Recognizing and Overcoming Challenges in the Treatment of Recurrent Ovarian Cancer

The following is a transcript from a CME-certified multimedia activity, which may be found at:

www.peerviewpress.com/d/e017

Expert Panel Discussions
Presented by
Course Director and Moderator
Maurie Markman, MD
University of Texas
M. D. Anderson Cancer Center
Houston, Texas

William Patrick McGuire, MD
Franklin Square Hospital Center
Baltimore, Maryland

Robert L. Coleman, MD
University of Texas
M. D. Anderson Cancer Center
Houston, Texas

Discussion 1:
Current Therapeutic Options and Clinical Issues in Recurrent Ovarian Cancer: Where Do We Stand?

Discussion 2:
Looking Ahead: Emerging Options in Treatment of Ovarian Cancer

CME Reviewer
Robert D. Marsh, MD
University of Florida College of Medicine
Gainesville, Florida

Detailed faculty disclosure statements are available online at: **www.peerviewpress.com/d/e017**

This CME activity is jointly sponsored by the University of Florida College of Medicine and PVI, PeerView Institute for Medical Education.

This activity is supported by an educational grant from Ortho Biotech, Inc.

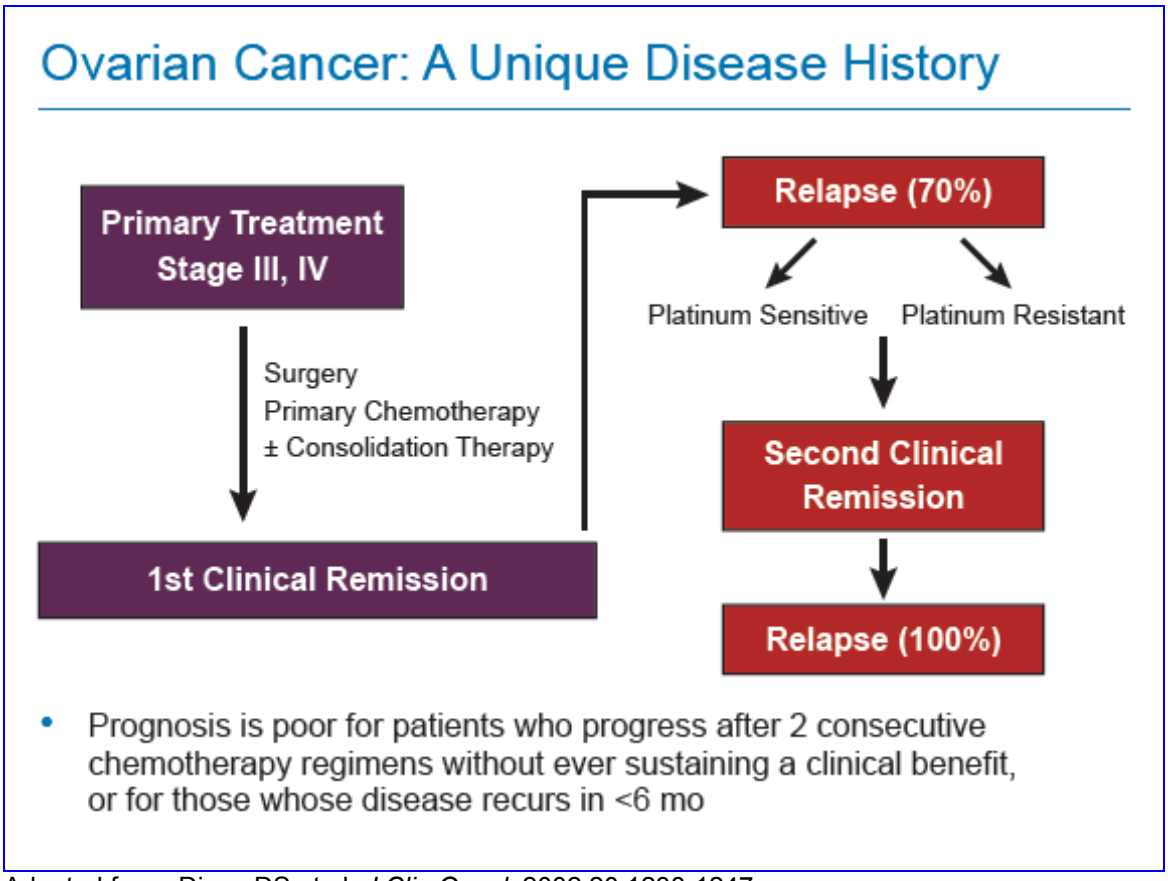
Go online to complete the post-test and evaluation for CME credit:
www.peerviewpress.com/d/e017

Slide 1

Dr. Markman:
It is well recognized that the standard of chemotherapeutic approaches to primary therapy of ovarian cancer are quite effective in achieving objective and subjective responses in a large majority of patients. Unfortunately, it's also very well recognized that the majority of patients with advanced ovarian cancer will ultimately experience recurrence of the disease process.

Narrator:
Recently, Dr. Maurie Markman led a panel discussion focusing on key issues related to treatment of patients with recurrent ovarian cancer. The panel included the following experts: Dr. William Patrick McGuire and Dr. Robert L. Coleman.

Slide 2

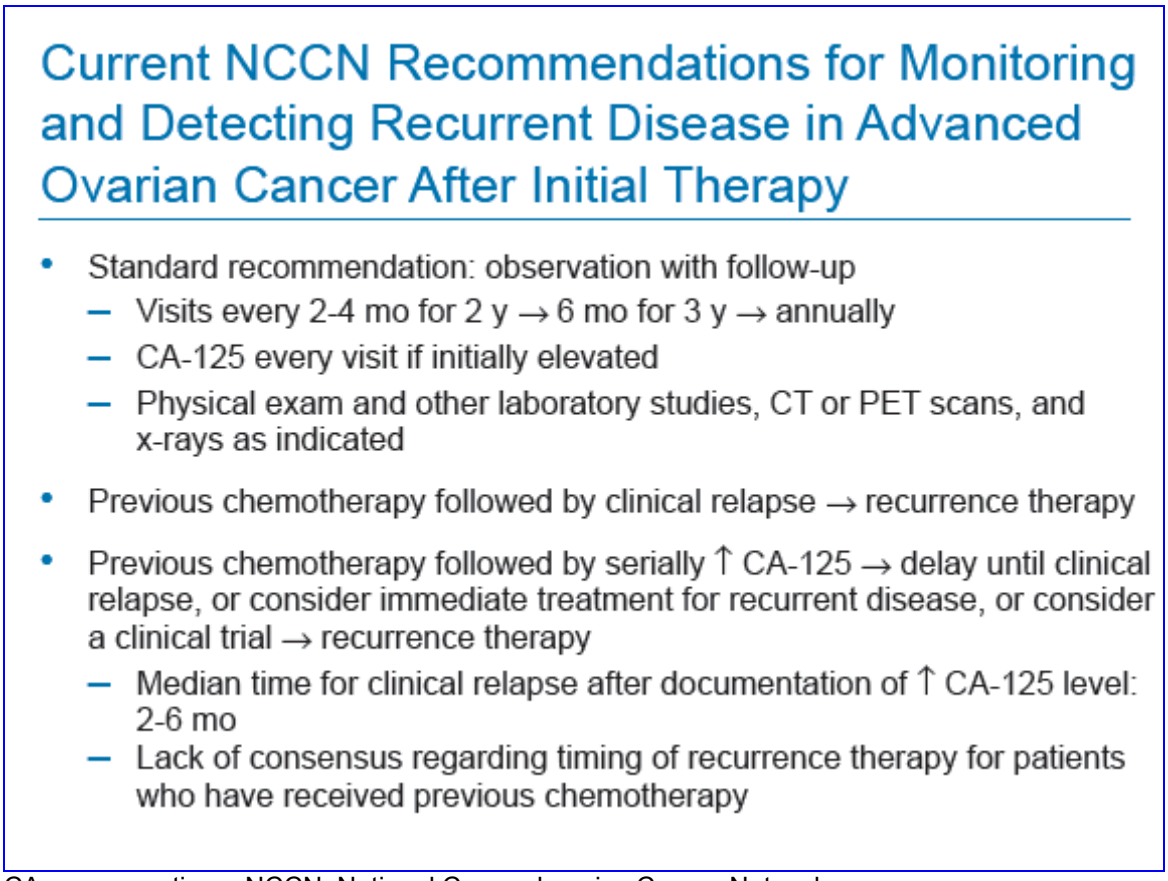


Adapted from: Dizon DS et al. *J Clin Oncol.* 2002;20:1238-1247.

Dr. Markman:
The management of patients who have either developed recurrent disease or have progressive disease during their primary therapy becomes a major therapeutic challenge in the management of ovarian cancer.

And there are a number of questions that come up very commonly in the practice setting that relate to this management, and we are going to try to cover a couple of those questions in this discussion.

Slide 3



CA: cancer antigen; NCCN: National Comprehensive Cancer Network.
Based on: The NCCN 1.2008 Ovarian Cancer Clinical Practice Guidelines in Oncology. © National Comprehensive Cancer Network, 2008. Available at: http://www.nccn.org. Accessed January 21, 2008. To view the most recent and complete version of the guidelines, go online to www.nccn.org

Dr. Markman:
The first question that's a very practical one is, how does one monitor [or] follow up patients who have received primary therapy to detect recurrent disease in ovarian cancer? Is it important to find it early? Should there be active surveillance?

Dr. Coleman:
The question of whether or not it's important to identify recurrent disease early rather than later is complex, and considers both a disease and patient standpoint. For patients, disease surveillance must balance rational practice guidelines and the patient's personal expectations for their own surveillance. At least in my practice, I'm encouraged to follow patients more closely for the first couple of years, because that's when most of the recurrences are going to occur. I tend to follow with 3- or 4-month serial pelvic exams, and CA-125. And I don't routinely order imaging as part of that surveillance, but getting back to the question that you asked, "is it important to actively survey these

patients for early recurrent disease?"—that's really the focus of the EORTC randomized trial, the OVO5/5595, and we're anxiously awaiting the results of this important study.

Dr. McGuire:
I think it's important to survey the patients every 3 months during the first year, maybe every 4 [months] in the second year. The issue really becomes how to deal with the patient who has a biochemical-only recurrence or the only evidence of cancer is CA-125 elevation. I agree there is no need, as long as that number remains in the normal range, to do any type of radiographic procedure, but when that number begins to rise, patients are going to pretty much demand some type of imaging procedure. If that imaging procedure does not show disease, is there any good indication for treating [based on] the rising tumor marker? I think very commonly that gets treated in this country, less commonly in Europe, and so I think we're all anxiously awaiting the results of the EORTC study. The only data that we have from this country was the recently completed GOG [Gynecologic Oncology Group] trial that taught us really only one thing, which is that the average time between that rise in CA-125 and the clinical development, either clinical symptoms or radiographic abnormalities, was about 3 1/2 months.

Dr. Coleman:
I would like to add to that the frequently asked question is, what's a significant rise in CA-125? The study that Dr. McGuire is referring to [GOG 198] had prespecified guidelines as to what that represents. The study required the CA-125 to be doubled over the upper limit of normal in 2 serial determinations or a single value over 100 [U/ml]. But as I am sure all of you recognize, the patient whose CA-125 was 9 [U/ml] for 6 months and rose to 18[U/ml], is already convinced that the disease has recurred, and there is probably some merit to that concern.

Dr. Markman:
The fundamental question is, does it make a difference in terms of the time-to-symptomatic disease progression or overall survival if you treat, versus the good quality of life the patient is having? And it's a balance.

Slide 4

Current NCCN Recommendations for Recurrence Therapy

Acceptable recurrence modalities:

	Cytotoxic Tx	Hormonal Tx	Targeted Tx
Preferred agents	Liposomal doxorubicin Topotecan Gemcitabine If platinum sensitive: Cisplatin Carboplatin Carboplatin/paclitaxel Gemcitabine/carboplatin		
Other potentially active agents	Altretamine Capecitabine Cyclophosphamide Docetaxel Etoposide, oral Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Vinorelbine	Anastrozole Letrozole Tamoxifen	Bevacizumab

Based on: The NCCN 1.2008 Ovarian Cancer Clinical Practice Guidelines in Oncology. © National Comprehensive Cancer Network, 2008. Available at: http://www.nccn.org. Accessed January 21, 2008. To view the most recent and complete version of the guidelines, go online to www.nccn.org.

Dr. Markman:
We have now documented recurrent disease, and that could be by a rising CA-125, it certainly could be by the development of symptoms that clearly are evidence of disease with perhaps CA-125, or it could be abnormalities on physical exam or radiographic imaging with any of the other symptoms or CA-125. And now we come into the question of what are the optimal strategies for the management of recurrent or persistent ovarian cancer? That's obviously a broad topic, and I will ask your opinion on how you approach the management of recurrent ovarian cancer.

Dr. McGuire:
I think the first thing that we all do is we begin to count, and we count the number of days from the end of chemotherapy until the first evidence of progressive disease. I think most of us still prefer to use progressive disease being the more typical symptomatic or radiographic progression of disease, but certainly if you use tumor marker, then you have to wind the clock back about 3 months. And I think we all understand that if that [is the] interval in the patient whose tumor grows on chemotherapy, that patient is basically not likely to respond to any currently available therapies and is a candidate for clinical trial. The patient whose tumor recurs within 6 months of completing that

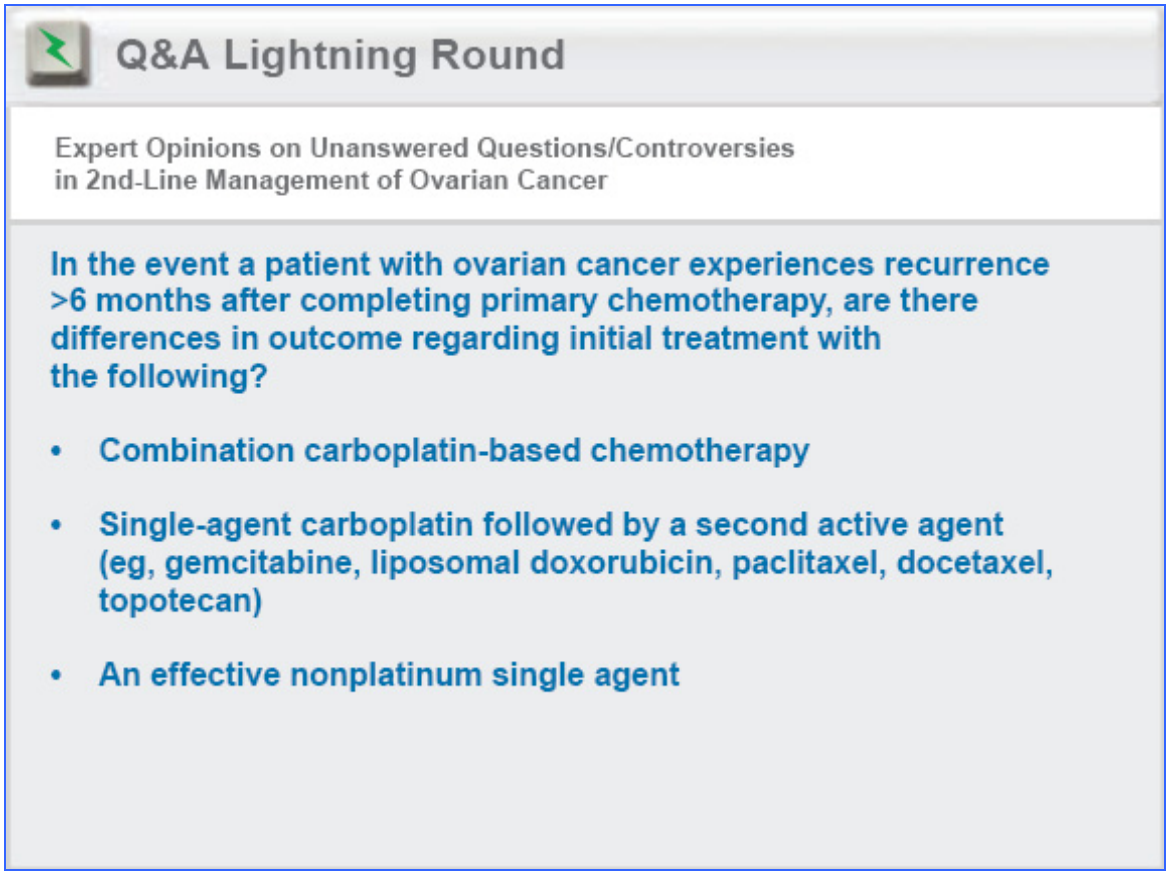
primary chemotherapy, I think also there are no good options for treating that patient, and certainly if one treats the patient with a commercially available option, it should almost certainly be a single agent and not drug combinations.

The drugs that most people utilize as monotherapy in the patient with platinum-resistant recurrent disease include pegylated liposomal doxorubicin, topotecan, and gemcitabine.

And then once you get past the 6-month time interval, then the reintroduction of a platinum most people would utilize, either with or without another agent. If we were to ask the three of us here today, we would probably get three different answers about what to do with that patient.

Dr. Coleman:
Very true. Although I have to admit I do the same type of counting, I really try to explain to patients that the difference between a 5.9- and 6.1-month recurrence is nothing. These patients have the same probability for response and, essentially, our choice [of] agent really reflects our estimate of the probability of response to reintroduction to platinum or to another agent. I think it's important to recognize that the characteristic, the phenotype of potential platinum sensitivity measured by disease-free interval, really extends to all the agents that are available. And so, if we were to study, for instance, one of the 2 drugs that were mentioned, either pegylated-liposomal doxorubicin or topotecan, in a platinum-sensitive cohort, we might expect that one patient would have a better response compared with another treated with that same agent, but with a much shorter treatment-free interval. So, it really gets down to estimating probability of response based on presenting characteristics. I think we have got very nice data to support our biases that have been around for more than 2 decades. But as the list of potentially active agents grows, the decision-making also becomes much more problematic and difficult to tease out.

Slide 5



Dr. Markman:
In the second-line recurrent setting, there is some evidence that combination therapy with platinum with paclitaxel or platinum with gemcitabine, or potentially in the future it might be platinum with another agent like liposomal doxorubicin, will be shown to be better than, say, a single agent?

The question is, is putting two drugs together better than one, or if one had a planned sequential use of those drugs, might you achieve the same outcome with less toxicity? And what I mean by less toxicity, of course, is you are simply not having the simultaneous toxicities of the two drugs together? And that's an important question that hasn't been addressed in a clinical trial, directly at least, in recurrent disease, but I [would be] interested in your thoughts on that strategy as opposed to combination therapy.

Dr. McGuire:
I think, before you can truly say that a combination therapy is better than a single-agent therapy, you really must analyze a second group of patients, which are patients who got that same combination but in sequence. In other words, they got one of the two agents followed by the other agent, and neither the ICON4 trial nor the AGO [Arbeitsgemeinschaft Gynaekologische Onkologie] trial that looked at the carbo[platin]/gemcitabine doublet reported that data.

Dr. Coleman:
I agree, and I think that we are all in desperate need of that kind of sequential data. The other point that needs to be addressed is, what do you call successful? The currently approved gemcitabine/carboplatin combination in platinum-sensitive patients did reach its benchmark for progression-free survival and demonstrated an improved response rate. It, however, did not show any difference in overall survival. Ultimately, I think, if we are looking at survival, no trial has move[d] that endpoint successfully, outside of ICON4.

Dr. McGuire:
If you are going, say—which I think is correct, the only one that has shown a survival advantage was the ICON4 trial—that if one really drills down on that data, the group of patients with the 6-12 month platinum-free interval really had minimal, if any, benefit from the combination therapy. And the second, more important point is that in that trial of the patients who entered, only 40% of those patients had received [a] taxane as part of their primary therapy, and so the results of that trial really don't have any bearing on the patients in this country, almost all of whom have had a platinum and a taxane as part of their primary therapy.

Slide 6

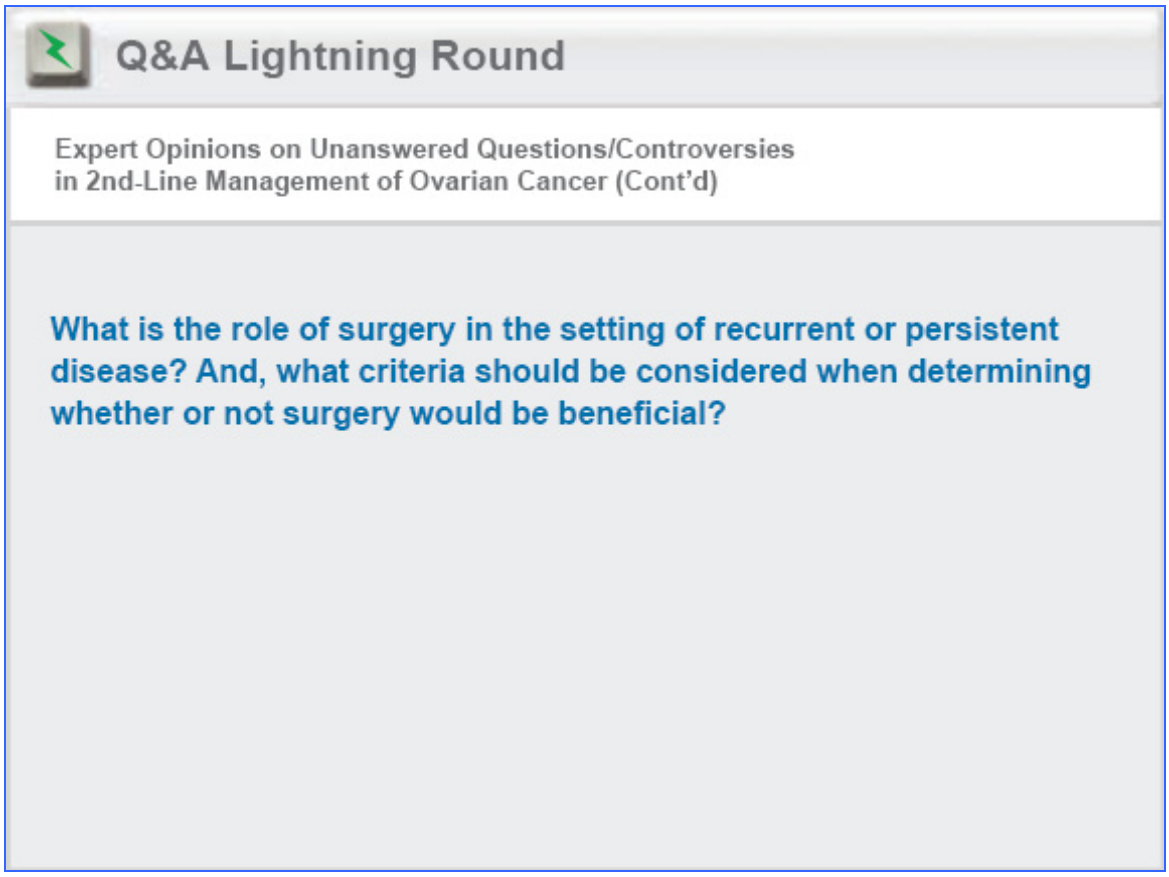
Dr. Markman:
One more question very commonly asked is, what is the role of in vitro chemoresistance or chemotherapy sensitivity testing in helping to select therapy in the recurrent, persistent setting? What do you think the current role is of using such assays, if any?

Dr. McGuire:
In terms of the oldest assay, which is the extreme drug resistance assay, I think two things can be said. Usually, the data that one has is dated from the primary tumor, and when we're using it, I hope, is at the time of recurrence. Assuming that one is using it to help select salvage therapy, I think the first thing is that there is not a significant level of discordancy in the few patients who have had tumor assayed primarily at the time of a secondary cytoreduction, at the time that one would select salvage chemotherapy, with the exception of the drugs that the patient had been exposed to as part of their primary therapies. So, in other words, the tumor may not show EDR [extreme drug resistance] to carboplatin initially, and then at the time of recurrence have extreme drug resistance to carboplatin, because they had recurred after receiving carboplatin. Other than that, I think the assay is valid for one thing, and that is to select drugs not to use, and those are the drugs that display extreme drug resistance. But what do I do in clinical practice if I have the data sitting in front of me? Do I use the data? Yes, I do, but I am not sure that's any better or worse than pulling something off the shelf.

Dr. Coleman:
We just don't have the data to have that strength of conviction. I think, as Bill nicely stated, the data for the EDR assay is actually fairly good for identifying drugs that are not going to work. The problem is the converse—that is, using it as a predictive marker so that you can actually alter outcome based on picking the right agents. The hypothesis is that if you decide to administer four different agents as A, then C, then B, then D, you are going to end up with a better outcome than if you just had done them in sequence. In order to validate that, the probability of response in the groups of patients that we choose, positive predictive value, which is really what we are going after, is going to be extremely low, and we need a very large patient population to address this concern.

In terms of my clinical practice, I tend to look at the complete spectrum and the growth characteristics of the individual drugs that are being tested against the tumor itself. But I have all the same concerns that Bill raised, and await very eagerly these ongoing correlative studies, which have now been embedded in several phase 3 trials across multiple tumor types.

Slide 7



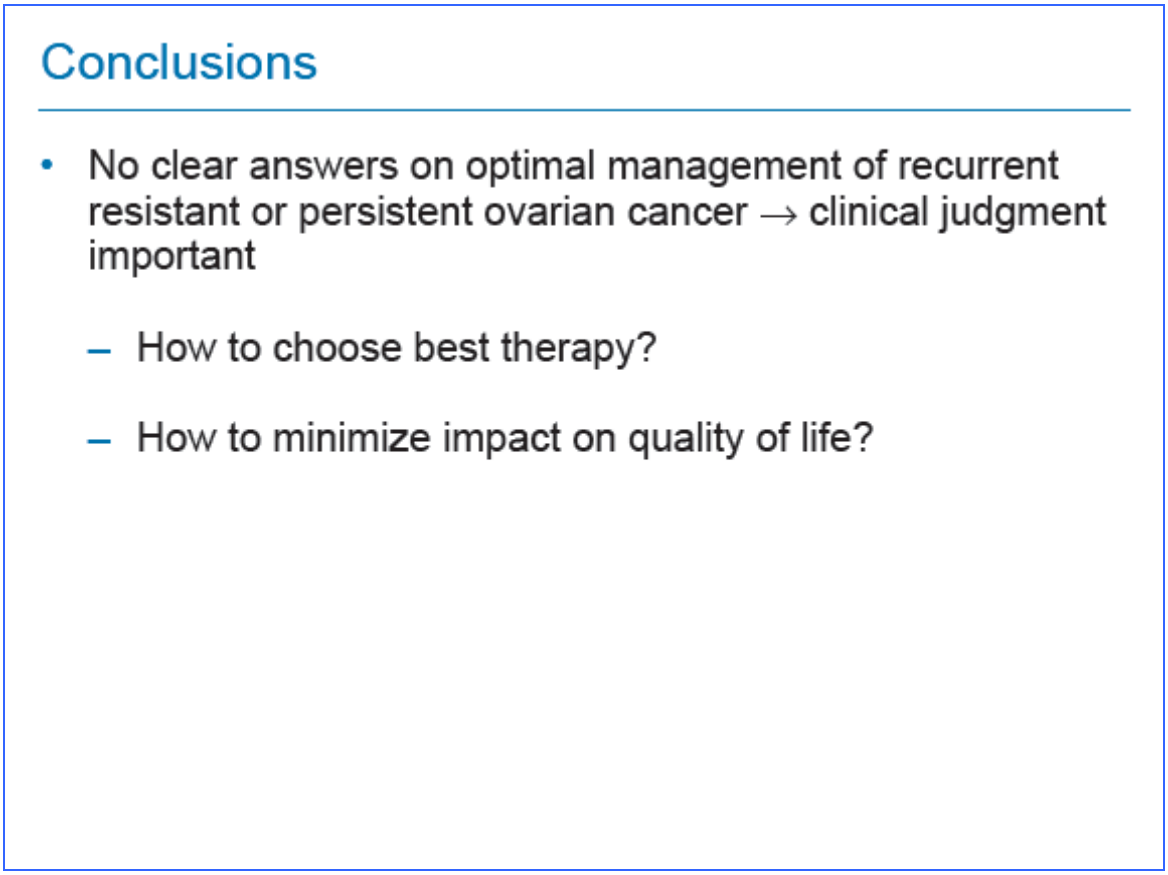
Dr. Markman:
I think we should address the other major modality that is employed in the management of ovarian cancer. What is the role of surgery in the setting of a woman who has been documented to have recurrent disease or even persistent disease? What are the criteria that might be employed to decide that a woman should undergo surgery or be considered for surgery? And conversely, what are the criteria, one might say, it just doesn't make any sense?

Dr. Coleman:
Surgery is used, as you know, for the identification of recurrence; the palliation of symptoms caused from progressive disease, such as bowel obstruction or the complications of a particular treatment like bowel perforation; and it is used with the same intent that we approached it in the primary setting, where most of us agree that it has a major role, debulking. So, from the palliative sense, emerging data are discriminating better in whom surgery for palliation actually may be of some benefit. Much of this information deals with expectations on duration of survival after surgery to know whether or not it is worth the considerable potential operative morbidity to palliate the woman. I think more to the point of this question though is, "in whom does surgical cytoreduction for recurrent disease benefit?" It has been a controversial topic, because many of us have realized that surgery and chemotherapy are a pair that have to be considered together. Surgery doesn't help much in patients who are chemoresistant—the disease just grows back on subsequent therapy. While [this] is easy to

understand, there is great difficulty in coming up with the exact criteria for whom surgery would be of merit. This question is actually going to be addressed in two prospective randomized trials: one being done in the US, GOG 213; and a second trial called the DESKTOP 3 trial, which is being done overseas. I should mention that there is also an EORTC trial, which is currently ongoing evaluating surgery in a neoadjuvant recurrent setting, in combination with chemotherapy [EORTC 55963].

While strict guidelines for surgery eligibility are as yet undefined, patients with isolated disease and in whom [the] potential for decent chemosensitivity exists because of long treatment-free interval are probably the ones best to be considered for this intervention.

Slide 8



Dr. Markman:
We've covered a lot of territory, addressing the fact that, in the recurrent resistant persistent disease setting, there are no easy answers. And clinical judgment becomes extremely important, as it is in all of cancer medicine, but particularly in this setting, because patients can live a very long time with ovarian cancer after it has progressed following initial therapy, and quality of life becomes very important. What drug or drugs we select and focusing on quality of life are becoming very important issues, and we often simply don't have the answers.

Slide 9

About This PeerView CME Activity

PVI, PeerView Institute for Medical Education, and the University of Florida College of Medicine are responsible for the selection of this report's topics, the preparation of editorial content, and the distribution of this report.

The preparation of PeerView reports is supported by educational grants subject to written agreements that clearly stipulate and enforce the editorial independence of PVI and the University of Florida College of Medicine. Our reports may contain references to unapproved products or uses of these products in certain jurisdictions.

For approved prescribing information, please consult the manufacturer's product labeling. No endorsement of unapproved products or uses is made or implied by coverage of these products or uses in our reports. No responsibility is taken for errors or omissions in reports.

Narrator:
This has been a CME-certified activity jointly sponsored by PVI and the University of Florida College of Medicine.