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ASCO SPECIAL ARTICLE

Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

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Editor's note: This American Society of Clinical Oncology (ASCO) clinical practice guideline endorsement provides recommendations based on the review and analyses of the relevant literature for each recommendation in "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline." Additional information, which may include a methodology supplement, data supplements, slide sets, patient versions, and other clinical tools and resources, is available at: www.asco.org/endorsements/NSCLCradiotherapy.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
The American Society for Radiation Oncology (ASTRO) produced an evidence-based guideline on external-beam radiotherapy for patients with locally advanced non–small-cell lung cancer (NSCLC). Because of its relevance to the American Society of Clinical Oncology (ASCO) membership, ASCO endorsed the guideline after applying a set of procedures and a policy that are used to critically examine and endorse guidelines developed by other guideline development organizations.

Methods
The ASTRO guideline was reviewed by ASCO content experts for clinical accuracy and by ASCO methodologists for developmental rigor. On favorable review, an ASCO expert panel was convened and endorsed the guideline. The ASCO guideline approval body, the Clinical Practice Guideline Committee, approved the final endorsement.

Results
The recommendations from the ASTRO guideline, published in *Practical Radiation Oncology*, are clear, thorough, and based on the most relevant scientific evidence. The ASCO Endorsement Panel endorsed the guideline and added qualifying statements.

Recommendations
For curative-intent treatment of locally advanced NSCLC, concurrent chemoradiotherapy improves local control and overall survival compared with sequential chemotherapy followed by radiation. The standard dose-fractionation of radiation is 60 Gy given in 2-Gy once-daily fractions over 6 weeks. There is no role for the routine use of induction therapy before chemoradiotherapy. Current data fail to support a clear role for consolidation therapy after chemoradiotherapy; however, consolidation therapy remains an option for patients who did not receive full systemic chemotherapy doses during radiotherapy. Important questions remain about the ideal concurrent chemotherapy regimen and optimal management of patients with resectable stage III disease.

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INTRODUCTION

Individuals with locally advanced non–small-cell lung cancer (LA NSCLC) comprise a significant and growing proportion of patients diagnosed with NSCLC each year in the United States[1] and elsewhere. Patients with LA NSCLC include those with unresectable stage II to III disease and selected patients with stage II to III disease who are candidates for surgery as part of a multimodality treatment approach. In 2014, the American Society for Radiation Oncology (ASTRO) produced an evidence-based guideline on external-beam radiotherapy (EBRT) for patients with LA NSCLC.[2,3] This American Society of Clinical Oncology (ASCO) endorsement reinforces the recommendations that were offered in the ASTRO guideline and acknowledges the effort put forth by ASTRO to produce an evidence-based guideline informing practitioners who care for patients with lung cancer.

The interventions addressed in the ASTRO guideline for patients with LA NSCLC, as well as in this endorsement, include curative-intent EBRT, plus or minus chemotherapy, and the use of

THE BOTTOM LINE BOX

ASCO Endorses American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

Overarching Guideline Question

What is the role of external-beam radiotherapy in the management of locally advanced non–small-cell lung cancer (LA NSCLC)?

Target Population

Patients with stage II or III LA NSCLC whose disease is unresectable, and patients with stage II or III disease who are eligible for surgery.

Target Audience

Medical, radiation, and surgical oncology clinicians and other providers.

Methods

The ASCO Endorsement Panel reviewed the American Society for Radiation Oncology (ASTRO) clinical practice guideline on radiotherapy in LA NSCLC. The recommendations were based on a systematic review of the medical literature and are considered evidence based. The panel reviewed the methodology that ASTRO employed using results from the Appraisal of Guidelines for Research and Evaluation II (AGREE II) review instrument and reviewed the ASTRO guideline content to determine appropriateness for ASCO endorsement.

ASCO Key Recommendations (extracted from ASTRO recommendations [with ASCO qualifying language in italics]; see Data Supplement 1 for reprint of all ASTRO recommendations)

- *For curative-intent treatment of locally advanced NSCLC*, concurrent chemoradiation *is recommended because it* improves local control and overall survival compared *with* sequential chemotherapy followed by radiation or radiation therapy alone.
- The standard dose-fractionation *of radiation* with concurrent chemotherapy is 60 Gy given in fractions *of 2 Gy once per day* over 6 weeks. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be *of* benefit.
- There is no role for the routine use of induction chemotherapy *before* chemoradiotherapy.
- There *is no* role for the routine use of consolidation chemotherapy after chemoradiotherapy. Current data fail to support routine use of consolidation chemotherapy after chemoradiotherapy, but this remains an option for patients who did not receive full systemic chemotherapy doses during radiotherapy.
- The ideal concurrent chemotherapy regimen has not been determined. The two most common regimens *are* cisplatin/etoposide and carboplatin/paclitaxel.
- For patients *who* cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical (*definitive*) radiation *is recommended because it improves* overall survival when compared to radiotherapy alone.
- Radiotherapy alone may be used for patients ineligible for combined modality *treatment*; *it may offer better* tolerability, *but poorer* survival.
- Postoperative radiotherapy *may be recommended for patients with* complete resect*ion of* N2 disease *to* improve local control, *but* should be delivered sequentially after *adjuvant* chemotherapy.
- Postoperative radiotherapy *is recommended* for patients with *incomplete resection* (microscopic or *gross* positive margin, or gross residual disease), *to be* given either concurrently or sequentially with chemotherapy.
- *Patients with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have* preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female *sex*, and *only* one involved nodal station.

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THE BOTTOM LINE (CONTINUED)

Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/NSCLCradiotherapy. Patient information is available at www.cancer.net.

Links to "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline" can be found at http://www.practicalradonc.org/article/S1879-8500(15)00082-X/fulltext and http://www.practicalradonc.org/article/%20S1879-8500(15)00083-1/fulltext.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

neoadjuvant or adjuvant radiotherapy. The ASTRO guideline did not include pretreatment imaging/staging, specific chemotherapeutic delivery, treatment volumes and margins, motion management, or dosimetric considerations, but referred users to information sources on these subjects. A reprint of the ASTRO recommendations can be found in Data Supplement 1 and online at www.asco.org/endorsements/NSCLCradiotherapy. A Definition of Terms section can be found in Data Supplement 2.

OVERVIEW OF ASCO GUIDELINE ENDORSEMENT PROCESS

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodologic quality using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[4] (See Methodology Supplement for more detail.)

Disclaimer

The clinical practice guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information therein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

Guideline and Conflicts of Interest

The Endorsement Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at http://www.asco.org/rwc). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include Employment; Leadership; Stock or Other Ownership; Honoraria, Consulting or Advisory Role; Speaker's Bureau; Research Funding; Patents, Royalties, Other Intellectual Property; Expert Testimony; Travel, Accommodations, Expenses; and Other Relationships. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

ASTRO CLINICAL QUESTIONS AND TARGET POPULATION

The ASTRO guideline addressed five key clinical questions: (1) What is the ideal external-beam dose fractionation for the curative-intent treatment of LA NSCLC with radiation therapy alone? (2) What is the ideal external-beam dose fractionation for the curative-intent treatment of LA NSCLC with chemoradiotherapy? (3) What is the ideal timing of EBRT in relation to systemic chemotherapy for the curative-intent treatment of LA NSCLC? (4) What are the indications for adjuvant postoperative radiotherapy for the curative-intent treatment of LA NSCLC? (5) When is neoadjuvant radiotherapy before surgery indicated for the curative-intent treatment of LA NSCLC?

The target patient population for the ASTRO guideline includes patients with stage II to III NSCLC who cannot undergo a definitive

resection (either because of surgical resectability and/or medical operability factors [see Definition of Terms in Data Supplement X]) and patients with stage II to III NSCLC who can undergo a definitive resection after assessment. Intended users of the ASTRO guideline are oncology clinicians and patients.

SUMMARY OF ASTRO GUIDELINE DEVELOPMENT METHODOLOGY

The ASTRO guideline was developed under the auspices of the Guidelines Subcommittee of the Clinical Affairs and Quality Committee of ASTRO. ASTRO decided that EBRT was a high-priority topic and initiated guideline development by following the ASTRO policies for creating a topic proposal, which was approved by the ASTRO Board of Directors. ASTRO convened a practice guideline task force composed of 12 radiation oncologists (including one resident), one medical oncologist, and a thoracic surgeon, led by George Rodrigues, MD, and Greg Videtic, MD. It also convened an external expert review panel of three radiation oncologists.

Five distinct systematic reviews were completed separately, one for each key question. The literature search included PubMed and meeting abstracts from relevant conference proceedings with date parameters of January 1, 1966, to March 15, 2013. Inclusion criteria included publications of randomized controlled trials and nonrandomized studies. ASTRO also cross-referenced published clinical practice guidelines, consensus statements, meta-analyses, and systematic reviews. Links to the ASTRO search terms are provided in Data Supplement 3.

The task force and its five subgroups met by telephone and e-mail to complete the systematic reviews, create evidence tables, evaluate the evidence quality, and draft the guideline. On the basis of the available evidence and expert opinion, the task force graded the evidence using the American College of Physicians methodology. ASTRO used a process similar to that of ASCO for conducting a formal expert consensus process.[5] The ASTRO guideline was reviewed by its external expert review panel and by the ASTRO legal counsel. After a public comment period, the guideline was approved by the ASTRO Board of Directors. The conclusions of the ASTRO guideline are provided in Data Supplement 1. More detailed recommendations with key evidence and methodology are found in the ASTRO guideline.[2,3]

RESULTS OF ASCO METHODOLOGIC REVIEW

The methodologic review of the ASTRO guideline was completed independently by two ASCO guideline staff members using the Rigour of Development subscale from the AGREE II instrument.[4] Results of the scoring for this guideline are available in the Methodology Supplement. Overall, the ASTRO guideline scored high (86% [six of seven]) in terms of methodologic quality, with only minor deviations from the ideal as reflected in the AGREE II items. Three ASCO volunteers initially reviewed the content. The preliminary ASCO content reviewers of this ASTRO guideline, as well as the ASCO Endorsement Panel, found the recommendations to be well supported by the evidence in the original guideline. Each section, including an introduction, methods and materials, conclusion, clinical questions, guideline statements, narrative, and summary tables for each of five key questions, was clear and well referenced from the systematic review.

RESULTS OF ASCO CONTENT REVIEW

The ASCO Endorsement Panel (Appendix Table A1, online only) reviewed the ASTRO guideline with standard criteria (see Methodology Supplement) and concurs that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. Overall, the ASCO Endorsement Panel agrees with the recommendations as stated in the guideline, with the following minor qualifications discussed here (in italics): ASTRO recommendations are followed by the ASTRO rating of the quality of evidence and the strength of the recommendation.

Relevant ASTRO Statements Concerning Role and Timing of Radiotherapy With or Without Chemotherapy for Patients With Unresectable LA NSCLC

- There is phase III evidence demonstrating improved overall survival, local control, and response rate associated with concurrent chemoradiotherapy when compared against sequential chemotherapy followed by radiation (high-quality evidence [HQE], "strong").
- For patients who cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by radical radiation has been shown to be associated with an overall survival benefit when compared with radiotherapy alone (HQE, "strong").
- Radiotherapy alone may be used as definitive radical treatment for patients with LA NSCLC who are ineligible for combined-modality therapy (ie, due to poor performance status, medical comorbidity, extensive weight loss, and/or patient preferences) but with a trade-off of survival for improved treatment tolerability (HQE, "strong").
- There is no proven role for the routine use of induction chemotherapy before chemoradiotherapy; although, this treatment paradigm can be considered for the management of bulky tumors to allow for radical planning after chemotherapy response (moderate quality evidence [MQE], "strong").
- There are no phase III data specifically supporting the role for consolidation chemotherapy after chemoradiotherapy for the improvement of overall survival; however, this treatment is still routinely given to manage potential micrometastatic disease particularly if full systemic chemotherapy doses were not delivered during radiotherapy (low-quality evidence [LQE], "strong").
- The ideal concurrent chemotherapy regimen has not been determined; however, the two most common regimens (cisplatin/etoposide and carboplatin/paclitaxel) are the subject of a completed phase III clinical trial (NCT01494558; no evidence rating, "strong").

ASCO comments. We agree and have summarized these statements as follows: *For curative-intent treatment of LA NSCLC, concurrent chemoradiotherapy is recommended because it improves local control and overall survival compared with sequential chemotherapy followed by radiation or therapy alone. For patients who cannot tolerate concurrent chemoradiotherapy, sequential chemotherapy followed by*

radical (definitive) radiation is recommended because it improves overall survival compared with radiotherapy alone. Radiotherapy alone may be used for patients who are ineligible for combined modality treatment; it may offer better tolerability but poorer survival.

There is no role for the routine use of induction chemotherapy before chemoradiotherapy. Current data fail to support routine use of consolidation chemotherapy after chemoradiotherapy; however, this treatment remains an option for patients who did not receive full systemic chemotherapy doses during radiotherapy. The ideal concurrent chemotherapy regimen has not been determined. The two most common regimens are cisplatin/etoposide and carboplatin/paclitaxel.

Relevant ASTRO Statements Concerning Appropriate Dose of Radiotherapy for Patients With Unresectable LA NSCLC

- In the context of conventionally fractionated radiotherapy, a minimum dose of 60 Gy is recommended to optimize important clinical outcomes such as local control (HQE, "strong").
- The standard thoracic radiotherapy dose-fractionation for patients treated with concurrent chemotherapy is 60 Gy given in 2 Gy once daily fractions over 6 weeks (MQE, "strong").
- Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be associated with any clinical benefits including overall survival (MQE, "strong").

ASCO comments. We agree and have summarized these statements as follows: *The standard dose fractionation of radiation with concurrent chemotherapy is 60 Gy given in fractions of 2 Gy once per day over 6 weeks. Dose escalation beyond 60 Gy with conventional fractionation has not been demonstrated to be of benefit.*

Relevant ASTRO Statements Concerning Role of Postoperative Radiotherapy in Resected LA NSCLC

- Phase III studies and meta-analyses of postoperative radiotherapy (PORT) in completed resected (R0) LA NSCLC with N2 disease suggest that its addition to surgery does not improve overall survival but may improve local control when compared with observation strategies (MQE, "strong").
- Phase III studies and meta-analyses of PORT in completely resected (R0) LA NSCLC with N0-1 disease demonstrate inferior survival when compared with observation strategies; therefore, PORT therapy for this patient population is not recommended (MQE, "strong").

ASCO comments. We agree and have summarized these statements as follows: *Postoperative radiotherapy may be recommended for patients with complete resection of N2 disease to improve local control, but should be delivered sequentially after adjuvant chemotherapy.*

Other ASTRO recommendations addressing the postoperative setting had LQE, which the ASTRO panel rated as "strong" recommendations. We endorse and summarize them as follows:

Postoperative radiotherapy is recommended for patients with incomplete resection (microscopic or gross positive margin, or gross residual disease), to be given either concurrently or sequentially with chemotherapy.

Relevant ASTRO Statements Concerning Role of Radiotherapy in Context of Trimodality Treatment of LA NSCLC

- There is no level I evidence recommending the use of induction radiotherapy (or chemoradiotherapy) followed by surgery for patients with resectable stage III NSCLC (HQE, "strong").
- In those patients who are selected for trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy), based on best surgical judgment, is preferable, since it was associated with survival benefit in the exploratory posthoc North American Intergroup study INT 0139 analysis (MQE, "strong").
- No definitive statement can be made about best patient selection criteria for the trimodality therapy, although no weight loss, female gender, and one (*v* more) involved nodal stations were associated with improved outcome in INT 0139 (MQE, "strong").

ASCO comments. We agree and have summarized these statements as follows: *Patients with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female sex, and only one involved nodal station.*

DISCUSSION

The ASCO panel wanted to highlight and qualify some statements from the ASTRO guideline, and, in particular, to summarize them in clinical language that can guide practice. One of the challenges is lack of a standard definition of what constitutes "locally advanced" and how to define "unresectable." The ASTRO guideline describes the target patient population as "stage III patients (TanyN2-3M0, T4N0-1MO, and T3N1MO) and those stage II patients (T2b-T3N0 and T1-2N1) who cannot undergo a definitive resection (either due to surgical resectability and/or medical operability) as well as resectable patients with stage II and III disease. . ." Its statement that "resectable LA NSCLC is practically defined as consisting of stage II-III patients who can undergo a definitive resection after assessment to ensure appropriate surgical resectability, adequate pulmonary reserve, and acceptable medical operability risk. . ." refers to patients who can undergo definitive resection as their primary cancer treatment (with possible adjuvant therapy), but could also be (mis)interpreted as referring to patients undergoing surgery after (re)assessment after induction therapy. This potential ambiguity underscores one of the major current clinical dilemmas: how to manage patients with potentially resectable tumors who are candidates for surgery and who have preoperative evidence of mediastinal nodal disease. Given the lack of high-quality evidence and the heterogeneity of patients, the ASCO panel concluded that "*patients with resectable stage III NSCLC should be managed by a multidisciplinary team that incorporates best surgical judgment*" but believes that it is not defined at this point which patients would be considered as having resectable disease.

The evidentiary basis for the guidelines suffers from many limitations, which are elaborated in the original ASTRO guideline. In general, the clinical trials did not include a large number of patients (typically hundreds of patients, as compared with breast and prostate

clinical trials, which may include > 1,000 patients); they included a heterogeneous group of patients with different histologic subtypes; many trials were conducted before the routine use of positron emission tomography staging, and thus may have included patients with occult stage IV disease, and therefore, any conclusions about evidence or lack of evidence need to be tempered by these and other caveats listed here. Prospective comparative trials are lacking in the comparison of different types of EBRT, such as three-dimensional conformal, intensity-modulated, and image-guided radiotherapy, nor are there high-quality data currently available on hyper- or hypofractionated radiotherapy. Therefore, there are too few data and few to no criteria on which to base recommendations on these topics. Even within the realm of standard fractionation (2 Gy per fraction once per day), there is controversy regarding which dose of radiotherapy to consider standard; therefore, the ASTRO guideline has two statements: "a minimum dose of 60 Gy is recommended. . . (HQE)," which refers to radiotherapy alone, without concurrent chemotherapy, and "the standard . . . dose-fractionation is 60 Gy given in 2 Gy once daily fractions over 6 weeks," which refers to concurrent chemoradiotherapy. Which radiotherapy dose should be considered standard is indeed a dilemma, because some studies suggest that higher doses do provide better local control, but phase III studies have not demonstrated the superiority of any doses higher than 60 Gy over 30 fractions. The ASCO panel believed that we cannot state that 60 Gy is optimal, but we can state that 60 Gy is standard.

Another area of current controversy is the role, if any, of consolidation chemotherapy after concurrent chemotherapy, an approach supported by early trials that has become standard in many centers, but which current interpretation of data does not support. Notably, the ASTRO guideline on this issue reflected low-quality evidence, and the ASCO panel emphasized lack of phase III evidence of the benefit.

These guidelines will no doubt require revisions as new evidence emerges from ongoing clinical trials and a better understanding of the complexity and biologic underpinning of the various types of NSCLC develops. However, careful patient assessment by a multidisciplinary team, with close collaboration between radiation oncologists, medical oncologists, thoracic surgeons, and others, attention to the many patient, tumor, and treatment factors, and attention and management of adverse effects and potential complications will continue to be important so that patients can achieve the best possible survival and quality of life.

ENDORSEMENT RECOMMENDATION

ASCO endorses "Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer: An American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline," summarized by Rodrigues et al[2,3] in 2015 in *Practical Radiation Oncology*, with minor qualifying statements. The full ASTRO guideline can be accessed in the supplementary materials of the executive summaries by Rodrigues et al.[2,3]

ADDITIONAL RESOURCES

More information, including a Data Supplement with a reprint of all ASTRO recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/NSCLCradiotherapy. Patient information is available at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. American Society of Clinical Oncology Endorsement Panel Members

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