Editorial

How many drugs in the maintenance setting for non-small-cell lung cancer? For what benefit?

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Abstract: Maintenance treatment has been used for several years inside clinical trials. Meta-analyses have been published. A new clinical trial (AVAPERL) has been recently published. Despite significant increase of progression-free survival (PFS), overall survival (OS) has not been changed with these strategies. Before a transfer into clinical practices and guidelines, new data on economic analyses (the cost effectiveness ratio was very high among specific studies) and quality of life are mandatory.

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Maintenance treatments are widely employed in oncology, but their use in the treatment of non-small-cell lung cancer (NSCLC) is relatively recent. Clinical trials have proliferated and several review articles have been published (1-6). Two principal strategies are used: administration of a drug not used in the initial platinum-based doublet (switch maintenance) or pursuit of the drug used in the initial doublet (continuation maintenance).

Despite the need for specific trials to validate continuation maintenance, bevacizumab maintenance after the end of doublet therapy was immediately adopted (6). However, the very concept of maintenance therapy remains controversial, because of its only modest impact on overall survival (OS), the risk of adverse effects, and the need to take into account both economic considerations and quality of life.

Several meta-analyses have recently been published (7-10). The results showed a prolongation of progression-free survival (PFS) but not of OS.

The article by Barlesi *et al.* (11), published in this issue, describes a phase III trial (AVAPERL) of bevacizumab maintenance therapy, with or without pemetrexed, following induction chemotherapy with cisplatin, pemetrexed and bevacizumab. PFS was significantly prolonged in the group receiving both bevacizumab and pemetrexed (3.7 versus 7.4 months, HR =0.48), regardless of age, subgroup, performance status, smoking history, or the response to induction therapy. The authors state that toxicity was moderate but offer no data on quality of life.

Recently, the PARAMOUNT phase III trial (12) showed an increase in PFS when pemetrexed was continued after induction chemotherapy, in keeping with the results of dual maintenance therapy in the AVAPERL trial. Several updates of AVAPERL trial were presented at the ASCO meeting (13). PFS was 3.7 months in the subgroup treated with bevacizumab alone, compared to 7.4 months in the group treated with both bevacizumab and pemetrexed ($P<0.0001$). In contrast, OS was not significantly different between bevacizumab alone (13.2 months) and bevacizumab plus pemetrexed (17.1 months) (13). It should be emphasized that this trial was not designed to show a difference in survival.

Existing studies of the efficacy of maintenance therapy are numerous and methodologically sound, and provide a high level of evidence. Barlesi's randomized phase III trial is well-designed, and could be added to these studies.

Although regulatory authorities have approved the use of maintenance treatment, clinical practice guidelines are more circumspect. The ESMO guideline (14) states that the value

of maintenance has not been convincingly demonstrated and that the decision must be taken on a strictly individual basis. It should be remembered that several randomized trials giving consistent results are required to induce a change in clinical practice (use of two drugs instead of one for maintenance therapy, for example).

The usual primary endpoint, PFS, is not necessarily the best choice. Most published studies showed an increase in PFS, but this did not translate into a gain in OS. Some critics consider that maintenance treatment is simply a form of advanced second-line therapy (3). The most convincing argument that could permanently change clinical practice in this setting would be a significant improvement in OS, as this would override most criticisms of maintenance therapy.

It is also important to take account of quality of life and toxicity. The lack of any increase in adverse events during maintenance therapy has been highlighted in numerous publications (15,16). However, no clinical trials have shown an improvement in quality of life, as underlined by the quality-of-life analysis of the PARAMOUNT trial (16). Until these therapies are at least shown to provide a clear improvement in quality of life, the final decision should be on an individual base after information of the risks and benefits of the different options.

Cost-effectiveness is the main factor to be considered. Consolidation treatments have become unaffordable (17). Many articles have been published on this subject, concerning different drugs. Articles on pemetrexed have reached much the same conclusion. Tsuchiya *et al.* (18) constructed an economic model based on the results of the clinical trial conducted by Ciuleanu *et al.* (19). The payer's perspective was adopted, and the cost-effectiveness figures thus obtained were far higher than any national health system could possibly accept. For Bongers *et al.* (20), analyzing the same database (19), pemetrexed was not cost-effective from a Swiss healthcare perspective [€106,222 per quality-adjusted life year (QALY)]. The two main drivers in the sensitivity analysis were utility value and palliative care costs in the pemetrexed group. Regarding bevacizumab, Goulart and Ramsey (21) constructed a model based on a single clinical trial (22) and concluded that consolidation therapy was not cost-effective for the US healthcare system. The UK's NICE conducted an analysis of erlotinib maintenance therapy and found that it was not cost effective (23), although thresholds are often lower in the UK than elsewhere. Walleser *et al.* found a cost-effectiveness ratio of less than €30,000 in several European countries when they analyzed patients included in the SATURN trial (24). The same conclusions were reached in the "stable disease" subgroup of the SATURN trial, in terms of cost per life-year saved (25). Overall, consolidation treatments have not yet been validated in economic terms (cost-benefit ratio), and further studies are therefore needed.

In conclusion, both continuation and switch maintenance therapy have shown a favorable profile in terms of toxicity and PFS. However, their use is limited by the lack of improvement of OS in most studies, together with the absence of data on quality of life and the potential impact on costs. Barlesi *et al.* (11) showed that PFS was improved by dual-agent continuation maintenance therapy, while the impact survival and quality of life will probably be reported in future publications. Further studies will be needed to confirm these results. This will provide the necessary basis for clinical practice guidelines to consider the role of the different types of maintenance therapy, including the use of single- versus dual-agent therapy. This publication provides additional elements of therapeutic choice. However, maintenance treatment remains an option and not a standard of care. The final decision must await further economic analyses.

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