

A strong step forward in maintenance therapy for non-small cell lung cancer treatment

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The PARAMOUNT trial results published by Paz-Ares *et al.* will have a significant impact on the ongoing debate on maintenance therapy in non-small cell lung cancer (NSCLC) (1).

Multiple randomized clinical studies have demonstrated that longer duration of platinum-based chemotherapy result in similar survival than shorter duration of treatment (2,3). These trials have led to the adoption of 4 to 6 cycles of platinum-based doublet as the standard of care for the treatment of NSCLC. The lack of benefit of prolonged therapy could be, at least in part, secondary to additional toxicity preventing the administration of as many cycles of treatment as intended. Thus, the recommendation of a “treatment break” after initial 4 to 6 cycles of treatment and offering further therapy at progression of disease became the usual practice. Ultimately, all patients with stage IV NSCLC progress, and a third of them for various reasons (as shown in clinical trials as well as market research) will never receive treatment beyond the first line therapy (4,5). Thus, continuation of a therapy, either with one or more of the agents used in the first line (continuation maintenance) or with different agents (switch maintenance) have been investigated.

Although trying to answer the same basic question, multiple clinical trials were conducted with different designs. The ECOG 4599 and FLEX trials used continuation maintenance in which bevacizumab or cetuximab respectively, were continued until progression of disease (PD) (6,7). The JMEN and SATURN trials used switch maintenance with pemetrexed or erlotinib

respectively, after completion of 4 cycles of platinum-based therapy (not including pemetrexed on the JMEN study) (5,8). All four trials showed improvement in progression-free survival (PFS) and overall survival (OS), albeit to several degrees. On the continuation maintenance studies such as ECOG 4599 and FLEX, it is not possible to dissect if the benefit of the targeted agent was secondary to the concurrent use with chemotherapy versus the maintenance phase. In the switch maintenance studies (JMEN and SATURN), the introduction of pemetrexed and erlotinib, respectively, is clearly responsible for the positive results observed. The criticism for both JMEN and SATURN was the imbalances in the type of therapy the placebo group received after progression of disease, with approximately a third of patients not receiving any further therapy at progression. Perhaps, the design of the clinical trial conducted by Fidias *et al.* using docetaxel as the active agent in maintenance phase will not be repeated even though it is the optimal design (considered by many researchers) to effectively measure the impact of maintenance therapy in NSCLC (9). Fidias *et al.* treated patients with platinum-based doublet followed by a randomization between immediate docetaxel until PD and placebo until PD with introduction of docetaxel at time of progression. Even with this trial design, approximately a third of patients never received second line treatment. Therefore, it is reasonable to postulate that the benefit observed in these maintenance trials can be merely because of the assured use of further therapy beyond first line rather than the timing of this therapy (before progression

versus at progression).

The PARAMOUNT trial provides the first evidence that continuation maintenance with a chemotherapeutic agent (pemetrexed) can lead to a clinical benefit in non-squamous NSCLC (1). For the last 4 years, pemetrexed has been the focus of attention due to its efficacy and tolerability in this population. The JMEN proved pemetrexed efficacy by increasing PFS and OS after patients were exposed to a non-pemetrexed platinum-based doublet (5). So, the question has been until now: for those patients who had pemetrexed as part of their initial regimen is it useful to continue this agent beyond 4-6 cycles when they are benefiting? Thus far, PARAMOUNT has reached its primary endpoint: PFS; therapy has also been well tolerated in comparison with placebo. Moreover, a preliminary survival analysis has shown that pemetrexed continuation offers a median survival of 13.9 *vs.* 11 months for those patients randomized into placebo arm (hazard ratio =0.78; P=0.034) (10). Ten percent more of patients were still alive for those randomized into the pemetrexed arm over the placebo group at the moment of preliminary survival analysis. This study will have major impact in clinical practice as pemetrexed is being increasingly used in the front-line treatment of patients with non-squamous histology thanks to the results from registration trial of pemetrexed in first line (11). PARAMOUNT results allow clinicians to obtain the most benefit from one drug (in this case pemetrexed) used in front-line and then continuation maintenance, and reserve other efficacious agents for later on.

The incorporation of pemetrexed in combination with bevacizumab whether in the front-line and/or maintenance setting remains a question of great interest. The combination of triplet induction including pemetrexed and bevacizumab is not recognized yet as category 1 by the US National Comprehensive Cancer Network or holds level 1 based-evidence. It will not take too long to know the results of POINTBREAK study which is comparing this triplet against the ECOG 4599 regimen (carboplatin/paclitaxel/bevacizumab). The AVAPERL trial using the combination of cisplatin/pemetrexed/bevacizumab followed by a randomization to either pemetrexed/bevacizumab *vs.* bevacizumab alone already demonstrated clear improvement in PFS for the combination compared to bevacizumab alone (7.4 *vs.* 3.7 months from randomization) (12) Thus far, we can say that PARAMOUNT has demonstrated feasibility, safety, PFS advantage, and encouraging preliminary OS data. Continuation maintenance with pemetrexed will likely be a new standard of care.

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