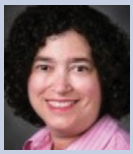
Thoracic Cancers: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner



Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC, of MD Anderson Cancer Center, reviews the major abstracts in thoracic cancers from the ASCO20 Virtual Scientific Program using coverage by *The ASCO Post* and offers considerations for advanced practitioners managing patients in this area.

Abstract LBA5

Adjuvant Osimertinib in Early-Stage *EGFR*-Positive NSCLC

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/191929/abstract to read the full abstract and view author disclosures.

Adjuvant osimertinib significantly improved disease-free survival compared with placebo in patients with stage IB to IIIA *EGFR*-mutated non–small cell lung cancer (NSCLC) who underwent complete resection of primary tumor and received chemotherapy if indicated. These results from the first interim analysis of the phase III ADAURA trial were reported at the ASCO20 Virtual Scientific Program and featured in a press briefing prior to the meeting.[1]

In patients with stage II to IIIA NSCLC, osimertinib improved disease-free survival by 83% vs placebo ($P < .0001$). The 2-year disease-free survival rate in patients with stage II to IIIA disease was 90% with osimertinib vs 44% with placebo. When adding in earlier-stage disease, in the overall study population of stage IB to IIIA NSCLC, osimertinib improved disease-free survival by 79% vs placebo ($P < .0001$), and the 2-year disease-free survival rate was 89% vs 53%, respectively.

"This trial is a home run. It exceeded our already high expectations," stated lead investigator Roy S. Herbst, MD, PhD, Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital and Associate Cancer Center Director for Translational Research at Yale Cancer Center, New Haven, Connecticut.

"Adjuvant osimertinib is the first targeted agent in a global randomized trial to show a statistically significant and clinically meaningful improvement in disease-free survival in patients with stage IB/II/IIIA *EGFR*-mutated NSCLC after complete tumor resection and adjuvant chemotherapy, when indicated. Adjuvant osimertinib is a highly effective, practice-changing treatment for patients with stage IB to IIIA NSCLC after complete tumor resection," Dr. Herbst said. Results were so positive in favor of osimertinib that the independent data monitoring committee recommended unblinding the trial early.

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor noted for its superior efficacy compared with the earlier-generation EGFR tyro-

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sine kinase inhibitors gefitinib or erlotinib; it is distinct for its activity against the *EGFR* T790M mutation and against brain metastases. Patients who present with stage I to IIIA NSCLC represent 30% of lung cancers, and up to 20% of them are *EGFR*-positive. Surgery is the primary treatment, and adjuvant chemotherapy is standard of care for patients with resected stage II, III, and selected IB disease. However, even with the best treatments available, the improvement in 5-year survival is only about 5% with platinum-based chemotherapy, Dr. Herbst noted. In addition, recurrence rates are high. At 5 years, the recurrence rate ranges from 45% in stage I disease to 76% in stage III disease.

Osimertinib is currently approved by the U.S. Food and Drug Administration as first-line treatment of *EGFR*-mutated advanced NSCLC and second-line treatment of *EGFR* T790M mutation–positive advanced NSCLC. The ADAURA trial results will likely move osimertinib up from the front-line setting to earlier in the adjuvant setting in patients who have undergone complete resection.

Study Details

ADAURA is a phase III, randomized, double-blind, placebo-controlled trial conducted in the United States, China, Korea, Australia, and Europe. The study included patients with primary nonsquamous NSCLC stage IB, II, or IIIA with confirmed *EGFR* mutation. Patients had fully recovered from surgery. Postoperative chemotherapy was given if indicated.

Patients (n = 682) were randomly assigned in a 1:1 ratio to receive osimertinib at 80 mg/d or placebo and treated for up to 3 years until disease progression or unacceptable toxicity. Participants were stratified according to disease stage (IB, II, or III), mutation type (ex19 del or L858R), and race (Asian vs non-Asian).

Baseline demographic and disease characteristics were well balanced between the two treatment arms. Approximately 31% had stage IB disease, and 69% had stage II/IIIA disease; 72% were female; 56% had ex19 del, and 44% had L858R.

Key Results

The median disease-free survival was not reached in patients with stage II to IIIA treated with osimertinib vs 20.4 months with placebo (hazard ratio [HR] = 0.17; $P < .0001$). The 2-year disease-free survival rate was 90% with osimertinib vs 44% with placebo. When patients with stage IB disease were added into the analysis, the median disease-free survival in this overall population was not yet reached in the osimertinib-treated group vs 28.1 months in those who received placebo (HR = 0.21; $P < .0001$). The 2-year disease-free survival rate was 89% with osimertinib vs 53% with placebo.

"The disease-free survival results are extraordinary. The disease-free survival data suggest that osimertinib will be useful in patients with stage II and III disease and in those with stage IB disease as well," Dr. Herbst commented. The subgroup analysis found that the disease-free survival benefit of osimertinib extended to every category, including sex, age, smoking status, race, stage of disease, *EGFR* mutation type, and prior chemotherapy. "You almost never see this in subgroup analysis of studies," Dr. Herbst noted.

The median duration of exposure to osimertinib was 22 months, confirming the ability to give the drug for a long period of time. The safety profile was consistent with what is known about osimertinib. The main side effects of osimertinib, as well as other EGFR tyrosine kinase inhibitors, included diarrhea, dry skin, pruritus, cough, and stomatitis. These were mainly grade 1 and 2, and the incidence of grade 3 adverse events was extremely low in patients randomly assigned to osimertinib (maximum of 1%–2%). The rate of interstitial lung disease, which is a concern in Asian patients, was just 3% and all low grade.

At the end of his presentation, Dr. Herbst referred to what George Sledge, MD, said when trastuzumab was first introduced in the early-stage setting at the 2005 ASCO Annual Meeting. With osimertinib, "biology has spoken again," Dr. Herbst stated. "It's the metastasis that kills patients. Targeted drugs like this one, based on biology with excellent [central nervous system] penetration, specifically kill tumors and prevent metastasis, allowing our patients to live longer with a better quality of life," he added. ●

Reference

1. Herbst RS, Tsuboi M, John T, et al: Osimertinib as adjuvant therapy in patients with stage IB-IIIA EGFR mutation positive NSCLC after complete tumor resection: ADAURA. ASCO20 Virtual Scientific Program. Abstract LBA5. Presented in premeeting press briefing on May 26, 2020.

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

Currently, adjuvant treatment for resected nonsquamous non–small cell lung cancer is four courses of cisplatin (or carboplatin) plus pemetrexed chemotherapy. The results from the interim analysis of the ADAURA trial are quite impressive.

The interim analysis revealed the significant benefit in disease-free survival of osimertinib in the adjuvant setting. The finding of improved disease-free survival in patients treated with osimertinib was seen in all stages (IB, II, IIIA) and demographic categories: gender, age, smoking status, race, stage of disease, *EGFR* mutation type, and prior chemotherapy. Additionally, at the interim analysis, the median disease-free survival for stages IB to IIIA was not reached. The results were so striking that the independent data monitoring committee recommended unblinding the study early.

The first interim analysis results from the ADAURA study show that the targeted therapy osimertinib has significant benefit for patients with *EGFR*-mutant resected nonsquamous cell carcinoma. The study also signifies the importance of mutation testing regardless of the stage of the disease. This study will change adjuvant treatment for early-stage (IB–IIIA) *EGFR*-mutant nonsquamous non–small cell lung cancer.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

Abstract LBA111

Study Finds Patients With Lung Cancer Infected With COVID-19 Are at High Risk for Hospitalization

By Jo Cavallo

Visit https://meetinglibrary.asco.org/record/191969/abstract to read the full abstract and view author disclosures.

Data from the global TERAVOLT Consortium, which is investigating the impact of COVID-19 infection on patients with thoracic cancers, have found that these patients are at high risk for hospitalization and death. Prior use of chemotherapy was associated with an increased risk of mortality, as was the use of steroids or anticoagulants. Prior administration of immunotherapy and chemoimmunotherapy were not associated with an increased risk of death, and prior treatment with tyrosine kinase inhibitors appeared to be associated with a decreased risk of hospitalization. The study was presented by Leora Horn, MD, at the ASCO20 Virtual Scientific Program and featured in a press briefing prior to the meeting (Abstract LBA111).

Early reports on patients with cancer infected with COVID-19 suggested a high mortality rate compared to the general patient population. Patients with thoracic malignancies are considered high-risk given their age and preexisting comorbidities, as well as due to the therapies administered to treat their illness. The global TERAVOLT consortium was launched to collect data on patients with thoracic malignancies diagnosed with COVID-19 infection to understand the impact of the virus on these patients.

"In less than a week we had a study enrolling patients," said Dr. Horn, the Ingram Associate Professor of Cancer Research and the Director of the Thoracic Oncology Program at Vanderbilt University Medical Center. "We have seen clinical trials being funded, approved and begin enrolling patients within weeks, when it can often take months or years to get approval for a trial."

Study Methodology

The goals of the consortium are to provide data to guide oncology professionals in managing patients with thoracic malignancies while understanding the risk factors for morbidity and mortality from the coronavirus. The researchers' updated analysis included data on 400 patients. Median age of the patient population was 68 years, the majority of the patients were male, and a small percentage of patients were never-smokers. Most of the patients had non–small cell lung cancer, and 60% to 75% had stage IV disease.

Study Results

Seventy-three percent of patients required hospitalization. The researchers' analyses found that of the 141 (35.5%) patients that died, 112 (79.4%) died from COVID-19, and 15 (10.6%) died from their cancer. Three hundred and thirty-four patients (78.3%) were hospitalized; 33 (8.3%) were admitted to the intensive care unit; and 20 (5%) needed mechanical ventilation. The median length of hospitalization among these patients was 10 days.

In addition, an analysis of patients' cancer therapy prior to their COVID-19 diagnosis found that 45% of the patients who died had received chemotherapy, 20% of the patients who died received immunotherapy, and ≤10% of patients who died received targeted therapy or radiotherapy. At the time of their COVID-19 diagnosis, the majority of patients were either untreated or on first-line therapy.

Risk factors associated with mortality were age over 65; the presence of comorbidities; Eastern Cooperative Oncology Group (ECOG) performance status greater than 1; treatment with steroids at ≥10 mg per day; and treatment with anticoagulants and chemotherapy.

The findings from this study could lead to a better understanding of the risk factors associated with poor outcomes in patients with thoracic cancer who become infected with COVID-19.

Perspective

"A number of factors—preexisting lung damage, smoking status, advanced age, and comorbidities—make patients with thoracic cancers especially vulnerable to COVID-19," said ASCO President Howard A. Burris III, MD, FACP, FASCO, in a statement. "There are a lot of questions right now, and not a lot of answers. These findings give us some insights into outcomes for patients with cancer who develop COVID-19." ●

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

The TERAVOLT Consortium is a global registry that was established to evaluate the impact of COVID-19 in patients with thoracic malignancies. The goals of the consortium are to provide oncology clinicians with data to assist in the management of patients with thoracic malignancies and understand risk factors for morbidity and mortality from COVID-19.

The study was a multicenter, international, observational study. Patient eligibility included diagnosis of any thoracic malignancy (non–small cell lung cancer, small cell lung cancer, mesothelioma, thymic epithelial tumors, other pulmonary neuroendocrine carcinomas) and diagnosis of COVID-19. Patients of any age, sex, histology, and stage of disease were eligible for participation in the study. An updated analysis of 400 participants showed that the median age of patients was 68 years, the majority of participants were male, a small percentage were never-smokers, and most of the patients had non–small cell lung cancer, with 60% to 75% having stage IV disease.

Significant points from the study analysis include risk factors associated with mortality: age over 65, the presence of comorbidities, ECOG performance status > 1, treatment with chemotherapy, steroids ≥ 10 mg/day, and anticoagulants. It is interesting that an increased risk of death was not associated with treatment with immunotherapy or tyrosine kinase inhibitors as it was with chemotherapy. This may be due to the fact that these treatments are not myelosuppressive.

Patients with thoracic malignancies are at an increased risk of being infected with the virus and having a poor outcome. It behooves oncology practitioners to educate their patients on the importance of all current practices to decrease patients' risk of exposure to COVID-19.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

Abstract 9001

First-Line Pembrolizumab Added to Standard Chemotherapy Improved Progression-Free Survival in Extensive-Stage Small Cell Lung Cancer

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/184545/abstract to read the full abstract and view author disclosures.

Pembrolizumab added to etoposide and platinum significantly improved progression-free survival compared with placebo and etoposide/platinum as first-line therapy in patients with newly diagnosed, extensive-stage small cell lung cancer (SCLC).[1] These results from the randomized, double-blind, phase III KEYNOTE-604 study were presented during the ASCO20 Virtual Scientific Program and published simultaneously in the *Journal of Clinical Oncology*.[2]

"Results of KEYNOTE-604 show that adding pembrolizumab to standard first-line therapy significantly improved progression-free survival in patients with extensive-stage SCLC and is associated with durable responses in a subset of patients. There was a trend toward improved overall survival as well, but this did not meet the threshold for statistical significance. Overall, these results add to the growing body of evidence in support of the value of immune checkpoint inhibitor in this historically difficult-to-treat cancer," said lead author Charles M. Rudin, MD, PhD, of Memorial Sloan Kettering Cancer Center, New York.

SCLC accounts for about 15% of all lung cancers, and it is strongly associated with tobacco use. SCLC is an aggressive cancer type, with a 5-year overall survival rate of about 6% to 7%. Although a number of combinations have been studied, until the recent advent of immune checkpoint inhibitors, standard first-line therapy for extensive-stage SCLC had remained etoposide/platinum for the preceding 30 years, Dr. Rudin noted. Although patients respond to etoposide/platinum, the median overall survival on this regimen is less than 1 year.

Pembrolizumab is currently U.S. Food and Drug Administration–approved for use as third-line or later therapy for metastatic SCLC. This study sought to explore its use in the first-line setting for SCLC.

Study Details

KEYNOTE-604 was conducted at 133 sites in 18 countries and randomly assigned 453 patients with previously untreated disease in a 1:1 ratio to pembrolizumab/etoposide/platinum or placebo/etoposide/platinum. Pembrolizumab was given as 200 mg once every 3 weeks for up to 35 cycles plus 4 cycles of etoposide/platinum. In the control arm, matching saline placebo was given with the same chemotherapy regimen. Platinum therapy was the investigator's choice of cisplatin or carboplatin. Treated and stable brain metastases were allowed at enrollment.

Baseline characteristics generally were well balanced between the two treatment arms, with the exception of more brain metastases in the pembrolizumab arm (14.5% vs 9.8%). The median age of study patients was 65 years. About 75% of participants had an Eastern Cooperative Oncology Group performance status of 1, more than 50% had an elevated level of lactate dehydrogenase, and 40% had liver metastases. About 41% tested positive for PD-L1 (ie, Combined Positive Score ≥ 1%).

At the final analysis, treatment was ongoing for 20 patients in the pembrolizumab arm vs 3 in the placebo arm. Disease progression was the most common reason for treatment discontinuation on both arms.

Survival Outcomes

At the second interim analysis, progression-free survival was significantly prolonged in the pembrolizumab group (hazard ratio = 0.75; P = .0023). The 12-month progression-free survival estimates were 13.6% and 3.1%, respectively.

"The progression-free survival curves overlapped during chemotherapy and then diverged in favor of pembrolizumab," Dr. Rudin said. "At the final analysis, the separation of curves was maintained, suggesting a long-term benefit in subsets of patients."

At the time of the final analysis, death was reported in 169 patients in the pembrolizumab group and in 188 patients in the control group. The hazard ratio for overall survival was 0.80 (95% confidence interval = 0.64–0.98; P = .0164). The

estimated overall survival rates at 24 months were 22.5% and 11.2%, respectively.

"Pembrolizumab appeared to prolong overall survival, but the threshold for statistical significance was narrowly missed," Dr. Rudin noted.

Subgroup analysis for progression-free and overall survival favored the addition of pembrolizumab to etoposide/platinum, with the exception of patients with baseline brain metastases and those with fewer than three metastatic sites. "Outcomes were similar regardless of PD-L1 positivity," added Dr. Rudin.

At the final analysis, the objective response rate was 70.6% with pembrolizumab/etoposide/platinum vs 61.8% with placebo/etoposide/platinum. "More important to me is the duration of response, which is longer with pembrolizumab. The curves diverged in favor of pembrolizumab, and at 12 months, ongoing responses were observed in 19% vs 3%, respectively," he said.

Toxicity

About 75% of patients in both arms experienced grade 3 or 4 adverse events. Discontinuation of treatment because of adverse events was reported in 14.8% of the pembrolizumab group and 6.3% of controls. Adverse events were generally similar in participants who received pembrolizumab or placebo. Adverse events leading to death occurred in 6.3% and 5.4%, respectively. The rate of death attributed to study treatment was identical in both arms (2.7%).

"The most common adverse events were hematologic, typical of platinum/etoposide, and this does not appear to be exacerbated by the addition of pembrolizumab," Dr. Rudin said.

"Consistent with prior studies, about 25% of patients in the pembrolizumab arm had immune-mediated adverse events. However, no patient died of an immune-related event. Most events were grades 1 and 2," he noted.

References

1. Rudin CM, Awad MM, Navarro A, et al: KEYNOTE-604: Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer. ASCO20 Virtual Scientific Program. Abstract 9001. Presented May 29, 2020.
2. Rudin CM, Awad MM, Navarro A, et al: Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. May 29, 2020 (early release online).

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

Immunotherapy has changed the treatment paradigm in non–small cell lung cancer and is showing impacts in small cell lung cancer as well. Recent studies of immunotherapy with chemotherapy for extensive-stage small cell lung cancer have shown benefit with the addition of immunotherapy.

Small cell lung cancer is an aggressive disease that is responsive to systemic treatment (chemotherapy) and radiation therapy. Platinum-based chemotherapy plus etoposide is the mainstay of treatment for SCLC. The phase III clinical trial, KEYNOTE-604, studied the addition of pembrolizumab to platinum-etoposide, evaluating progression-free survival and overall survival.

A total of 453 untreated patients were enrolled in this study and randomized in a 1:1 ratio to pembrolizumab/etoposide/platinum or placebo/etoposide/platinum with platinum (cisplatin or carboplatin) treatment selected by the investigators. The treatment consisted of four courses of either pembrolizumab or placebo plus chemotherapy with continuation of single-agent pembrolizumab (or placebo) for up to 35 cycles.

At the primary progression-free survival analysis, with a median follow-up of 13.5 months, the median progression-free survival was 4.5 months for the pembrolizumab arm vs. 4.3 months for the control group. At the final analysis, with a median follow-up of 21.6 months, the median overall survival was 10.8 months in the pembrolizumab group vs. 9.7 months in the control group; however, the statistical significance threshold was not met.

This study demonstrated improvement in progression-free survival with pembrolizumab added to platinum/etoposide. This combination gives clinicians another treatment option for patients with extensive-stage small cell lung cancer.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.

Abstract 9556

Tepotinib Shows Activity in Patients With NSCLC and MET Exon 14–Skipping Mutation

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/184859/abstract to read the full abstract and view author disclosures.

Patients with advanced non–small cell lung cancer (NSCLC) and a mutation that leads to mesenchymal-epithelial transition (*MET*) exon 14 skipping had a 46.5% objective response rate to the targeted therapy drug tepotinib, as shown in a study presented during the ASCO20 Virtual Scientific Program (Abstract 9556) and published simultaneously by Paik et al in *The New England Journal of Medicine*.

"The success of this trial, alongside other studies on the same class of drugs, establishes *MET* exon 14 as an actionable target for non–small cell lung cancer," said senior author Xiuning Le, MD, PhD, Assistant Professor of Thoracic/Head & Neck Medical Oncology at The University of Texas MD Anderson Cancer Center, in an institutional press release. "We're pleased to show that another group of [patients with] lung cancer may benefit from precision medicine."

MET exon 14 skipping is a mutation that drives cancer growth and occurs in 3% to 4% of all patients with NSCLC. Patients with *MET* exon 14 skipping tend to be older—with a median age of 74—and typically do not have other actionable mutations with existing targeted therapy options.

VISION Trial

The study results represent cohort A of the single-arm, international phase II VISION trial, which is ongoing with additional cohorts. More than 6,700 patients with NSCLC were prescreened for *MET* alterations through liquid and/or tissue biopsy. A total of 152 patients with advanced NSCLC and *MET* exon 14 skipping were treated with tepotinib. Patients with prior treatment and/or stable brain metastasis were enrolled, and participants were treated with 500 mg of oral tepotinib daily.

The primary endpoint was objective response rate, defined as complete or partial response, according to the RECIST version 1.1 criteria and confirmed by independent review.

Results

After 9 months follow-up, the primary efficacy population of 99 patients had a 46.5% objective response rate, with a duration of response of 11.1 months.

"The median duration of response of almost 1 year is very meaningful for this patient population," said Dr. Le. "It's important for these elderly patients to have another treatment option other than traditional chemotherapy in oral form that can improve their quality of life for a long duration."

Toxicities were manageable, with grade ≥ 3 treatment-related adverse events reported in 27.6% of patients. The most common side effect was peripheral edema. Eleven percent of patients discontinued treatment due to adverse events.

The study also collected patient-reported outcomes, which indicated an improvement in coughing and overall maintenance of quality of life.

Use of Liquid Biopsy in the Trial

The VISION study represents the largest *MET* exon 14–skipping cohort to be identified prospectively through liquid biopsy, verifying that liquid biopsy is a reliable method to detect the mutation. The study also showed that liquid biopsy was a useful tool to identify response to the drug.

Matched liquid biopsy samples were available for 51 patients at baseline and on treatment. Next-generation sequencing found 34 of those patients had a molecular response, with a complete or deep reduction of the mutation, and radiographic response was confirmed in 68% of patients who had a molecular response.

"This study marked a major advance in that we now have a highly effective oral therapy for a group of [patients with] NSCLC that previously did not have any targeted therapy options," said study coauthor John Heymach, MD, PhD, Chair of Thoracic/Head & Neck Medical Oncology at MD Anderson.

Tepotinib was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration in September 2019 based on early data from the VISION study. It was approved for use as the first oral targeted therapy for *MET*-positive NSCLC in Japan in March 2020.

The Advanced Practitioner Perspective

Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
MD Anderson Cancer Center

The results of this study show there is an effective targeted therapy drug for a subset of patients with non–small cell lung cancer and the *MET* exon 14 skipping mutation. The objective response rate of 46.5 % and the median duration of response (11.1 months) with tepotinib is remarkable.

The rarity of this mutation (3%–4%) is exemplified by the number of patients who were prescreened for *MET* alterations (over 6,709) and the number of patients treated with tepotinib (152). Patients with *MET* exon 14 skipping mutations, whether found on tissue or through liquid biopsy, were eligible for study participation. The VISION study verified the benefit of using liquid biopsy for mutation testing and evaluating response to treatment. This is a potential new way of evaluating treatment response for targeted therapies.

Tepotinib is a well-tolerated once-daily oral targeted therapy. It is beneficial for an older patient population (the median age of patients with *MET* exon 14 skipping mutation is 74 years) who would otherwise have standard therapies. This study also validated the use of liquid biopsy for mutation testing and treatment response; this may add a new criteria for response to treatment in addition to objective responses by RECIST criteria.

Disclosure: Ms. Waxman has no conflicts of interest to disclose.