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:

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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

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Slide 1

Narrator:
Despite the availability of a number of effective systemic therapy options for ovarian cancer, there is a strong need for additional therapies to improve outcomes in this disease. Recently, Dr. Maurie Markman led a panel discussion focusing on emerging treatment options for ovarian cancer. The panel included the following experts: Dr. William Patrick McGuire and Dr. Robert L. Coleman.

Slide 2

Novel Targeted Agents Under Development for Ovarian Cancer

Clinical trials with bevacizumab in recurrent ovarian cancer:

Reference	Patients, n	Treatment	CR, %	PR, %	SD, %	PFS, mo
Cohn et al, 2006[1]	10	Bev + weekly taxane	0	0	100	–
Monk et al, 2006[2]	23	Bev monotherapy	4	18	78	5.5 (median for 32 pts)
	7	Bev → Bev + chemo	0	0	14	
	2	Bev + chemo	0	0	0	
Numnum et al, 2006[3]	4	Bev monotherapy	0	0	100	>5.5
Wright et al, 2006[4]	23	Bev at varying doses + cytotoxic agents	0	35	44	5.5 for PR; 2.3 for SD
Burger et al, 2007[5]	62	Bev monotherapy	3	18	52	10.3
Cannistra et al, 2007[6]	44	Bev monotherapy	0	16	NR	4.4
Garcia et al, 2008[7]	29	Bev + cyclophosphamide	0	24	63	7.2
Friberg et al, 2006[8]	12 evaluable	Bev + erlotinib	0	1	8	–

Bev: bevacizumab; CR: complete response; PFS: progression-free survival; PR: partial response; SD: stable disease.

1. Cohn DE et al. *Gynecol Oncol.* 2006;102:134-139. 2. Monk BJ et al. *Gynecol Oncol.* 2006;102:140-144. 3. Numnum TM et al. *Gynecol Oncol.* 2006;102:425-428. 4. Wright JD et al. *Cancer.* 2006;107:83-89. 5. Burger RA et al. *J Clin Oncol.* 2007;25:2902-2908. 6. Cannistra SA et al. *J Clin Oncol.* 2007;25:5180-5186. 7. Garcia AA et al. *J Clin Oncol.* 2008;26:76-82. 8. Friberg G et al. *J Clin Oncol.* 2006;24:260s (Abstract 5018).

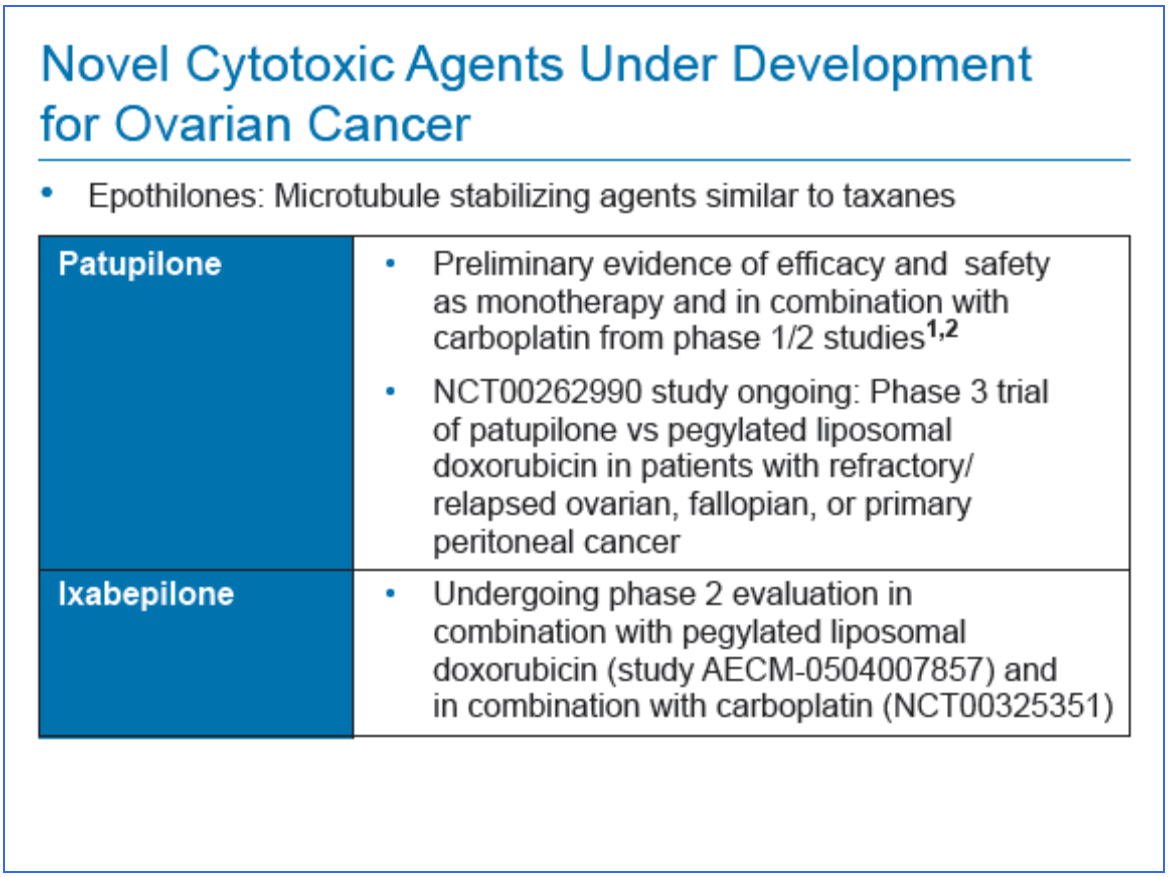
Dr. Markman:
We know that we've impacted in a significant manner both the extent of survival and the quality of life of women with advanced ovarian cancer over the last 30, 40, 50 years with the introduction of platinum-based chemotherapy, excellent surgery, surgical techniques, standards of surgery, and agents for the second-line setting. But recently, there has been a paucity of studies that have actually had positive outcomes relative to new drugs. And so the question comes up, what's the future? What are the new things that are out there that are being examined now in trials, or [are] ready to be examined in trials, or maybe at this point are only in the preclinical setting that look particularly promising?

Dr. Coleman:
Right now, I think the most exciting avenues would be in the field of targeted therapies. The recognition of specific pathways that are relevant to ovarian cancer, or solid tumors in general, really represents the platform upon which many new agents are being developed. There are several active agents that are under clinical development in various phases of study throughout the world. In ovarian cancer, the documentation of the activity of single-agent bevacizumab in patients with recurrent ovarian cancer, I think, was quite remarkable, particularly as there were complete responders identified in that paper. This was unexpected and raises bevacizumab as an important potential addition to our therapeutic options for our patients. In GOG 213, mentioned in the first discussion, bevacizumab is being looked at in the setting of chemotherapy randomization. But worldwide, there are several randomized trials that are considering these biological agents.

So the novel biologic agents under development cover a broad spectrum of targets, and therefore, provide many different avenues in which to proceed. There are probably more drugs than we have patients to study, so prioritization of these novel agents is going to be just as important as their discovery.

Dr. McGuire:
I think what Rob said is true. I think it's remarkable and unexpected, the activity in terms of true clinical response that we have seen and really did not expect with bevacizumab, I think in part because we really didn't understand totally how the drug worked. I think we still need to look at how many of those patients, even though [they] may not respond, have long periods of disease stability, because I think that, at least certainly conceptually, these targeted therapies may not actually cause apoptosis of the cell but certainly may shut down the ability of the cell to divide. And so, I think we may have to change some of the paradigms that we've used heretofore in terms of measuring drug efficacy. I think that's just a note of caution, and I think that finally we are beginning to look at the inner workings of the cell and look at some of these growth potentiating targets and aiming at those rather than at rather crude enzyme or mechanistic things within the nucleus that the cell was able to get around very easily. I think [that] may be a little more difficult with some of the targeted therapy. So, I still hold out some hope, but I have been around too long to be excited yet.

Slide 3



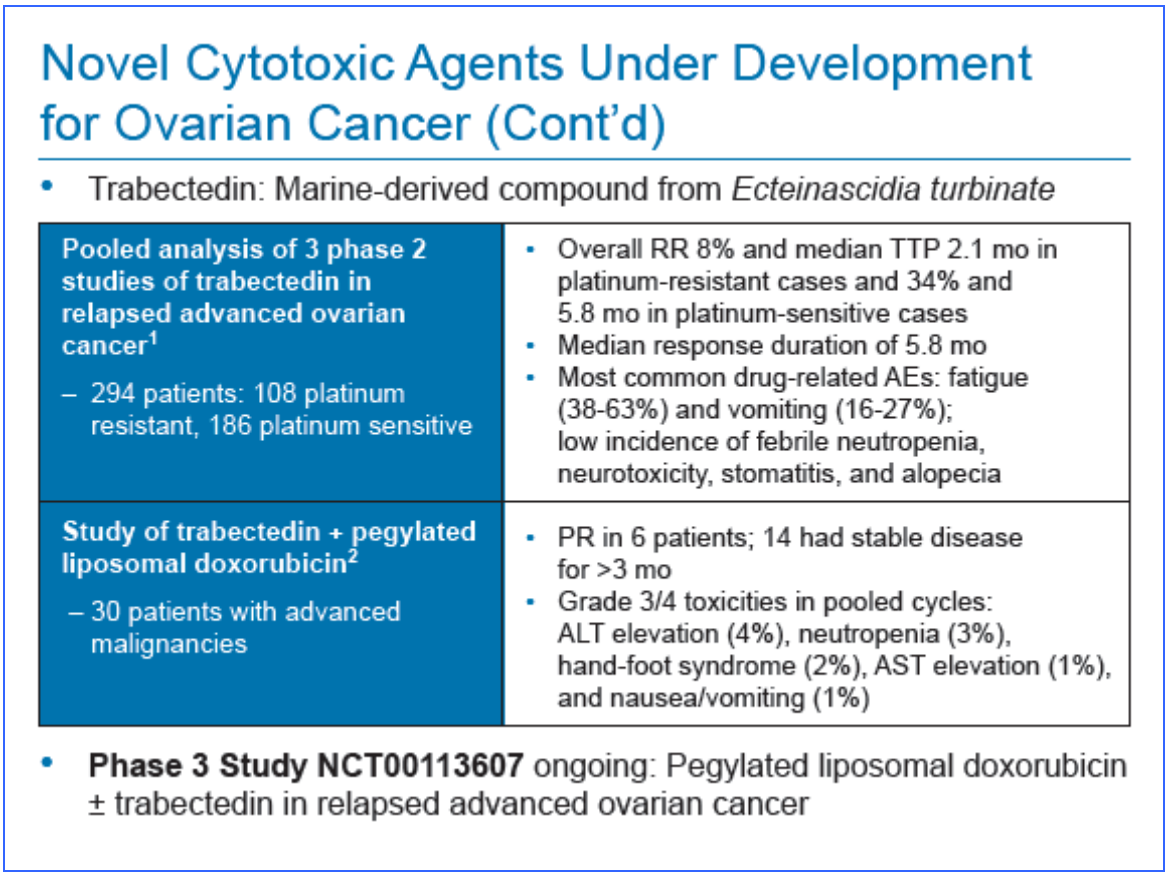
1. Smit WM et al. *Proc Am Soc Clin Oncol.* 2005;23:5056a. 2. Gore M, et al. *Proc Am Soc Clin Oncol.* 2005;23:5087.

Dr. Coleman:
I think in addition to that, there are some new cytotoxics. A number of these are under development right now, in phase 2 and in phase 3 studies. Probably the two most mature would be the epothilones and the drug trabectedin, both of which are in phase 3 investigation right now.

The epothilones are anticancer agents that target and stabilize microtubules through a mechanism of action different from that of paclitaxel. The epothilones mechanistically work similar to the taxanes, disrupting microtubule homeostasis [by] inducing polymerization and bundling, thereby leading to cell-cycle arrest and apoptosis. The epothilones are more potent than the taxanes and appear to bind [to] different subunits of the tubulin molecules, bypassing taxane-resistance mechanisms. Ixabepilone, one of the 2 under development [in] ovarian cancer, is already FDA approved for recurrent, taxane-resistant breast cancer.

In light of the role the taxanes play in gynecologic cancers, it's clear why these agents are of interest. Several different schedules have been addressed and toxicity profiles better defined. Phase 2 studies in ovarian cancer patients have demonstrated responses, which has encouraged the development of at least one phase 3 trial involving the epothilone analog, patupilone.

Slide 4

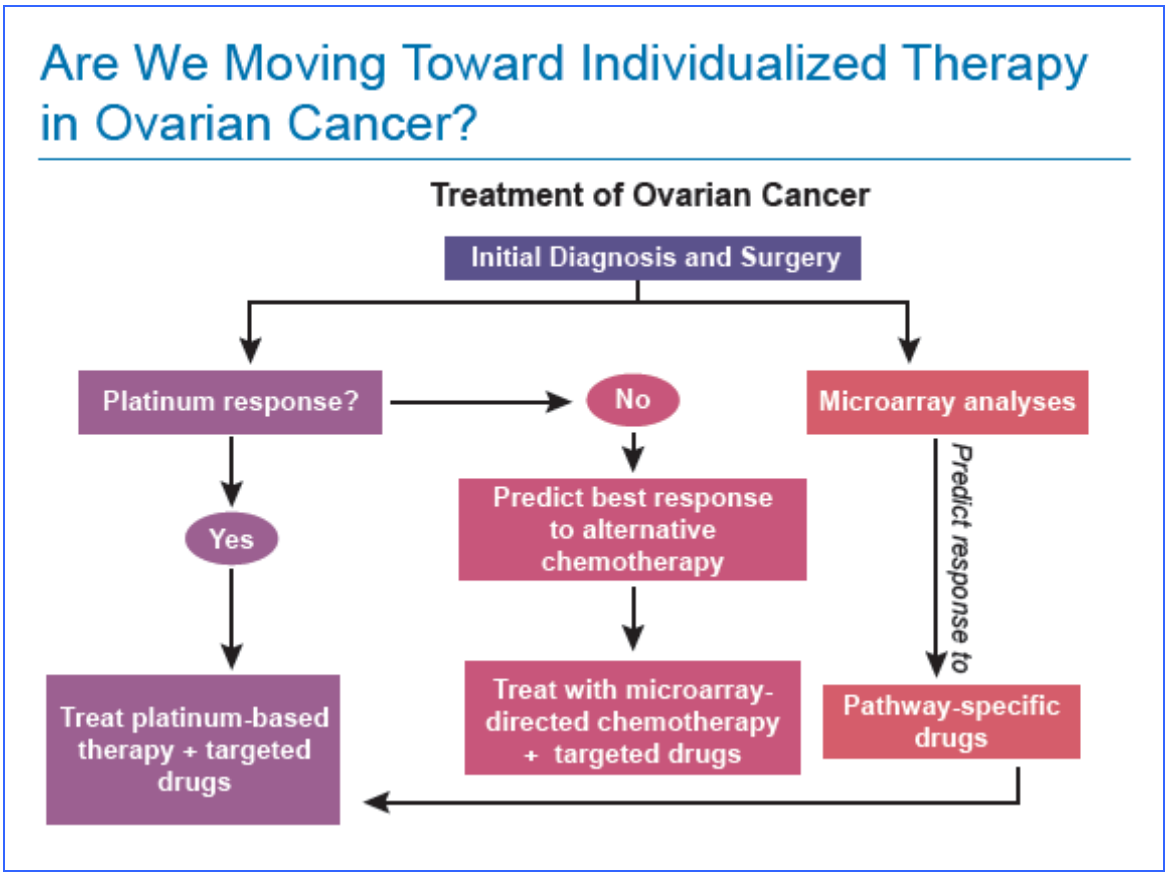


1. McMeekin et al. *Proc Am Soc Clin Oncol.* 2007;25:5579a. 2. Cohen RB et al. *Proc Am Soc Clin Oncol.* 2005;23:3074a.

Dr. Coleman:
Trabectedin is a novel antineoplastic agent that binds to DNA and interferes with nucleotide excision repair, induces lethal DNA strand breaks, and blocks cell division. It appears to induce apoptosis in a P53-independent fashion. Preclinical development has demonstrated synergy with platinum and taxane agents, and a few phase 2 clinical trials of single-agent trabectedin have demonstrated some responses, particularly in platinum-sensitive patients with recurrent ovarian cancer. Based on these observations, a randomized phase 3 trial of combination trabectedin and pegylated liposomal doxorubicin versus pegylated-liposomal doxorubicin alone has finished accrual and is awaiting maturity for efficacy evaluation.

Each of these novel agents are poised to enter the domain of active therapeutics should they reach their primary endpoints.

Slide 5



Dr. Markman:
One of the things that has been talked about is the ability to develop reliable biological markers for selection of therapies. The classic, of course, is estrogen receptor positivity hormones in breast cancer, and HER2 in breast cancer. So, the question is, what do you think about the future as a strategy moving forward, not only developing more effective drugs, but coming up with ways to predict which drug will work in which patient? How likely is that to happen?

Dr. McGuire:
I think it has to be done, but I think it is going to be a long, troubling, and frustrating trip. All you have to do really is look at the two that you have already mentioned. We [have] got 30 or 35 years of experience with that now, and people even tell us, well, if you are using the wrong monoclonal antibody, you may be calling something ER negative that is really ER-positive, and excluding antiestrogen therapies from a patient who may benefit. And very clearly in the HER2/neu scenario, the original studies were two monoclonal antibodies and then we went to the FISH analysis, but even the FISH analysis didn't give us everything that we needed. People are even now saying that the monoclonal antibodies weren't such a bad idea to begin with, and certainly a lot cheaper. So, it's something that has to be done, but they are certainly not perfect now and likely are never going to be perfect in terms of 100% ability to predict response or resistance.

Dr. Coleman:
I think our greatest successes with targeted agents have come in diseases that are defined by gain of function-binding domain mutations. The experience with leukemia and GIST, gastrointestinal stromal tumors, are good examples. However, as we learn more about how tyrosine kinases behave, it is likely that more clinical scenarios will be described. Conditions that are defined by a mutation, which is the target of a specific compound, can bring dramatic effects. Ovarian cancer, unfortunately, is just much more complicated in terms of what's driving an individual patient's tumor. So, the cadre of drugs that we have available right now, while making some impact, is simply inadequate. The question about moving chemosensitivity assays to the molecular level where we actually find out what are the critical "turned-on" and "turned-off" genes, and how we can silence those or activate them, becomes an nth-degree complexity problem. Nonetheless, I think we have seen how bevacizumab, targeting VEGF [vascular endothelial growth factor], can impact tumor growth, and we've discovered now that there are multiple targets in that microenvironment that can work synergistically, such as targeting the pericytes and the utilization of cytotoxics when the pericytes have been targeted or normalized. We've also described the interplay between multiple different receptors on the vascular endothelium, such as [the] neuorpilins and notch family. Added to this are the non-surface-receptor targets such as FAK and Src. Even targets within the well-described PI3 kinase pathway are all very important avenues to look. But I think, again, the interplay, the workaround, and the survival mechanisms these cancer cells have obtained over time make it very difficult to expect that a single drug will be able to be selected for a single ovarian cancer patient.

One of the critical factors in the development of these new drugs is determining precisely (through tumor measures) or indirectly (through biomarkers) whether or not we're affecting the target or making a difference at the tumor cell level. Given the difficulty of performing serial biopsies, much less a single one, we need to find methodologies that can be accessed peripherally, such as circulating tumor cells and cell-free nucleic acids, and to figure out ways to perform pharmacodynamic profiling on these particular cells in response to therapy.

Dr. Markman:
Well, I would like to personally thank both of you for participating with me in this program. This is a very complex, but a very exciting area, and certainly the future has the potential to lead to increasing our understanding of both fundamental biology, but most importantly improvement in outcome for our patients with ovarian cancer.

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Narrator:
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