Conflict of Interest Disclosures: None reported.

1. Wang X, Wang SS, Huang H, et al; South China Breast Cancer Group. Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: the SYSUCC-001 randomized clinical trial. *JAMA*. 2021;325(1):50-58. doi:10.1001/jama.2020.23370

2. Cardoso F, Kyriakides S, Ohno S, et al; ESMO Guidelines Committee. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194-1220. doi:10.1093/annonc/mdz173

3. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645

4. BC Cancer Agency. Capecitabine. Accessed January 30, 2021. http://www.bccancer.bc.ca/drug-database-site/Drug Index/Capecitabine_monograph.pdf

In Reply We agree with Drs Du and Yuan that the optimal dosage of capecitabine is important and remains unclear. The regimen used in our study[1] (650 mg/m^2 twice daily continuously) was selected based on the study by Stockler et al[2] that demonstrated no difference in efficacy between this metronomic regimen and the intermittent regimen (1000 mg/m^2 twice daily on days 1-14 for 21 days). Our regimen resulted in fewer adverse effects, including diarrhea, compared with the standard dose used in the CREATE-X trial,[3] as mentioned by Dr Chakrabarti and colleagues.

Capecitabine was given sequentially following adjuvant chemotherapy in the SYSUCC-001 study but concomitantly with adjuvant chemotherapy in the CBCSG-010 study.[4] In these 2 studies, none of the clinicopathological parameters, including nodal involvement, demonstrated a statistically significant interaction with capecitabine benefit. Therefore, it is difficult to identify patients who benefit more based on current studies. An exploratory analysis of pharmacokinetics and molecular biomarkers to predict the efficacy of capecitabine is ongoing by our group.

We agree with Chakrabarti and colleagues that neoadjuvant chemotherapy (NAC) is widely used for TNBC, which helped identify patients with nonpathological complete response who may benefit from additional capecitabine in the CREATE-X study.[3] However, the CREATE-X study did not include patients with nonpathological complete response who had received NAC containing platinum or immunotherapy. Therefore, whether conclusions can be extrapolated to other NAC regimens remains unknown. Our study was initiated 10 years ago, when most patients did not receive NAC. In fact, NAC was used in less than 20% of patients with stage I-II disease (accounting for 80% of patients in our study) in clinical practice during that era.[5]

Our study provides evidence supporting the use of capecitabine without NAC, which accounts for a considerable proportion of patients currently. Overall survival in our study was numerically but not statistically significantly improved for several reasons, including limited sample size and potentially imbalanced salvage treatment. However, it is important to note that improvement in overall survival in the CREATE-X study was drawn from subgroup analysis, which limits its statistical power.

Our study included patients with pathologic stage Ib-IIIc disease without internal mammary or supraclavicular node involvement, so only those with pT1b-3N0-3a disease were included. All patients in our study had been clinically evaluated as having operable disease, but some were staged up to pN2-3a disease after surgery. These patients received adjuvant treatment and were included in our study. Of the 94 events observed, 54 (57.4%) occurred in patients with stage I-II disease and 40 (42.6%) in those with stage III disease. There was no significant interaction effect between stage I-II vs stage III disease and capecitabine benefit (P = .19). The dissimilar distribution of radiotherapy between the 2 groups was due to 8 patients who all received radiotherapy in the control group but withdrew after randomization. We performed a sensitivity analysis and found that the benefit of capecitabine was consistent with the present outcome in patients with or without radiotherapy.

Xi-Wen Bi, MD
Xin Hua, MD
Zhong-Yu Yuan, MD

Author Affiliations: Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China.

Corresponding Author: Zhong-Yu Yuan, MD, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, 651 Dongfeng Rd E, Guangzhou 510060, China (yuanzhy@sysucc.org.cn).

Conflict of Interest Disclosures: None reported.

1. Wang X, Wang SS, Huang H, et al; South China Breast Cancer Group. Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: the SYSUCC-001 randomized clinical trial. *JAMA*. 2021;325(1):50-58. doi:10.1001/jama.2020.23370

2. Stockler MR, Harvey VJ, Francis PA, et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. *J Clin Oncol*. 2011;29(34):4498-4504. doi:10.1200/JCO.2010.33.9101

3. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645

4. Li J, Yu K, Pang D, et al; CBCSG010 Study Group. Adjuvant capecitabine with docetaxel and cyclophosphamide plus epirubicin for triple-negative breast cancer (CBCSG010): an open-label, randomized, multicenter, phase III trial. *J Clin Oncol*. 2020;38(16):1774-1784. doi:10.1200/JCO.19.02474

5. Mougalian SS, Soulos PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. *Cancer*. 2015;121(15):2544-2552. doi:10.1002/cncr.29348

Management of Crohn Disease

To the Editor We would like to add 2 treatment options not mentioned in the recent extensive review on the management of Crohn disease by Drs Cushing and Higgins[1] because an estimated 6 million to 8 million people worldwide have inflammatory bowel disease (IBD), of whom the majority live in lower- and middle-income countries (LMICs) or lack access to health insurance and drugs.[2] The affordability and accessibility to monoclonal biologic therapies for these patients with IBD leaves local gastroenterologists with limited treatment options.[3] Under the United Nations Good Health and Well-Being Sustainable Development Goal, the World Health Organization has made accessibility to medicine one of its priorities. Therefore, it is important to mention

and investigate accessible and affordable therapies, especially for those who are treating patients with IBD without significant resources.

The first option is to combine low-dose thiopurines (approximately 25% of the normal dose) with allopurinol. This combination therapy is effective for patients with IBD who are considered *shunters*, those with subtherapeutic 6-thioguanine nucleotide (6-TGN) levels and high 6-methylmercaptopurine levels.[4] However, it is often too expensive for patients to obtain these levels, and most LMICs lack the facilities to perform 6-TGN measurements. If this combination treatment option is used, patients should be carefully monitored for bone marrow suppression. Furthermore, thiopurines, such as azathioprine and mercaptopurine, are well-established maintenance treatments for IBD, which cost approximately €1 to €3 ($1.19-$3.58) per day.[5]

Another effective and safe treatment option for IBD is the thiopurine thioguanine. In the Netherlands, thioguanine is conditionally registered and frequently used as maintenance therapy for patients with IBD who do not respond to conventional therapy with azathioprine and mercaptopurine.[6]

In the future, if biologic therapies become more available and affordable, these therapies could be prescribed to patients with IBD in LMICs as either monotherapy or in combination with thiopurines.

Ahmed B. Bayoumy, BSc, BPharm
Nanne K. H. de Boer, MD, PhD
Chris J. J. Mulder, MD, PhD

Author Affiliations: Faculty of Medicine, Amsterdam UMC, Amsterdam, the Netherlands (Bayoumy); Department of Gastroenterology and Hepatology, Amsterdam UMC, Amsterdam, the Netherlands (de Boer, Mulder).

Corresponding Author: Ahmed B. Bayoumy, BSc, BPharm, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands (a.b.bayoumy@amsterdamumc.nl).

Conflict of Interest Disclosures: Dr de Boer reported receiving grants from and serving as a consultant and principal investigator for Takeda and Teva Pharmaceuticals; receiving personal fees from AbbVie and Merck, Sharp and Dohme; and receiving research grants from Dr Falk and Maag Lever Darm Stichting. Dr Mulder reported receiving grants from HLW Pharmaceutical, Douglas Pharmaceuticals, and Arega. No other disclosures were reported.

1. Cushing K, Higgins PDR. Management of Crohn disease: a review. *JAMA*. 2021;325(1):69-80. doi:10.1001/jama.2020.18936

2. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):17-30. doi:10.1016/S2468-1253(19)30333-4

3. Bazargani YT, de Boer A, Schellens JH, Leufkens HG, Mantel-Teeuwisse AK. Selection of oncology medicines in low- and middle-income countries. *Ann Oncol*. 2014;25(1):270-276. doi:10.1093/annonc/mdt514

4. Friedman AB, Brown SJ, Bampton P, et al. Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study). *Aliment Pharmacol Ther*. 2018;47(8):1092-1102. doi:10.1111/apt.14571

5. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;(9):CD000478. doi:10.1002/14651858.CD000478.pub3

6. Bayoumy AB, Simsek M, Seinen ML, et al. The continuous rediscovery and the benefit-risk ratio of thioguanine, a comprehensive review. *Expert Opin Drug Metab Toxicol*. 2020;16(2):111-123. doi:10.1080/17425255.2020.1719996

In Reply The goal of our Review[1] was to provide an overview of the management of Crohn disease for the internal medicine community. Although there are important therapeutic considerations in LMICs, we stress that the highlighted medical approaches are complex and best managed by an IBD subspecialist.

Thiopurines are purine analogs that have immunosuppressive effects and thus serve an important role in the medical management of Crohn disease. Thiopurines are not effective for induction of clinical remission in Crohn disease[2] but are effective in the maintenance of remission.[3] The 2 most commonly used thiopurines, azathioprine and 6-mercaptopurine, are metabolized by xanthine oxidase into the inactive metabolite 6-thiouric acid, thiopurine methyltransferase (TPMT) into the inactive metabolite 6-methylmercaptopurine, and several enzymes into the active metabolites 6-TGNs.[4] Before starting thiopurine therapy, gastroenterologists routinely check TPMT enzyme activity because patients with low TPMT enzyme activity levels are more likely to shunt toward increased production of 6-TGNs. High 6-TGN levels may be associated with potentially life-threatening bone marrow suppression; therefore, thiopurine therapy is deferred in those with low TPMT enzyme activity. Alternatively, patients with high TPMT enzyme activity may preferentially shunt toward increased production of 6-methylmercaptopurine and decreased production of active 6-TGN metabolites. As Mr Bayoumy and colleagues mention, a strategy to improve clinical response is to shift the metabolism toward 6-TGN production by reducing the thiopurine dose to 25% of the normal dose and adding allopurinol. We emphasize that this strategy should be performed with close laboratory monitoring and implemented only by an experienced gastroenterologist given the potential for significant bone marrow suppression.

Bayoumy and colleagues also discuss the use of thioguanine for patients who do not improve with conventional thiopurines and have limited access to biologic therapies. Rigorous studies of thioguanine use in Crohn disease are limited, but observational data suggests a clinical benefit with low-dose thioguanine therapy.[5] This therapeutic approach fell out of favor due to a high incidence (53%) of nodular regenerative hyperplasia[6] and increased availability of effective biologic therapies. The use of thioguanine as a treatment for Crohn disease involves close laboratory monitoring, recognition of signs and symptoms consistent with nodular regenerative hyperplasia, and management by an experienced gastroenterologist.

Gastroenterologists must weigh several considerations when making therapeutic decisions, including a patient's age, medical comorbidities, disease severity, and disease behavior. Access to and affordability of medications are also important considerations because the cost of many biologic therapies is prohibitively high for most patients. Patient assistance programs through companies or institutional support mechanisms may be available to support the cost of these medications. When unavailable, more nuanced therapeutic approaches can be considered, as highlighted by Bayoumy and colleagues. However, such complex therapeutic strategies should be reserved for IBD refractory to conventional treatments and should be managed by

gastroenterologists experienced with IBD and familiar with the safety profiles of the medications.

Kelly Cushing, MD, MSCI
Peter D. R. Higgins, MD, PhD, MSc

Author Affiliations: Division of Gastroenterology, University of Michigan, Ann Arbor.

Corresponding Author: Peter D. R. Higgins MD, PhD, MSc, SPC 5682, 1150 W Medical Center Dr, University of Michigan, Ann Arbor, MI 48109 (phiggins@med.umich.edu).

Conflict of Interest Disclosures: Dr Higgins reported receiving grants from AbbVie, Janssen, Eli Lilly, PRIME Medical Education, the National Institutes of Health, Pfizer, and the Rainin Foundation. No other disclosures were reported.

1. Cushing K, Higgins PDR. Management of Crohn disease: a review. *JAMA*. 2021;325(1):69-80. doi:10.1001/jama.2020.18936

2. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2013;(4):CD000545. doi:10.1002/14651858.CD000545.pub4

3. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;(10):CD000067. doi:10.1002/14651858.CD000067.pub3

4. Ha C, Dassopoulos T. Thiopurine therapy in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol*. 2010;4(5):575-588. doi:10.1586/egh.10.59

5. Taylor KM, Ward MG, Blaker PA, Sparrow MP. Is there a role for thioguanine therapy in IBD in 2017 and beyond? *Expert Rev Gastroenterol Hepatol*. 2017;11(5):473-486. doi:10.1080/17474124.2017.1294062

6. Geller SA, Dubinsky MC, Poordad FF, et al. Early hepatic nodular hyperplasia and submicroscopic fibrosis associated with 6-thioguanine therapy in inflammatory bowel disease. *Am J Surg Pathol*. 2004;28(9):1204-1211. doi:10.1097/01.pas.0000128665.12063.97

CORRECTION

Incorrect *P* Value and Figure Label Error: In the Original Investigation titled "Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke: The SKIP Randomized Clinical Trial,"[1] published in the January 19, 2021, issue of *JAMA*, the *P* value for the modified Rankin Scale score reduction (shift analysis) should have been reported as .37 in the Results section and Table 2. Also, the labels in the forest plot in Figure 3 should have been switched, so that "Favors intravenous thrombolysis plus mechanical thrombectomy" was on the left and "Favors mechanical thrombectomy alone" was on the right. This article was corrected online.

1. Suzuki K, Matsumaru Y, Takeuchi M, et al; SKIP Study Investigators. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA*. 2021;325(3):244-253. doi:10.1001/jama.2020.23522

Guidelines for Letters

Letters discussing a recent *JAMA* article should be submitted within 4 weeks of the article's publication in print. Letters received after 4 weeks will rarely be considered. Letters should not exceed 400 words of text and 5 references and may have no more than 3 authors. Letters reporting original research should not exceed 600 words of text and 6 references and may have no more than 7 authors. They may include up to 2 tables or figures but online supplementary material is not allowed. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters not meeting these specifications are generally not considered. Letters being considered for publication ordinarily will be sent to the authors of the *JAMA* article, who will be given the opportunity to reply. Letters will be published at the discretion of the editors and are subject to abridgement and editing. Further instructions can be found at http://jamanetwork.com/journals/jama/pages/instructions-for-authors. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment are required before publication. Letters should be submitted via the *JAMA* online submission and review system at https://manuscripts.jama.com. For technical assistance, please contact jama-letters@jamanetwork.org.

Section Editor: Jody W. Zylke, MD, Deputy Editor.