VOLUME 25 · NUMBER 26 · SEPTEMBER 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Diffusion Magnetic Resonance Imaging: A Biomarker for Treatment Response in Oncology

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Submitted March 30, 2007; accepted May 14, 2007.

Supported by National Institutes of Health Research Grants No. P01CA85878, R24CA83099, and P50CA093990.

A.R. and B.D.R. have a financial interest in the underlying technology (patent No. 6,567,684) discussed in this article. Furthermore, this technology is licensed to ImBio LLC, in which A.R. and B.D.R. have a financial interest.

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

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0732-183X/07/2526-4104/$20.00

DOI: 10.1200/JCO.2007.11.9610

A B S T R A C T

Imaging of response to oncology treatments, either on clinical protocol or as part of standard practice, is a complicated process that has evolved during the last 10 years due to the improvement of existing imaging technologies and the introduction of newer modalities. Diffusion magnetic resonance imaging is a technique that measures the mobility of water within tissues and, as such, may function as a surrogate marker for both tissue cellularity and response to treatment that occur earlier than usual measures of tumor response. This review highlights the development of this technique and the state of current clinical understanding of its utility.

J Clin Oncol 25:4104-4109. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Radiographic imaging plays a significant role in the management of patients with solid malignancies and is crucial for diagnosis, treatment planning, and assessment of response or recurrence. Advances in cross-sectional imaging and three-dimensional reconstruction of computed tomography (CT) or magnetic resonance images (MRIs) have made radiographic measurements of tumor size more precise, reproducible, and accurate. Despite their common use, there is not agreement on which imaging modalities to use, how tumors and tumor boundaries should be defined, or how response/progression should be scored. Concurrent with implementing the optimal strategy for conventional imaging, newer functional imaging technologies are being developed that not only capture cross-sectional tumor information, but also reveal insights about underlying tumor biology or response to therapy.

WHAT DEFINES TUMOR RESPONSE OR PROGRESSION?

A single method to determine tumor response is not universally accepted; however, a new definition for solid tumor responses based on a single linear summation of a small number of target lesions, termed Response Evaluation Criteria in Solid Tumors (RECIST),[1] has been adopted for clinical protocols. This linear summation is both rapid and reproducible to facilitate its use in clinical trials. RECIST is also a step forward from previous response criteria because it takes into account differences in scan thickness, minimum tumor sizes, and frequency of evaluations. Nevertheless, despite broad adoption of this technique, there is a growing appreciation that measurement of response is often not adequately addressed by RECIST when tumors are treated with conventional cytotoxic therapy.[2] In addition, newer molecularly targeted agents may cause a meaningful clinical impact without significantly altering tumor dimensions.[3,4] Therefore, there is a need to develop measures of response that are more accurately linked to clinical outcome and that can evaluate response to treatment sooner than current imaging methodologies.

FUNCTIONAL IMAGING OF TUMOR RESPONSE TO THERAPY

With the ability to obtain greater resolution and reproducibility of traditional volumetric data along with the development of functional imaging modalities, such as perfusion MRI, diffusion MRI, [^{18}F]fluorodeoxyglucose positron emission tomography (PET), or PET with newer tracers, there is now the need to evaluate these potential new biomarkers for tumor response. One of the goals of these tests would be not only to measure the characteristics of the tumor before therapy, which may have prognostic value in and of themselves, but also to evaluate changes in tumors in response to treatment, which may function as a surrogate for clinical efficacy in a manner that conventional imaging cannot. The capacity to use these new biomarkers along with

established clinical end points has become important in clinical trial development and will continue to gain importance as newer targeted molecular therapies replace traditional cytotoxic treatments. The extension of these same biomarkers to preclinical model systems will provide a unique method to translate validated preclinical imaging biomarkers directly into clinical trials.

Recent reviews have focused on PET[5] and MRI technologies,[6,7] so this review will instead focus on diffusion MRI in tumor response evaluation. However, there certainly are instances for which different functional imaging techniques may provide unique or complementary information. For example, a recent report of pretreatment evaluation of head and neck cancer patients found areas both in common and different when comparing CT-, MRI-, or PET-based definitions of tumor volume.[8] PET on average provided the smallest tumor volumes; however, despite this fact there were still areas identified by PET that were not initially included within the tumor volumes on CT or MRI. In addition, when compared with surgical specimens, all three imaging techniques underestimated the mucosal extent of the tumor. One of the strengths of PET is that it does not simply depend on volumetric information, but in turn gives some measure of underlying tumor metabolism, which may not necessarily correlate with tumor volume by CT or MRI. In addition, the continuing development of newer PET tracers will offer additional options to explore other areas of tumor biology.[5] However, because of the physical constraints of positron disintegration, there are inherent limits in the spatial resolution of PET. In addition, because areas of infection and/or inflammation may also have increased uptake on [^{18}F]fluorodeoxyglucose PET, this limits the use of PET during or shortly after radiation therapy, when mucosal inflammation may cause false-positive results.[9] Dynamic contrast enhanced MRI, like diffusion MRI, has high spatial resolution and may offer a benefit in the evaluation of tumor vasculature or response to antiangiogenic therapies.[10] However, it requires the use of intravenous contrast and relatively complicated postprocessing of acquired images.

DIFFUSION MRI: BACKGROUND

Diffusion MRI differs from conventional MRI in that it measures the mobility of water within tissues in addition to reflecting tumor size and shape. This technology gained its first clinical application in the evaluation of ischemic cerebral infarction, where changes in the cellular diffusion of water were documented as early as 30 minutes after acute ischemia.[11] Diffusion changes have been used subsequently to determine the chronicity of ischemic injury, to map the size of the injury, and to select the appropriate treatment. The utility of diffusion MRI in evaluation of stroke led to its exploration as an early marker of tumor response to therapy, and during the last 12 years, similar early diffusion changes have been demonstrated to occur in both preclinical and clinical settings. Currently, although the technique is commonly included as a feature on most modern MRI scanners, diffusion MRI is not well appreciated by the oncologic community.

At the most basic level, diffusion is defined as a random (Brownian) process by which molecules migrate down a concentration gradient, as observed for the equal distribution of a solute within a solution (for example when a drop of dye is added to a glass of water). MRI techniques have been used to measure the diffusion of molecules in the fluid phase for decades, but only more recently has the principle of magnetic resonance evaluation of diffusion been applied to complicated biologic systems.[12] Given the high concentration of water within biologic tissues, diffusion MRI has been focused primarily on measuring the diffusion of protons present within water molecules. With the use of this technique, the movement of water molecules within a cell can be differentiated from that in the extracellular space; however, because extracellular water has a greater freedom to diffuse than intracellular water, it is usually the predominant signal in most biologic systems. For instance, diffusion MRI can accurately discriminate a fluid-filled cyst from a cellular mass that would have more restricted movement of water molecules.

Because of a complex interplay of factors in vivo, the actual diffusion coefficient of water cannot be measured directly by MRI; instead, the diffusion coefficient obtained from orthogonal diffusion-weighted MRI in all three planes is obtained and is termed the apparent diffusion coefficient (ADC).[13] Although initially quite time consuming and susceptible to motion artifact, diffusion MRI techniques have improved during the last 15 years such that echo-planar sequences that are resistant to patient motion are now used. These sequences increase sensitivity to diffusional changes, are independent of magnetic field strength, do not require contrast administration, and can be performed in less than 2 minutes.[13]

Diffusion MR measurements are sensitive and can be used to detect and quantify tissue water diffusion values, which have been proposed to be related to the ratio of intracellular water to extracellular water; thus, changes in ADC are inversely correlated with changes in cellularity (Fig 1). In this scenario, increases in ADC would reflect an increase in the mobility of water, either through the loss of membrane integrity or an increase in the proportion of total extracellular fluid with a corresponding decrease in cellular size or number, as seen with necrosis or apoptosis. In contrast, decreases in ADC reflect a decrease

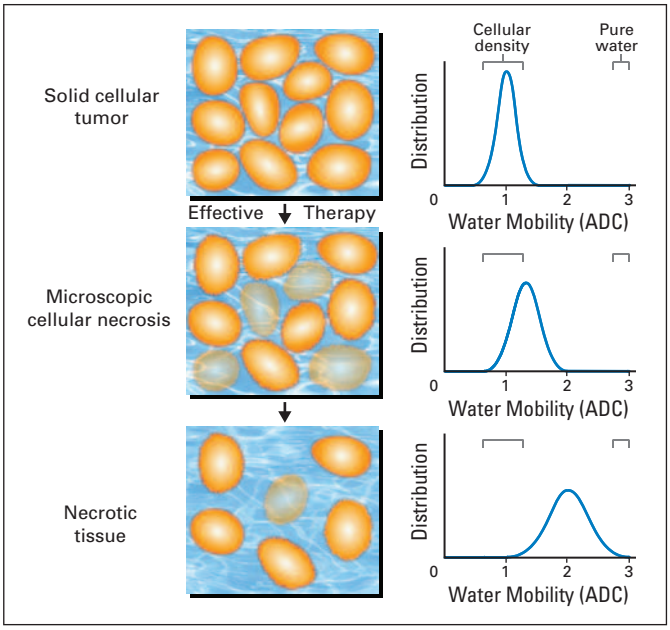

Fig 1. A schematic of the change in cellularity (left) and increased molecular water mobility measured as an apparent diffusion coefficient (ADC; right) as a tumor responds to treatment (top to bottom). For a tumor responding to therapy, an increase in extracellular space/membrane permeability allows greater water mobility and an increase in the ADC.

in free extracellular water, either through an increase in total cellular size or number, as can be seen with tumor progression, fibrosis, or edema.[14] Given that molecular and cellular changes in response to stress, cytotoxic, or oxidative injury precede volumetric changes, changes in diffusion MRI have been hypothesized to serve as an early surrogate for later pathologic or radiologic end points.

PRECLINICAL EVALUATION OF DIFFUSION MRI

Early studies with rodent brain and breast tumor models revealed that the change in ADC accurately reflected a change in cellularity and could be measured earlier than changes in tumor volume.[15,16] In animal models, treatment of breast cancer xenografts with cyclophosphamide (150 or 300 mg/kg) produced a significant 30% to 40% increase in ADC 2 days after treatment, which preceded volumetric response as measured using a non–image-based spectroscopic method.[16] Studies in rodent brain tumors demonstrated that as soon as 2 days after treatment with a systemic alkylating agent (carmustine), the tumor ADC increased significantly and subsequently peaked 50% higher than baseline. In comparison, there was no change in ADC from the normal brain tissue throughout the course of the experiment.[17] More importantly, although changes in ADC could be detected as early as 2 days after treatment, tumors did not show evidence of regression until day 8, when ADC was already declining toward its initial pretreatment value. Histologic analysis revealed an inverse correlation between cell density and ADC as tumors became necrotic (ie, increasing ADC correlated with cellular necrosis), but with subsequent recurrence, ADC values again decreased back to baseline, reflecting the dense cellular nature of the recurrence.[17,18]

It was later noted that changes in ADC were not uniform across tumors[19-21]; in regions where there were minimal changes in ADC, the tumor was more likely to progress as compared with areas where the ADC had increased significantly. To address this heterogeneity, an image postprocessing technique was developed, called the functional diffusion map (fDM), which takes into account regional changes in diffusion instead of analyzing the mean ADC across the tumor.[21] In a rodent glioma model, the percentage of the tumor responding to therapy (as determined by the fDM) correlated directly with both the dose of carmustine administered as well as biologic end points: the extent of tumor-cell kill, the development of regional necrosis, and the increase in animal survival.[21] Other preclinical studies have extended these observations to include tumors of diverse histologic origin and a variety of treatments,[19,21-27] which led to the logical extension of diffusion-weighted imaging to clinical studies (Table 1 summarizes the relevant clinical studies).

CLINICAL EVALUATION OF DIFFUSION MRI AS A BIOMARKER FOR TREATMENT RESPONSE

Given its role in evaluating ischemic changes in stroke patients, the initial studies of diffusion-weighted MRI as a prognostic imaging biomarker of response in cancer patients were performed predominantly in patients with brain tumors.[18,28,29] Anecdotal evidence demonstrated that in two patients with high-grade primary brain tumors, changes in ADC were observable many weeks before tumor response, and as in the preclinical models, by the time tumors were observed to be objectively responding, the ADC value had already begun to decline back to baseline.[18] In a second study, using convection-enhanced delivery of chemotherapy directly into the tumor, changes in ADC were observed as early as 24 hours after treatment and preceded any change in tumor volume.[28] In a third study using radiation therapy of 10 metastatic or primary brain tumors,[29] six of the treated tumors regressed by 35% to 89%, reaching this nadir at days 19 to 55, and in all six tumors there was a significant increase in diffusion as early as 3 days after treatment. In contrast, four lesions were stable or progressive (mean volume change of +1% to 60%) 50 to 62 days after treatment, and diffusion MRI was either stable or decreased in each of these lesions. The early change in mean ADC in this series was highly correlated with subsequent tumor response ($P < .006$).[29] Additional studies demonstrated that both pretreatment ADC[47] and the change in ADC[30,31] are predictors of response in brain tumors treated with chemotherapy,[31] or fractionated[47,31] or stereotactic radiotherapy.[30,47]

A prospective trial of diffusion MRI in patients with primary brain tumors was initiated at the University of Michigan (Ann Arbor, MI). All patients underwent a baseline scan within 1 week before the start of treatment, followed by the first intratreatment scan at 3 weeks. The majority of patients were treated with a 6-week course of fractionated radiation; therefore, when assessed for response, less than half of the total course of radiation had been delivered. In an initial report, mean ADC was weakly correlated with later radiographic response. However, fDMs were able to quantify a relatively small responsive mean + SEM volume within the tumors of only 8.1% ± 3.1% (range, 0% to 25%), and the fDM was able to discriminate accurately between patients who had progressive disease, stable disease, or a partial response.[32] Furthermore, these regional changes, as evaluated with an fDM threshold, were also less susceptible to changes secondary to corticosteroid dosing.[14] In a companion study, a total of 34 patients with WHO grade 3/4 glioma were evaluated by fDM 3 weeks into radiation therapy, at which time fDM not only correlated with radiographic response but also with both progression-free and overall survival.[33] The median survival of the whole group was 11.9 months; however, for those patients stratified by fDM as having progressive disease, overall survival was 8.2 months, whereas for those patients stratified as having a favorable response to therapy, overall survival was 18.2 months ($P < .008$). These results are being validated in a larger patient cohort.

Changes in diffusion imaging in response to therapy have now been analyzed in other anatomic sites, including rectal cancer,[34,35,48] primary or metastatic cancer to the liver,[36-39] breast cancer,[40,41] carcinoma metastatic to the spine,[42] and primary sarcomas of bone.[43,44] In rectal cancer, pretreatment ADC was negatively correlated with eventual tumor shrinkage or the ability to obtain appropriate surgical margins. It was suggested that higher pretreatment ADC likely reflected necrotic tumors that were resistant to therapy.[34,35,48] Interestingly, at later time points after treatment, mean ADC was consistently lower than at the start, perhaps reflecting fibrosis and scarring in response to treatment. In an additional series, patients who had a favorable pathologic response to neoadjuvant chemoradiotherapy exhibited an initial increase in ADC 1 week after treatment, followed by a later decrease in ADC, whereas those who had an unfavorable pathologic response did not exhibit this initial increase in ADC.[35] This highlights the fact that the timing of evaluation relative to treatment is a key variable in diffusion MRI that remains incompletely evaluated.

For either primary or metastatic cancer confined to the liver, there is convincing evidence that changes in ADC precede or can be

Table 1. Studies Evaluating Diffusion-Weighted MRI As a Surrogate for Treatment Response

Study	Site	No. of Lesions	No. of Patients	Treatment	Timing*	Conclusion
Chenevert et al[18]	Brain	2	2	Cm/RT	Serial	Increase in ADC preceded tumor response
Mardor et al[28]	Brain	3	3	CED	Serial	Changes in ADC preceded tumor response and greater increase in ADC in patients receiving more treatment
Mardor et al[29]	Brain	10	8	RT	3-10 days	Increased in ADC preceded tumor response ($P < .006$)
Tomura et al[30]	Brain	20	20	Stereotactic RT	2-4 weeks	Increased ADC change between responders and nonresponders ($P < .05$)
Schubert et al[31]	Brain	6	3	Cm/RT	NA	Increased ADC in responding lesions compared with nonresponding lesions
Moffat et al[32]	Brain	20	20	Cm/RT	3 weeks	fDM discriminates later radiographic response ($P < .001$)
Hamstra et al[33]	Brain	34	34	RT ± Cm	3 weeks	fDM predicts OS ($P < .01$) and PFS ($P < .04$)
Dzik-Jurasz et al[34]	Rectum	14	14	Cm then RT	NA	Decreased ADC correlated with radiographic response
Kresmer et al[35]	Rectum	8	8	Cm/RT	1 weeks	Increased ADC at week 1 predicts response ($P < .01$) with a later decline in ADC in all patients
Thielmann et al[36]	Liver	60	13	Cm	4 and 11 days	Correlation of ADC with radiographic response better at 11 days than 4 days
Kamel et al[37]	Liver	38	38	TACE	4-6 weeks	Increased ADC ($P < .03$) and decrease in AFP but no response by RECIST
Deng et al[38]	Liver	6	6	^{90}Y microspheres	6 weeks	Increased ADC ($P < .05$), no response by RECIST
Kamel et al[39]	Liver	19	13	^{90}Y microspheres	4 weeks	Increased ADC in treated ($P < .001$) but not untreated lesions
Pickles et al[40]	Breast	10	10	Cm	3 weeks	Increased ADC after first ($P = .005$) and second cycles ($P = .004$), with marginal change by RECIST after second cycle ($P = .057$)
Yankeelov et al[41]	Breast	11	11	Cm	15-18 weeks	Increased ADC after treatment ($P < .05$)
Byun et al[42]	Spine	24	24	RT	1-6 months	Increased ADC in those with clinical response and not in those with persistent pain
Hayashida et al[43]	Bone	18	18	Cm	NA	Increased ADC greater in those with histologic response than in those without response ($P = .003$); no change by RECIST
Uhl et al[44]	Bone	8	8	Cm	NA	Higher ADC in necrotic areas *v* non-necrotic areas ($P = .01$)
Liapi et al[45]	Uterus	32	11	Embolization	99-239 days	Decrease in ADC late after treatment in treated fibroids ($P < .01$) but not in surrounding normal tissue
Jacobs et al[46]	Uterus	14	14	Ultrasound	Early and 6 months	Initial decrease in ADC ($P = .001$) followed by late increase ($P < .001$) in treated lesions

Abbreviations: MRI, magnetic resonance imaging; Cm, systemic chemotherapy; RT, radiation therapy; ADC, apparent diffusion coefficient; CED, convection enhanced delivery of chemotherapy; NA, not available in text; fDM, functional diffusion map; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; RECIST, Response Evaluation Criteria in Solid Tumors.
*Timing of response evaluation relative to start of treatment.

observed in the absence of radiographic response to systemic chemotherapy,[36] chemoembolization,[37] or targeted radiation therapy using yttrium-90 microspheres.[38,39] After systemic chemotherapy, quantifiable and statistically significant changes in ADC in 60 metastatic breast cancer lesions to the liver were documented 4 and 11 days after treatment in those tumors that were radiographically documented as responsive 6 weeks from the start of treatment, whereas in nonresponding tumors there were no significant ADC changes.[36] In a later study, patients with hepatocellular cancer underwent chemoembolization followed by resection, and there was a direct correlation between increasing ADC and increasing necrosis within the specimens ($r = 0.95$; $P < .05$).[49] In a subsequent report, after chemoembolization, none of 38 hepatocellular cancers met RECIST criteria for partial response despite dramatic declines in mean alpha-fetoprotein levels before and after treatment (40,339 and 18,370 ng/mL, respectively; $P < .005$).[37] However, there were significant increases in mean ADC (20%) after treatment ($P < .03$), whereas ADC was unchanged in untreated lesions, and in non–tumor-bearing liver, spleen, or skeletal muscle.[37]

Neoadjuvant treatment is commonly used for patients with breast cancer (as it is for rectal cancer) when pathologic response to treatment can be used to guide additional chemotherapy selection.[50] Evaluation of response using conventional criteria (palpation, mammography, ultrasound, and MRI) showed only 19%, 26%, 35%, and 71% agreement, respectively, with pathologic response.[51] Although dynamic contrast enhanced MRI[41,52] or PET[53] has shown promise in predicting response to neoadjuvant therapy, it may take as long as 12 weeks to detect this change.[54] Magnetic resonance spectroscopy has been able to reveal responses to treatment within 1 day of treatment but is technically demanding, time consuming, and may require nonstandard MRI equipment that is not readily available.[55] In comparison, a recent study that used diffusion MRI before the start of

neoadjuvant chemotherapy and again after both the first and second 3-week cycles revealed that ADC was significantly increased after the first (+16%; $P = .005$) and second (+27%; $P = .004$) cycles, whereas the largest transverse diameter by MRI was decreased only marginally after the second cycle ($P = .057$).

Most studies of diffusion MRI have focused on early prediction and detection of radiographic response compared with conventional imaging. However, there may also be a role for diffusion MRI as a noninvasive biomarker for response when it cannot be assessed accurately using conventional imaging. For instance, there is no accepted method to measure response of either primary or metastatic cancers within skeletal sites where response is considered unmeasurable by RECIST.[1] The ability to determine response of osseous lesions would also be of benefit in some sarcomas; for example, when a significant pathologic response has been demonstrated to be of prognostic value even when no radiographic response was identified.[56] In one recent series, correlations were made between the ADC in osteosarcomas after chemotherapy with the corresponding regions on pathologic analysis. Necrotic areas, confirmed by macroscopic/histologic examination, showed ADC values up to 2.7 (mean, 2.3 ± 0.2), whereas areas of viable tumor revealed lower ADC (mean, 0.8 ± 0.3; $P = .01$).[44]

In another series of 18 patients with Ewing sarcoma or osteosarcoma treated with neoadjuvant chemotherapy before surgical resection, patients were divided into those who had less than 90% necrosis versus those who had 90% or greater necrosis, a value that previously has been associated with improved prognosis.[56] Pre- and intratreatment diffusion scans were used to assess response and revealed changes in mean ADC after chemotherapy, with the lower responding group demonstrating only a 25% mean increase in ADC, whereas the higher responding group had a 95% mean ADC increase ($P < .003$).[43] Despite the increase in ADC, there were no differences between these groups based on conventional imaging criteria.

Diffusion MRI was also used in a cohort of 24 patients with metastatic lesions within the spine treated with radiation therapy.[42] Neither T1 or T2 nor the volume of abnormality correlated with clinical improvement. In contrast, in the one patient who had increasing symptoms after radiation therapy, the mean ADC decreased, whereas in the remaining 23 patients who experienced clinical improvement, mean ADC increased by 56%.

Another scenario in which RECIST has proven to be of limited value is in the assessment of response to treatment of uterine fibroids. Two studies addressed the use of diffusion MR after embolization[45] or focused ultrasound ablation,[46] and in both studies, alterations in the mean ADC were detected in treated lesions without meeting RECIST criteria, although the differences in the timing of the follow-up scans limits the ability to interpret these data. Thus, there is growing evidence that diffusion MRI appears not only to be an early marker of response, but also to be an effective biomarker when conventional imaging is ineffective.

In conclusion, significant preclinical and clinical evaluations have been performed that support the hypothesis that diffusion MR is an early surrogate biomarker for tumor response. In addition, it may also provide a noninvasive measure of response in anatomic areas or histologic subtypes, or after novel molecular therapies that have not been amenable to conventional radiographic evaluation. Furthermore, the high spatial resolution of MRI may enable it to be incorporated into adaptive radiotherapy techniques to adjust treatment based on intratherapy evaluations. This technology is at a unique crossroad. It could be readily adopted and performed on most current clinical MRI scanners. However, despite initial promising results, the field has been hampered by the wide variety of ways the diffusion MRI data have been collected and analyzed, with no uniform standards for data acquisition, postimage processing, timing of evaluation, or the means by which changes were subsequently assessed (which have included absolute ADC, mean ADC, normalized ADC, threshold changes in ADC, and functional diffusion maps). In addition, the true validity of diffusion-weighted imaging will not be addressed fully until large, prospective, multi-institutional trials are performed that incorporate diffusion-weighted imaging in a uniform fashion.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Alnawaz Rehemtulla, Im Bio LLC (U); Brian D. Ross, Im Bio LLC (U) **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Daniel A. Hamstra

Manuscript writing: Daniel A. Hamstra, Alnawaz Rehemtulla, Brian D. Ross

Final approval of manuscript: Daniel A. Hamstra

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Acknowledgment

We thank Joe Contessa and Felix Feng for critical review of the manuscript and Swaroop Bhojani for graphical assistance.