

Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer ASCO Guideline Update

Virgo, KS et al.

Overview

- 1. Background & Methodology
 - Introduction
 - ASCO Guideline Development Methodology
 - Clinical Question
 - Target Population and Audience
- 2. Summary of Recommendations
- 3. Additional Information
 - Additional Resources
 - Expert Panel Members





1

Background & Methodology

Introduction

- In 2021, ASCO updated a guideline on the initial management of noncastrate recurrent, advanced or metastatic prostate cancer.¹
- The current update is primarily driven by new clinical trial results (ARASENS², PEACE-1³, ENZAMET⁴, and ARCHES⁵) comparing triplet therapies to standard of care as well as one meta-analysis of triplet therapy.⁶
- Further informing this update is one network meta-analysis comparing ADT plus an androgen receptor axis targeted agent (ARTA) to ADT plus docetaxel,⁷ a comparison not yet directly tested in clinical trials but of great interest.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
 - a systematic literature review by ASCO guidelines staff
 - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
 - final guideline approval by ASCO EBMC
- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Question

This clinical practice guideline addresses one clinical question:

1. What are the standard initial treatment options for metastatic non-castrate prostate cancer?

Target Population and Audience

Target Population

Patients with noncastrate advanced, recurrent, or metastatic prostate cancer.

Target Audience

 Medical oncologists, radiation oncologists, urologists, nurses, other healthcare practitioners, social workers, patients, and caregivers.





2

Summary of Recommendations

Recommendation 1.0 (Updated)

 Docetaxel, abiraterone, enzalutamide, apalutamide, or darolutamide each when administered with ADT, represent five separate standards of care (SOCs) for noncastrate metastatic prostate cancer. With the exception of the triplet therapies of docetaxel plus abiraterone plus ADT and docetaxel plus darolutamide plus ADT, the use of any of these agents in any other particular combination or in any particular series cannot yet be recommended. Evidence-based benefits-harms ratio unknown

Evidence Quality

_

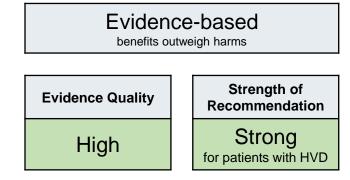
Strength of Recommendation

Strong



Recommendation 1.1 (Updated)

 For patients with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED⁸ (four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease) who are candidates for treatment with chemotherapy but are unwilling or unable to receive triplet therapy (e.g. due to insurance constraints), docetaxel plus ADT should be offered.



Practical Information for Recommendation 1.1 (Updated)

 Patients should be made aware that doublet therapy (docetaxel plus ADT) has proven inferior OS compared to triplet therapy, such as abiraterone and prednisone plus docetaxel plus ADT.



Recommendation 1.11 (Updated)

• For patients with de novo metastatic noncastrate prostate cancer with high-volume disease as defined per CHAARTED⁸ who are being offered ADT plus docetaxel chemotherapy, triplet therapy (abiraterone and prednisone plus ADT and docetaxel), should be offered per PEACE-1.³ Abiraterone and prednisone plus ADT and docetaxel demonstrated significant OS and radiographic progression-free survival benefits compared to ADT and docetaxel alone for patients with high-volume disease.

Evidence-based
benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

for patients with HVD as defined per CHAARTED¹

Practical Information for Recommendation 1.11 (Updated)

• OS data for patients with low-volume de novo metastatic noncastrate prostate cancer from PEACE-1³ are still too immature to justify recommending abiraterone-based triplet therapy (abiraterone and prednisone plus ADT and docetaxel).



Recommendation 1.15 (Updated)

• For patients with de novo metastatic noncastrate prostate cancer who are being offered ADT plus docetaxel chemotherapy, triplet therapy (darolutamide plus ADT and docetaxel) should be offered per ARASENS.² Compared to placebo plus ADT and docetaxel, darolutamide plus ADT and docetaxel demonstrated significant OS benefits, in addition to significantly longer times to castrationresistant prostate cancer, pain progression, first skeletal event, and initiation of subsequent systemic antineoplastic therapy. Evidence-based benefits outweigh harms

Evidence Quality

High

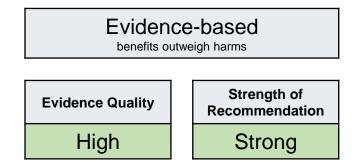
Strength of Recommendation

Strong



Recommendation 1.16 (Updated)

 The recommended regimen for patients with metastatic noncastrate prostate cancer treated with darolutamide, docetaxel and ADT is darolutamide (600 mg as two 300 mg tablets orally with food) twice daily (to a total daily dose of 1200 mg) with ADT. Docetaxel administration (75 mg/m²) should begin within 6 weeks of the first dose of darolutamide. Docetaxel should be administered intravenously every 3 weeks for up to six cycles.



Practical Information for Recommendations 1.15 & 1.16 (Updated)

 Discussions with patients should include the cost of darolutamide treatment compared with other options such as abiraterone.



Recommendation 1.2 (Updated)

 For patients with low-volume metastatic disease (LVD) as defined per CHAARTED⁸ who are candidates for chemotherapy, docetaxel plus ADT should not be offered due to lack of sufficient evidence. Evidence-based benefits outweigh harms

High

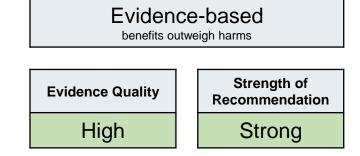
Evidence Quality

Strength of Recommendation

Strong for patients with LVD

Recommendation 1.3 (Updated)

 For patients with metastatic noncastrate prostate cancer treated with docetaxel, the recommended regimen is six doses administered at 3-week intervals at 75 mg/m² either alone (per CHAARTED⁸) or with prednisolone (per STAMPEDE).⁹



Practical Information for Recommendation 1.3 (Updated)

 The strongest evidence of benefit for docetaxel is for those patients who were diagnosed with de novo metastatic disease or HVD (defined per CHAARTED⁸ as four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease). The criteria apply independent of the presence or absence of nodal disease. 10



Practical Information for Recommendation 1.3. (Updated) (continued)

- Patients with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an OS benefit is not compelling for patients who do not have de novo metastatic disease and/or who do not meet the HVD criteria. Longterm survival data from CHAARTED and a post hoc aggregated analysis of CHAARTED and GETUG-AFU-15 data only showed an OS benefit for patients with HVD and de novo metastases. There was no OS benefit for LVD, irrespective of whether the patients had metastases at diagnosis or after failure of prior local therapy. Clarke et al 2 re-examined OS by disease burden using STAMPEDE data with longer follow-up, but the analysis had inadequate statistical power (<80%) to detect an OS difference by disease burden if in fact one existed.
- As a chemotherapy agent, docetaxel is associated with somewhat greater toxicity than androgen-targeted therapies (novel hormone therapies), but the treatment course is relatively short (limited to 6 cycles), much less costly and generally covered by insurance, hence reducing the financial toxicity.



Recommendation 1.4

 For patients with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE.¹⁴

Recommendation 1.5

 For patients with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE.¹⁵

Evidence-based

benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

for patient with highrisk disease as defined per LATITUDE¹⁴

Evidence-based

benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Moderate

for patient with lowrisk disease as defined per STAMPEDE¹⁵



Recommendation 1.6

 The recommended regimen for patients with metastatic noncastrate prostate cancer is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until progressive disease is documented. Evidence-based benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong



Recommendation 1.7 (Updated)

 ADT plus enzalutamide should be offered to patients with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as RP or RT for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (PSA Evidence-based benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

progression-free, clinical progression-free, and overall) when compared with ADT alone for patients with metastatic noncastrate prostate cancer as a group per ENZAMET.¹³ Enzalutamide also has long-term survival benefits overall, for those with low- or high-volume disease, and those with low- or high-volume disease and no docetaxel use.⁴ Per ARCHES,⁵ enzalutamide significantly improved time to first subsequent antineoplastic therapy in addition to survival benefits overall and among those with high volume disease, no prior docetaxel and

previous use of ADT or orchiectomy.5

Recommendation 1.8 (Updated)

 The recommended regimen for patients with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT.

Evidence-based
benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

Practical Information for Recommendation 1.8. (Updated)

 Discussions with patients should include the cost of enzalutamide treatment compared with other options, such as abiraterone.



Recommendation 1.9

 ADT plus apalutamide should also be offered to patients with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as RP or RT for localized disease per TITAN.¹⁶

Evidence-based

benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

Recommendation 1.95

 The recommended regimen for patients with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT. Evidence-based

benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong



Practical Information for Recommendations 1.9 and 1.95 (Updated)

• Discussions with patients should include the cost of apalutamide treatment compared with other options, such as abiraterone.

Recommendation 2.1

 ADT plus abiraterone and prednisolone should be considered for patients with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failurefree survival benefit per STAMPEDE.¹⁵ RT to the primary was mandated in STAMPEDE¹⁵ for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, DP, or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for 2 or less years to patients with nonmetastatic disease.

Evidence-based benefits outweigh harms

Evidence Quality

High

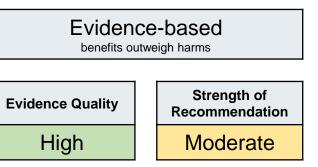
Strength of Recommendation

Strong



Recommendation 2.2

 In resource-constrained settings where drugs such as abiraterone may not be available, combined androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide, may be offered to patients with locally advanced nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses.



Practical Information for Recommendation 2.2 (Updated)

For patients with high-risk nonmetastatic prostate cancer progressing after RP or RT or both, it
is currently unclear whether enzalutamide (160 mg) plus leuprolide improves metastasis-free
survival compared with enzalutamide monotherapy or placebo. Although recruitment is
complete for the ongoing phase III EMBARK trial, which is designed to answer this question,
results are not yet available. Thus, no recommendation can be made at this time.

Recommendation 3.1

 Early (immediate) ADT may be offered to patients who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo RT based on evidence in one metaanalysis of a modest, but statistically significant benefit in terms of both OS and cancer-specific survival among the larger population of patients with locally advanced nonmetastatic disease.

Evidence-based benefits outweigh harms

Evidence Quality

Intermediate

Strength of Recommendation

Moderate

Practical Information for Recommendation 3.1

- Discussions with patients regarding early ADT should include the risk of short- and long-term side effects. Deferred ADT is often preferred by patients who desire to avoid, or at least delay, potential ADT side effects. Consideration should be given to restricting deferred ADT to those patients who are asymptomatic.
- No recommendation can be provided at this time for patients with PSA relapse after local treatment. Although existing studies suggest a potential OS benefit, additional research is needed as such studies were underpowered.



Recommendation 4.1

 Intermittent therapy may be offered to patients with high-risk biochemically recurrent nonmetastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the noninferiority of IADT when compared with CADT with respect to OS.¹⁷ This is further supported by evidence from four Evidence-based
benefits outweigh harms

Evidence Quality

High

Strength of Recommendation

Strong

meta-analyses¹⁸⁻²¹ testing superiority. Low-risk biochemical recurrence after RP is defined as a PSA doubling time < 1 year and pathologic Gleason score < 8. Low-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence > 18 months and clinical Gleason score < 8. High-risk biochemical recurrence after RP is defined as a PSA doubling time < 1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence < 18 months or a clinical Gleason score of 8-10.²³ Active surveillance may be offered to patients with low-risk biochemically recurrent nonmetastatic prostate cancer.



Practical Information for Recommendation 4.1

- Although patients with noncastrate de novo metastatic prostate cancer were included in the studies reviewed for this clinical question, alternative standard-of-care therapies with proven survival benefits now exist, as outlined in Recommendation 1 to include ADT plus docetaxel, ADT plus abiraterone, ADT plus enzalutamide, or ADT plus apalutamide. Similar support for these existing SOCs does not universally exist for patients with LVD or those who develop M1 disease after prior local therapy, and further research is needed. No specific additional recommendation with respect to the use of IADT in the noncastrate metastatic prostate cancer population was possible at this time because IADT has not been studied in combination with additional cytotoxic or hormonal agents in this population.
- Patients considering IADT should be made aware of the potential benefits of IADT associated with the off-treatment intervals, such as reduced treatment side effects, quality-of-life benefits, and lower cost. As patients on IADT require close follow-up, they must be motivated to adhere to frequent doctor visits for monitoring, even during off-treatment periods.





3 Additional Information

Additional Resources

 More information, including a supplement and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines

Patient information is available at <u>www.cancer.net</u>



Guideline Panel Members

Name	Affiliation/Institution	Role/Area of Expertise
Katherine S. Virgo, PhD, MBA, FASCO (co-chair)	Rollins School of Public Health, Department of Health Policy and Management, Emory University, Atlanta, GA	Health Services Research and Health Economics
James Talcott, MD, SM (co-chair)	Nanthealth, Inc, Culver City, CA	Medical Oncology
Charles L. Bennett, MD, PhD	University of South Carolina College of Pharmacy, Columbia, SC	Hematology/Medical Oncology
Prof. Ronald de Wit, MD, PhD	Lead, Experimental Systematic Therapy of Urogenital Cancers, Erasmus MC, Rotterdam, NL	Internal Medicine, GU Oncology
Martin Gleave, MD	University of British Columbia, Vancouver, BC, Canada	Urology/Surgery
David L. Graham, MD, FACP, FASCO	Levine Cancer Institute, Charlotte, NC	Medical Oncology/PGIN
Terry M. Kungel, MBA	Woolwich, ME	Patient Representative
Andrew Loblaw, MD, MSc	Sunnybrook Health Sciences Centre, Toronto, ON, Canada	Radiation Oncology
Scott C. Morgan, MD, MSc	The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada	Radiation Oncology
Paul L. Nguyen, MD	Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA	Radiation Oncology
Sean Sachdev, MD	Northwestern University, Chicago, IL	Radiation Oncology/PGIN
Thomas J. Smith, MD, FACP, FASCO, FAAHPM	Johns Hopkins Medicine, Baltimore, MD	Medical Oncology, Hospice and Palliative Medicine, Pain Management, Palliative Care
Mary-Ellen Taplin, MD	Dana-Farber Cancer Institute, Boston, MA	Hematology/Medical Oncology
Winston Tan, MD	Mayo Clinic, Jacksonville, FL	Medical Oncology/PGIN
Neha Vapiwala, MD, FACR	University of Pennsylvania Perelman School of Medicine, Philadelphia, PA	Radiation Oncology
James L. Wade III, MD, FASCO	Cancer Care Specialists of Illinois, Decatur, IL	Medical Oncology
Howard I. Scher, MD	Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY	Medical Oncology
R. Bryan Rumble, MSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)



Abbreviations

- ADT, androgen deprivation therapy
- ARTA, androgen receptor axis targeted agent
- ASCO, American Society of Clinical Oncology
- CADT, continuous androgen deprivation therapy
- DP, disease progression
- EBMC, Evidence Based Medicine Committee
- FDA, U.S. Food and Drug Administration
- HVD, high-volume disease

- IADT, intermittent androgen deprivation therapy
- LVD, low-volume metastatic disease
- OS, overall survival
- PSA, prostate-specific antigen
- RP, radical prostatectomy
- rPFS, radiographic progression-free survival
- RT, radiotherapy
- SOCs, standards of care



References

- 1. Virgo KS, Rumble RB, de Wit R, et al: Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update. J Clin Oncol 39:1274-1305, 2021
- 2. Smith MR, Hussain M, Saad F, et al: Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. N Engl J Med 386:1132-1142, 2022
- 3. Fizazi K, Foulon S, Carles J, et al: Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 399:1695-1707, 2022
- 4. Davis ID, Martin AJ, Zielinski RR, et al: Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). Journal of Clinical Oncology 40:LBA5004-LBA5004, 2022
- 5. Armstrong AJ, Iguchi T, Azad A, et al: Overall survival (OS) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated with enzalutamide (ENZA)+ androgen deprivation therapy (ADT) by high or low disease volume and progression to mHSPC (M0 at diagnosis) or de novo mHSPC (M1 at diagnosis): Post hoc analysis of the phase 3 ARCHES trial, American Society of Clinical Oncology, 2022
- 6. Ciccarese C, Iacovelli R, Sternberg CN, et al: Triplet therapy with androgen deprivation, docetaxel, and androgen receptor signalling inhibitors in metastatic castration-sensitive prostate cancer: A meta-analysis. European Journal of Cancer 173:276-284, 2022
- 7. Ferro M, Lucarelli G, Crocetto F, et al: First-line systemic therapy for metastatic castration-sensitive prostate cancer: An updated systematic review with novel findings. Critical reviews in oncology/hematology 157:103198, 2021
- 8. Sweeney CJ, Chen YH, Carducci M, et al: Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 373:737-46, 2015
- 9. James ND, Sydes MR, Clarke NW, et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet 387:1163-1177, 2016
- 10. Morris MJ, Rumble RB, Basch E, et al: Optimizing anticancer therapy in metastatic non-castrate prostate cancer: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology 36:1521-1539, 2018
- 11. Kyriakopoulos CE, Chen Y-H, Carducci MA, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. Journal of Clinical Oncology 36:1080, 2018



References

- 12. Clarke NW, Ali A, Ingleby F, et al: Addition of docetaxel to hormonal therapy in low-and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Annals of oncology 30:1992-2003, 2019
- 13. Davis ID, Martin AJ, Stockler MR, et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. New England Journal of Medicine 381:121-131, 2019
- 14. Fizazi K, Tran N, Fein L, et al: Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 377:352-360, 2017
- 15. James ND, de Bono JS, Spears MR, et al: Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 377:338-351, 2017
- 16. Chi KN, Agarwal N, Bjartell A, et al: Apalutamide for metastatic, castration-sensitive prostate cancer. New England Journal of Medicine 381:13-24, 2019
- 17. Magnan S, Zarychanski R, Pilote L, et al: Intermittent vs continuous androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. JAMA oncology 1:1261-1269, 2015
- 18. Botrel TEA, Clark O, Dos Reis RB, et al: Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. BMC urology 14:1-14, 2014
- 19. Brungs D, Chen J, Masson P, et al: Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer and Prostatic Diseases 17:105-111, 2014
- 20. Niraula S, Le LW, Tannock IF: Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. Journal of clinical oncology 31:2029-2036, 2013
- 21. Tsai H-T, Penson DF, Makambi KH, et al: Efficacy of intermittent androgen deprivation therapy vs conventional continuous androgen deprivation therapy for advanced prostate cancer: a meta-analysis. Urology 82:327-334, 2013



Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon 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 specify the level of 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" indicates 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 does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. 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.

