantly increased survival but only a delay in PFS, with early vs. delayed docetaxel, in a randomized phase III trial of switch maintenance (6). If the same concept is true with continuous maintenance is presently unknown.

Other open question are maintaining (or improving) the quality of life parameters, and the costs/benefits ratio. In a separate paper Gridelli and colleagues explored the quality of life aspects of the trial, and resource use (6). Overall the use of P maintenance did not worsen the quality of life according to EQ-5D questionnaire but patients on maintenance P required more transfusions, granulocyte colony- or granulocyte-macrophage colony-stimulating factors, anti-infectives, and hospitalizations because of study drug (8.4% versus 3.3%, P=0.028) than placebo-treated patients required. In Ciuleanu trial of switch P maintenance quality of life was similar to placebo, except for a small increase in loss of appetite, and significantly delayed worsening of pain and haemoptysis (7). Overall it can be stated that quality of life during P maintenance is similar, even not better, than no maintenance patients.

In our opinion, this maintenance trial adds new opportunity to the current treatment of NSCLC patients, but does not resolve the problem. In fact, this is a potential treatment option for all patients with excellent performance status with stable or responding metastatic disease after the induction platinum/P-based chemotherapy; the ideal candidate for maintenance is not yet known. However fit and young subjects with nonsquamous NSCLC histology seem to be the ideal candidates. This option has to be carefully discussed with the patient according to the fact that, if his/her conditions remain optimal after the disease will progress, the same treatment could be delivered as second line with likely similar benefit in survival. Current guidelines, NCCN in particular, report maintenance as a possibility. Another question is also is the benefit observed with agent different from P. In at least 2 trials in fact, maintenance gemcitabine did not result in an improved outcome compared with observation alone after cisplatin/gemcitabine induction (8-10).

In conclusion, there are no doubts that PARAMOUNT trial offers a significant benefit with maintenance P after cisplatin/P induction to all patients with NSCLC and nonsquamous histology. This study gives a relevant contribute to the treatment of NSCLC, opening a new window in a never ended discussion.

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References


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