# ISSUE BRIEF

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## PANEL 2
## Evidence for Use of Maintenance Therapy

*Richard L. Schilsky*, Deputy Director, University of Chicago Comprehensive Cancer Center
*Margaret Mooney*, Chief, Clinical Investigations Branch, National Cancer Institute
*Anthony Murgo*, Associate Director for Regulatory Science, US Food and Drug Administration
*Tal Zaks*, Vice President, Oncology, Sanofi-Aventis
*Patty Spears*, Susan G. Komen for the Cure

**Rationale for maintenance therapy**

Given that many cancers will inevitably progress following initial response to treatment, and that newer targeted cancer drugs often have fewer side effects than standard chemotherapy, maintenance therapy to prevent or delay cancer progression or slow cancer growth is increasingly being considered as an option. Maintenance trials are currently being conducted despite a lack of consensus on appropriate design; additionally, it is often hard to interpret the results of these trials due to confounding effects such as patient drop out and crossover to alternative treatments. Therefore, this panel was convened with the goal of reaching consensus on the optimal design of clinical studies to assess the utility of maintenance therapy.

The term "maintenance therapy" can have many specific meanings, but one usage refers to treating a patient with a second-line drug immediately after that patient obtains maximal response to first-line induction therapy (defined as "switch maintenance" by the NCCN). In many advanced cancers, patients may respond well to first-line therapy but then progress and deteriorate so rapidly that they are unable to receive second-line therapy. Thus, switch maintenance increases the number of patients exposed to an active drug and, in theory, extends the progression-free period for these patients. Switch maintenance may also prevent or delay the development of tumor-related symptoms. This form of maintenance therapy has recently been studied in the treatment of non-small cell lung cancer (NSCLC), an aggressive malignancy in which those patients who respond to first-line chemotherapy typically relapse quickly and have a median survival of approximately one year. Specifically, three agents that have shown efficacy in the second-line setting- docetaxel, pemetrexed, and erlotinib- have been tested as maintenance therapies (1-3), and pemetrexed and erlotinib have received FDA approval for this use (4, 5).

Another common form of maintenance therapy is referred to as "continuation maintenance", in which a patient continues to receive a targeted drug after induction therapy with that drug in combination with chemotherapy. This form of maintenance therapy is based on the premise that persistent suppression of certain molecular pathways may help restrain tumor growth. In some settings long term use of an active targeted agent has been associated with better treatment outcomes. A prime example of this is the anti-CD20 monoclonal antibody rituximab, which is regarded as the standard-of-care first-line treatment for follicular lymphoma and has recently been approved for continuation maintenance of this disease (6, 7). Rituximab has minimal toxicity, targets a relatively stable epitope, and can be administered infrequently due to its long half-life, making its use as a maintenance therapy against this incurable disease appealing. Continuation maintenance can also refer to continuing a targeted therapy that was a component of an

induction regimen even after disease progression. This strategy has been employed with trastuzumab in breast cancer (8) and with bevacizumab in a variety of malignancies (9, 10).

Although an attractive approach for staving off the progression of cancer and its symptoms, maintenance therapy is not without its drawbacks. First, while targeted therapies may be more tolerable than standard chemotherapy, they do have toxicities. By exposing patients to a targeted therapy for an extended duration, the exposure to the toxicities of that therapy is expanded and the risk of cumulative toxicities is increased. Second, while there are some tools available to demonstrate an improvement in QOL or a reduction in symptoms, the direct benefit to patients of delaying tumor progression (whether assessed by imaging or symptoms) is difficult to determine unless it results in prolongation of overall survival. In addition, the risk of developing resistance to the therapy is increased, leaving the patient with one less therapeutic option in the future. Third, it is not clear that maintenance therapy is necessarily superior to administering or resuming the maintenance treatment at the time of tumor progression. Fourth, although not a component of the risk-benefit ratio, maintenance therapy significantly increases cost and inconvenience for the patient. With both the potential benefits and risks in mind, studies should be designed to show that a patient obtains a true clinical benefit from receiving a maintenance therapy. The ultimate goal of maintenance therapy should be to improve overall survival or patient quality-of-life compared with either no maintenance or application of the "maintenance" treatment at the time of tumor progression.

**Case studies**

The panel examined two clinical trial scenarios to evaluate the use of maintenance therapy in cancer treatment. For each, the group considered how the studies can be optimally designed, what endpoints are appropriate, and how large the trials must be to demonstrate a meaningful clinical benefit. To help with this, a retrospective statistical analysis of previous and existing trials for each scenario was performed.

*Scenario 1: Switch Maintenance*

The first scenario is a clinical trial design that could be used to demonstrate the value of immediate introduction of Drug X following achievement of best response to standard first-line chemotherapy with the goal of maintaining remission as opposed to waiting until disease progression to begin treatment with Drug X. This scenario is first examined assuming that Drug X has already demonstrated activity against the cancer being treated, but has not been used in the course of treatment thus far. We then examine this scenario for situations when Drug X has not yet been tested for efficacy in the cancer being treated.

The exemplar trial for this scenario is the SATURN trial used to support FDA approval of erlotinib for maintenance therapy in NSCLC following 1$^{st}$ line platinum chemotherapy (3, 11). This trial compared first-line maintenance erlotinib treatment to placebo followed by the physician's choice of second-line therapy at the time of progression (Figure 1A). The SATURN trial demonstrated improvements in progression-free survival (PFS) and overall survival (OS) with erlotinib maintenance: median PFS in the placebo group was 2.6 months compared to 2.8 months in the erlotinib group (hazard ratio [HR] = 0.71), and median OS in the placebo group was 11 months compared to 12 months in the erlotinib group (HR= 0.81). Because erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR), tumors were analyzed by immunohistochemistry for EGFR expression (EGFR+ tumors). Among patients with EGFR+ tumors, the median OS in the placebo group remained 11 months while the median OS in the erlotinib group was increased to 12.8 months (HR= 0.77).

Because erlotinib is an agent with demonstrated activity in the second-line setting, the efficacy seen in the SATURN trial might not be surprising: in the placebo arm of this study, many patients may never have received erlotinib at any point in their treatment regimen. Thus, although the control arm of the SATURN trial might be a more accurate representation of clinical practice, the trial did not answer the question of

whether or not a patient truly benefits more from receiving erlotinib as first-line maintenance than they would have by simply waiting until disease progression to receive erlotinib. To specifically answer this question, a trial comparing first-line erlotinib maintenance with second-line treatment (i.e. maintenance vs. delayed treatment) would need to be performed (Figure 1B). A delay in tumor progression is likely a predictable outcome of maintenance therapy but may come with increased toxicities; therefore, the primary endpoint should be overall survival or some other endpoint that reflects clinical benefit, such as delay in onset of tumor-related symptoms. We performed a calculation using outcomes from the SATURN trial and applied them retrospectively to assess what sample size would be needed to show a similar improvement in OS (HR= 0.81, one-sided type 1 error =0.25, power=90%) using the maintenance vs. delayed therapy trial design. Given a median OS = 11.0 months in the control arm, a target hazard ratio of 0.81 would correspond to an improvement in median OS to 13.6 months in the experimental arm if the data were exactly exponentially distributed. This would require 1170 patients to be randomized over a period of 3.25 years. Although NSCLC is a common disease, completing such a large trial in a timely fashion might be difficult with an OS endpoint.

Of note, a confirmatory trial comparing first-line erlotinib maintenance with second-line erlotinib therapy as depicted in Figure 2B is currently being performed (NCT01328951). This trial includes overall survival as the primary endpoint and has an estimated enrollment of 610 patients. Eligibility criteria for this trial are similar to those for the SATURN trial, with the exception that the current trial is restricted to patients who do not have an EGFR-activating mutation (EGFR- tumors). The reason for the smaller sample size than in our estimate is not clear but could be the result of targeting a smaller hazard ratio in the trial.

In some situations, there may be compelling scientific rationale and data from preclinical studies to suggest that the activity of a new drug would be optimal if given in the maintenance setting. In such an instance, it would not be necessary to compare maintenance treatment with Drug X to delayed treatment with Drug X. The trial design could be set up similarly to the SATURN trial used to test the utility of maintenance erlotinib, but an important distinction would be that all patients would receive the same therapy post-progression (Figure 1C). This post-progression therapy ("Drug Y") should be the current standard-of-care and would be specified in the protocol. This trial would use overall survival as the primary endpoint.

*Scenario 2: Continuation Maintenance*

The second scenario is a clinical trial design that could be used to address the value of continuation of Drug X for persistent target suppression through disease progression as other elements of the treatment regimen are changed. One important aspect of this scenario is that it attempts to test whether there is a risk to stopping target suppression rather than testing for a benefit of maintaining it. For this scenario, we will examine continuation maintenance trials that have been performed with bevacizumab.

Bevacizumab inhibits the formation of new blood vessels by suppressing vascular endothelial growth factor (VEGF). Some studies have suggested that there is a benefit to maintaining VEGF-suppression throughout treatment and following remission. Further, because bevacizumab targets normal blood vessels and has no direct effects on tumor cells, withdrawing VEGF-suppression may actually pose a risk to patients. Calculation of tumor growth rates in renal cell carcinomas treated with bevacizumab has suggested that withdrawing bevacizumab even after disease progression can have the undesirable effect of accelerating tumor growth kinetics (12). This hypothesis provides one possible explanation for the discrepancy between observed magnitudes of benefits in PFS and OS in cancers treated with bevacizumab.

Bevacizumab in combination with chemotherapy extends overall survival in metastatic colorectal cancer (mCRC) in the first and second-line settings (13, 14). An observational cohort study of bevacizumab

combined with standard first-line chemotherapy in mCRC found that patients who continued to receive bevacizumab even after disease progression had improved overall survival compared to patients who discontinued bevacizumab at the time of progression (31.8 months OS vs. 19.9 months OS) (10). An ongoing randomized Phase 3 trial, Hoffmann-LaRoche ML18147 (AIO_0504/NCT00700102), seeks to test whether there is truly a survival advantage to continuing bevacizumab in metastatic colorectal cancer past tumor progression (15). In this trial, patients who had received first-line chemotherapy with bevacizumab are randomized at disease progression to receive second-line chemotherapy either with or without continuing bevacizumab until disease progression, unacceptable toxicity, or patient refusal (Figure 2A).

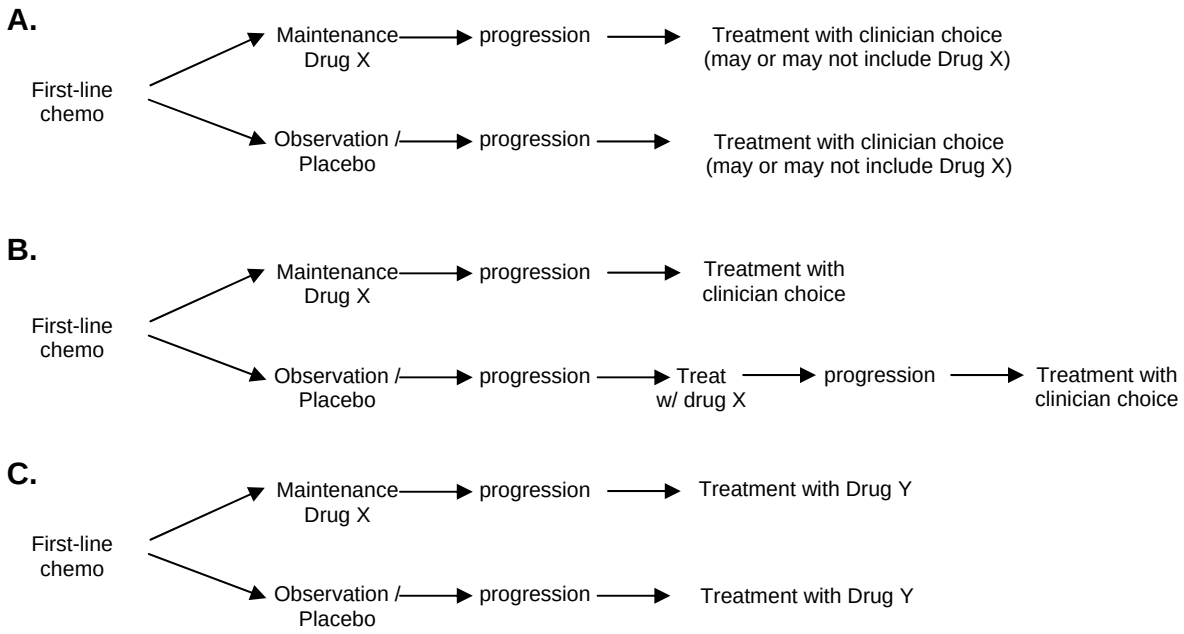
Here we describe a hypothetical trial assessing the benefit of bevacizumab continuation maintenance in ovarian cancer. Bevacizumab has been shown to prolong PFS when given for a prolonged duration (15 months) following first line chemotherapy and as maintenance until progression following second line therapy (16-18). This trial would use overall survival as the primary endpoint. In the ovarian cancer setting, the median overall survival is approximately 35-45 months following first-line therapy; we will use 36 months for a baseline and assume a clinically relevant improvement would require a hazard ratio of 0.8, or an improved OS of 45 months. The design of this trial is similar to that of the ongoing ML18147 trial, except that our hypothetical trial includes a third arm in which bevacizumab is not continued after induction (see Figure 2B). This design includes two randomization points: the first occurs after induction therapy; the second randomization point occurs at progression on the arm of the study where patients received bevacizumab after induction (combined 1/2 arm). The first randomization will be a 2:1 randomization and the second will be a 1:1 randomization. To have 80% power to detect a 20% reduction in hazard of death (HR=0.8) the study will need to randomize 1500 patients between the 3 arms (500 per arm). This design will also have 90% power to detect a HR of 0.8 between Arms 1 and 2 (18 vs. 22.5 months median OS), and 80% power to detect a HR of 0.8 between Arms 2 and 3 (36 vs. 45 months median OS). This calculation assumes an overall accrual rate 300 patients per year.

For the analysis, Arm 1 will first be compared to Arm 3 at a 0.025 one-sided significance level. If Arm 1 is shown to be significantly better than Arm 3, this will demonstrate that continuing bevacizumab past induction is beneficial. Arm 1 will then be compared to Arm 2 and Arm 2 will be compared to Arm 3 (both at 0.025 one-sided significance level). This strategy controls the overall type-one error of the design. If Arm 1 is shown to be significantly better than Arm 2, this will demonstrate that treating with bevacizumab through progression is beneficial.

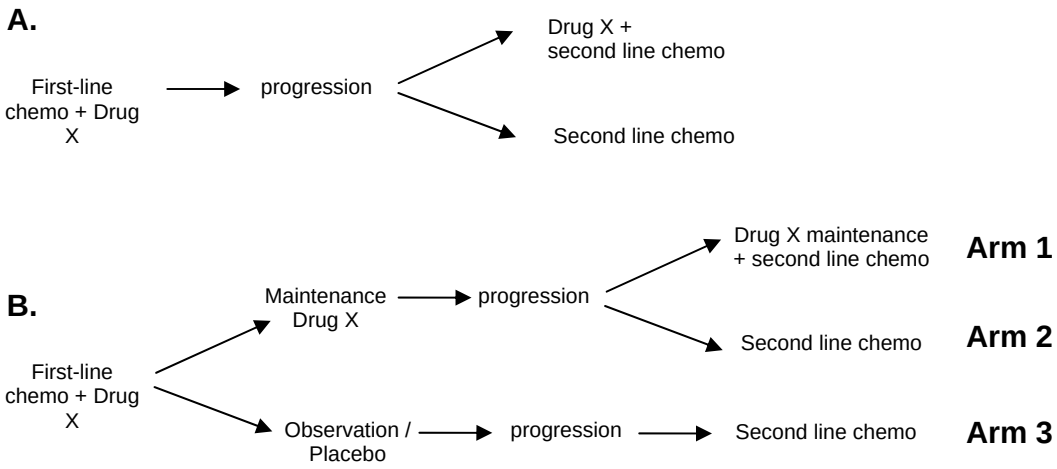
**Conclusion**

While maintenance therapy can provide significant benefit to patients by suppressing tumor growth and the development of tumor-related symptoms, it may be difficult to measure this adequately with hard endpoints such as overall survival. Thus, this is a situation where alternative endpoints, such as patient-reported outcomes, are sorely needed, and endpoints such as overall response rate (ORR) or PFS should be explored with the aim to show that the activity of next-line therapy is not decreased. Also, although PFS is generally not considered a sufficient measure of clinical benefit for drug approval as it is difficult to quantify the benefit of time without progression (even for symptomatic progressions), progression is typically considered an endpoint at which treatment stops or changes. Thus, both scenarios describe trial designs that continue the study intervention beyond the first progression, and may necessitate a second randomization. The feasibility of such designs, while theoretically attractive, will need to be determined, as they will require more resources and will face real-world challenges to enrollment and timely completion especially for drugs that are already available in the marketplace.

## Figure 1: Switch Study Layouts




## Figure 2: Continuation Maintenance

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