

## Current Approaches to the Treatment of Early Hepatocellular Carcinoma

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**Key Words.** Hepatocellular carcinoma • Liver transplantation • Ablation techniques • Operative surgical procedure

**Disclosures:** Sheng-Long Ye: None; Tadatoshi Takayama: None; Jeff Geschwind: *Consultant/advisory role:* Biosphere Medical, Biocompatibles, Bayer HealthCare, Guerbet; *Research funding/contracted research:* Biosphere Medical, Biocompatibles, Genentech, Bayer HealthCare, Philips Medical, Context Vision, Gideon, RSNA; Jorge A. Marrero: *Honoraria:* Bayer, Onyx; *Research funding/contracted research:* Bayer; Jean-Pierre Bronowicki: *Honoraria:* Bayer Pharma, Bristol-Myers Squibb.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

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### ABSTRACT

For patients with early-stage hepatocellular carcinoma (HCC), potentially curative treatment options exist, including liver transplantation, surgical resection, and ablation therapy. These treatments are associated with survival benefits, and outcomes are optimized by identification of appropriate patients. However, further studies are needed to definitively confirm optimal treatment approaches for all patients.

Treatment patterns vary in different parts of the world as a result of geographic differences in the incidence and presentation of the disease. In particular, because of successful screening programs, a high proportion of tumors that are identified in Japan are amenable to curative treatments, which are appropriate in a

smaller proportion of patients in the west, although screening is now widely carried out in industrialized countries. Differences in the applicability of transplantation are also evident between the west and Asia.

Although existing treatments for early-stage HCC are supported by considerable evidence, there remain significant data gaps. For example, further data, ideally from randomized controlled trials, are needed regarding: the use of neoadjuvant and adjuvant therapy to decrease the rate of recurrence after resection or ablation, further investigation of the role of chemoprevention following resection, and prospective analysis of outcomes of living donor compared with deceased donor liver transplantation. *The Oncologist* 2010;15(suppl 4):34–41

## INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the third most common cause of cancer-related death [1, 2]. The presence of cirrhosis is a key risk factor [3]. HCC is a complex disease involving many factors, and HCC staging systems can be very complicated [4]. The widely used, comprehensive Barcelona Clinic Liver Cancer staging system takes into account variables related to tumor stage, liver function, physical status, and cancer-related symptoms to generate a treatment algorithm [5].

Treatment is most effective in the early stages of disease, but diagnosing early-stage HCC is difficult because the diagnosis of cirrhosis is often not made before the emergence of HCC. Patients at high risk for developing HCC (e.g., those with cirrhosis, hepatitis B virus, or hepatitis C virus) should be entered into surveillance programs using ultrasound and serum  $\alpha$ -fetoprotein (AFP) [3, 6, 7]. Based mainly on observational data on tumor-volume doubling time, a screening interval of 6 months is commonly used by physicians in the West, in contrast to the Far East, where a 3-month screening interval is generally implemented [8]. In a recent meta-analysis, a significantly higher sensitivity for early HCC was observed with a 6-month interval than with annual surveillance [9]. Because of the high rates of false-positive and false-negative results in patients with chronic liver disease, the American Association for the Study of Liver Diseases (AASLD) does not recommend the use of AFP alone as a screening method, unless ultrasound is not available. Information from a recent meta-analysis demonstrated that AFP provided no additional benefit to ultrasound, further supporting this guidance [9]. In contrast, abdominal ultrasonography combined with measurements of tumor markers is recommended for HCC screening, and assessments of AFP, protein induced by vitamin K absence or antagonist-II, or AFP lectin fraction are routinely performed in Japan [10].

Individuals with abnormal screening results require further investigation (e.g., with computed tomography scanning, magnetic resonance imaging, or liver biopsy) to confirm a diagnosis of HCC. Although surveillance programs can lead to detection of HCC at early stages when the tumors are amenable to curative treatment, guidelines are not always followed and are not always reproducible from large hospitals to nontertiary hospitals. Further studies are warranted to determine the optimal surveillance methods, which may also involve evaluation of novel biomarkers in the future.

Treatments for early-stage HCC include hepatectomy, liver transplantation, and local ablation therapy (Fig. 1) [6, 10–13]. However, there are no large randomized controlled trials (RCTs) comparing these treatments directly, nor are

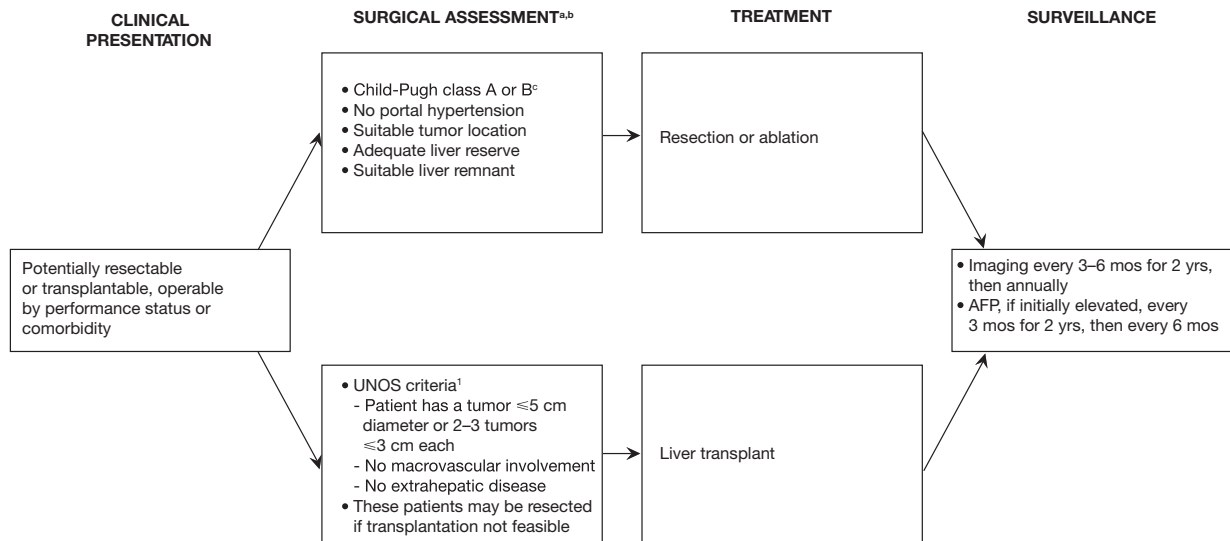
there any studies comparing these treatments with best supportive care [6]. In an intent-to-treat analysis in cirrhotic patients with HCC, early findings suggested similar survival rates in a comparison of resection with transplantation [14]. However, patient dropouts from waiting lists significantly impacted the longer-term findings in the transplantation group, and the authors concluded that resection may provide a better outcome for properly selected candidates. Further research is needed to confirm the optimal strategy based on the currently available treatments, and careful selection of patients is important in all approaches. Applicability of these treatments varies according to geographic distribution, with 50%–70% of cases in Japan (where there is widespread surveillance and a broad application of treatments) being suitable for curative treatment, compared with 25%–40% of cases in Europe and the U.S., and <10% in Africa [15]. Data from a nationwide survey in Japan indicate that a single early HCC patient has a high chance of prolonged survival with resection, ablation, or transplantation [16]. The aim of this article is to review the therapeutic options and associated outcomes for the management of patients with early HCC.

## OUTCOMES AND TOLERABILITY OF EARLY-STAGE HCC TREATMENTS

### Resection

Patients with early-stage HCC are those most likely to benefit from curative interventions. In a study of patients diagnosed with HCC in 1988–1998 in the Surveillance, Epidemiology, and End Results database, 417 of the 4,008 patients were candidates for surgical resection. The study showed that surgery was associated with longer survival in patients with unifocal, nonmetastatic HCC tumors <5 cm. In patients receiving surgery, the 5-year overall survival (OS) rate was 33%, compared with 7% without surgery [17].

Surgical resection is recommended as treatment for early HCC in noncirrhotic patients, or in patients with cirrhosis who have a single lesion and well-preserved liver function, normal bilirubin, and no portal hypertension [6, 13]. However, there are data that suggest that portal hypertension may not necessarily be a contraindication for resection. Patients with the same model for end-stage liver disease score and extent of hepatectomy had similar outcomes, whether or not they had portal hypertension [18], whereas several other studies found that resection can be performed safely in selected patients even in the presence of portal hypertension [19, 20]. Patients with multiple tumors may also be suitable for resection, although tumor multiplicity is an independent risk factor for postoperative recur-



**Figure 1.** National Comprehensive Cancer Network guidelines for the treatment of potentially resectable disease.

<sup>a</sup>Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

<sup>b</sup>Patients with Child-Pugh class A liver function who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

<sup>c</sup>In highly selected Child-Pugh class B patients with limited resection.

<sup>1</sup>Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–700.

Abbreviations: AFP,  $\alpha$ -fetoprotein; UNOS, United Network for Organ Sharing.

From National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers V. 1.2010. Available at [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Reproduced with permission from The NCCN Clinical Practice Guidelines in Oncology™ Hepatobiliary Cancer Guidelines. ©2009 National Comprehensive Cancer Network, Inc. All rights reserved. These Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.

rence, and the OS time is shorter in these patients [20]. However, among patients with both multiple tumors and better liver function (Child-Pugh class A), an absolute 5-year survival rate of 58% was achieved. Although there is no limitation on tumor size for resection, the risk for vascular invasion and dissemination increases with size. The amount of liver that can be resected depends on the degree of cirrhosis, the functional liver reserve, and the regenerative capacity of the liver [7]. Strict selection criteria are required in order to avoid treatment-related complications such as liver failure. Survival rates of ~70% at 5 years have been achieved in patients with a normal bilirubin concentration and no clinically significant portal hypertension [6]. In Japan, the indocyanine green retention rate, a marker of hepatic clearance, is commonly used to predict the safe limit of liver resection and posthepatectomy liver failure [21]. Preoperative portal vein embolization (PVE) has been used to evaluate the regenerative abilities of the liver, with lack of hypertrophy following PVE indicating an inability of the liver to regenerate, therefore contraindicating major liver resection [22]. Furthermore, preoperative PVE has

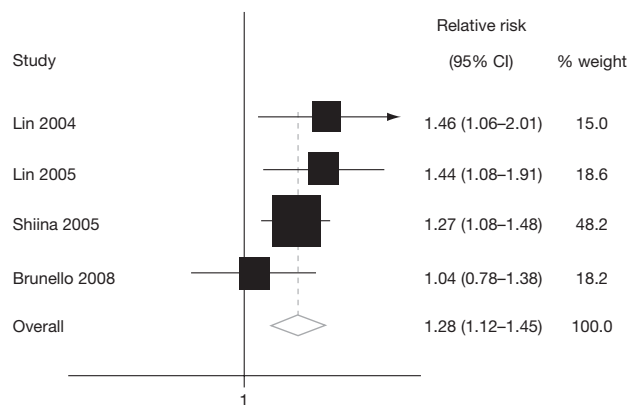
been shown to improve outcomes following major hepatectomy [23]. In patients with very early HCC (carcinoma in situ) undergoing surgery, the best 5-year survival rate so far, 93%, was demonstrated [24]. Only 10%–30% of HCC cases are suitable for “curative” surgical resection at the time of diagnosis, and recurrent HCC has been reported in 50%–80% of patients 5 years after resection [7]. Key predictors of recurrence are the presence of microvascular invasion and/or further tumor sites in addition to the primary lesion. Preoperative transcatheter arterial chemoembolization (TACE) has been evaluated but has shown no benefit in this setting [7]. AASLD and Japanese guidelines conclude that there is currently no preoperative or postoperative adjuvant therapy that can be recommended for improving prognosis after hepatic resection [6, 10]. Further investigation is required for neoadjuvant and adjuvant therapies that may decrease the incidence of recurrence following resection.

### Transplantation

Liver transplantation as a treatment for early-stage HCC is well established in the U.S. and Europe and is associated

with 5-year survival rates of ~70% [6], comparable with those of noncancer liver recipients. In most centers, candidates for transplantation are deemed not resectable. In some parts of the world, transplantation is not available or has very limited applicability [6]. The benefits of liver transplantation over resection include removal of the tumor and the underlying diseased liver and also improvement in portal hypertension. Because of the limited supply of donor organs, identification of the patients most likely to receive maximum benefit from a transplant is of utmost importance. For over a decade, the Milan criteria for HCC (one lesion  $\leq 5$  cm or two to three lesions  $\leq 3$  cm) have been widely used for the selection of candidates for liver transplantation. However, there is an ongoing debate on whether expanded criteria may be adopted, to enable patients with slightly more advanced HCC to also benefit from liver transplantation [25]. A 5-year survival rate of ~50% was described in patients selected with such expanded criteria, but there are currently no clear data to define the new limits [6]. In addition, expanding the criteria may cause harm to other patients without cancer who need a transplant, as a result of fewer donors being available [26]. Because the waiting time for an organ to become available may exceed 12 months in some western countries [27], the dropout rate is high (up to 50%). Most centers administer adjuvant treatments to prevent tumor progression while patients are on the waiting list, but these are often chosen based on observational studies, because robust data from RCTs are not available. Such bridging therapy before transplantation may include locoregional therapy such as chemoembolization, which has been investigated as a means of downstaging tumors to facilitate liver transplantation [25]. Information from a liver transplant waiting list in the U.S. showed that HCC patients who received pretransplant ablation treatments had a higher adjusted 3-year post-transplant survival rate than HCC transplant patients who did not (79% versus 75%;  $p = .03$ ) [28]. However, in another retrospective cohort study in the U.S., using data from a liver transplant waiting list, the authors concluded that the effects of downstaging with neoadjuvant treatment were difficult to evaluate [29]. It has also been suggested that resection can be used as a bridging therapy for patients who have already been enlisted for liver transplant [30]. There is no definitive evidence confirming that the use of bridging therapies confers an advantage post-transplantation in terms of survival and recurrence rates, and no specific recommendations in relation to bridging strategies (for either TACE or local ablation therapy) are currently made in the guidelines [7, 13].

An alternative strategy to increase the pool of available donor livers is the use of live donor transplantation, which



**Figure 2.** Radiofrequency ablation versus percutaneous ethanol injection: results of the meta-analysis on overall survival at 3 years. All based on random-effects meta-analysis.

Abbreviation: CI, confidence interval.

From Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol* 2009;9:31, with permission. Originally published by BioMed Central.

originated in Asia as a result of the legal and societal constraints on cadaveric liver transplantation [27, 31]. The results appear to be comparable with those from cadaveric donation [7, 32]; however, this is a complex intervention and may not have wide applicability.

### Ablation

Local ablation therapy, with either radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), is commonly used to treat small HCCs confined to the liver that may be unresectable because of the poor general condition or compromised liver function of the patient. In an RCT comparing RFA with PEI for early HCC, the 1-year complete response rate was better with RFA than with PEI, although no clear survival advantage was observed in cirrhotic patients [33]. However, other RCTs [34–36] and a recent meta-analysis [37] have shown evidence of the superiority of RFA over PEI, in terms of longer survival and better local control of disease, in patients with relatively preserved liver function and early-stage nonsurgical HCC (Fig. 2). At 3 years, the pooled analysis showed an OS rate of 73% in the RFA group, compared with 58% in the PEI group ( $p < .001$ ) [37]. However, RFA was associated with a statistically significant higher rate of adverse events ( $p < .001$ ), with 19% of patients (95% confidence interval [CI], 15%–23%) experiencing complications, compared with 10.5% of those treated with PEI (95% CI, 7%–13.5%) [37]. The most frequent complication observed in that study was severe pain, which was more common with RFA than with PEI [37]. For studies that reported major complications, the



incidence in RFA-treated patients was 4.1% (95% CI, 1.8%–6.4%), including hemothorax requiring thoracotomy drainage, gastric bleeding, hemoperitoneum, transitory icterus, liver infarction, cutaneous burn, and tumoral cell seeding, and in PEI-treated patients it was 2.7% (95% CI, 0.4%–5.1%), including liver abscess, hemoperitoneum, tumoral cell seeding, and one procedure-related death; however, this difference was not statistically significant. This safety profile should be taken into consideration as part of the overall risk–benefit profile in each individual case. Further support for the benefit of RFA was provided by a different meta-analysis, which was more selective in the studies that it included and showed a higher 3-year OS rate with RFA than with PEI (odds ratio, 0.47; 95% CI, 0.340–0.670;  $p < .001$ ) in patients with small HCCs [38].

Local ablation therapy has been compared with resection in a number of retrospective studies and clinical trials. Long-term outcomes in 87 patients with single-nodule HCCs treated with either surgical resection or RFA were similar [39]. Similarly, 5-year survival rates were comparable in a study of 224 patients with Child-Pugh class A cirrhosis treated with either resection (70.4%) or RFA (76.8%) ( $p = .561$ ) [40]. A study of 186 patients with small (<5 cm) HCCs found that the choice of treatment should be based on local factors, such as the availability of resources and expertise [41]. In contrast to these findings, a study of 149 patients with HCCs  $\leq 4$  cm comparing resection with percutaneous ablation found that resection provided better local control and better long-term survival (median survival time, 122 months after hepatectomy compared with 66 months after ablation;  $p = .0123$ ) [42]. A nationwide survey in Japan generated data on survival following resection or RFA [16]. In 2000–2003, 1,235 patients with a single early HCC (<2 cm) underwent resection and 1,315 patients received RFA. Although, with a median follow-up of 37 months, the disease-free survival rate was significantly better after resection than after RFA (1 year, 91% versus 84%; 2 years, 70% versus 58%;  $p = .001$ ), there was no significant difference in the OS rate between the two groups (98% versus 99%; 94% versus 95%;  $p = .28$ ). However, it is currently unknown whether the better disease-free survival seen with resection will translate into longer survival over a longer time period following therapy. Local ablation therapy was compared with resection in two RCTs in patients with small HCCs, with comparable survival results [43, 44]. Based on a trial of 180 patients, Chen et al. [43] concluded that RFA was as effective as surgical resection in the treatment of solitary and small HCCs, with the advantage of being less invasive. In a smaller study of 76 patients, Huang et al. [44] reported that PEI appeared to be as safe and effective as resection. Recent studies have shown that, in

some centers, RFA is regarded as the first-line treatment for small, operable HCCs ( $\leq 2$  cm), with 68.5% of patients surviving at 5 years [45]. Furthermore, in a simulated randomized trial comparing hepatic resection with RFA for very early HCCs (<2 cm), the OS times were similar for resection and RFA followed by resection for cases of initial local failure, suggesting that RFA could be considered as a primary treatment for very early HCC [46]. Given these equivocal results, larger RCTs are needed before there is any change in the recommended treatment of patients with good surgical risk and before ablation therapy is confirmed as an alternative to surgery for potentially resectable HCC.

### TACE

Embolization procedures are used in patients with inoperable or unresectable disease. However, the place of TACE for the treatment of early HCC is not clear, and official guidelines do not currently recommend it. Caution should be exercised regarding the use of TACE for early HCC, and it should be considered only when curative treatment (e.g., transplantation, resection, or RFA) is contraindicated.

### DIFFERENCES IN THE TREATMENT OF EARLY HCC AND OUTCOMES BETWEEN POPULATIONS

As described above, well-defined treatment options for early HCC exist; however, there are inevitable differences in the treatment received, and hence the outcome achieved, in different populations worldwide. There are geographic variations in the incidence and etiology of HCC, and a difference in tumor size at presentation. Japanese patients have been shown to present with smaller tumors than patients in the U.S. and Europe, likely as a result of the more widespread screening carried out in Japan [47]. This, together with differences in hepatitis B or C virus status, has resulted in more limited surgical resections being necessary in Japan, compared with more extended resections in the U.S.

In a more recent comparison, analysis of the medical records of 353 patients subject to surgical resection for HCC at two referral centers in China and Japan highlighted differences between populations [48]. As well as demographic differences in age of incidence, serum examination, and history of viral infection, differences in outcome were observed. Patients in Japan were diagnosed earlier, were subject to more standard treatment, and had better prognoses than those in China. However, these results were based only on HCC at each center and not on HCC detected in a surveillance program. In addition, the demographic disparities in survival in patients with localized HCC in the U.S. were investigated in a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results

population-based cancer registry [49]. That study found substantial and significant disparities by race/ethnicity in the 3-year survival rate, therapy administered, and stage-specific survival rate for individual therapies. These differences were not explained by age, date of diagnosis, or geography, but may have resulted from differences in treatments received by different demographic groups or variations in treatment response, which may be influenced by compliance or differences in disease biology. However, these patients were not identified through a surveillance program, but were patients diagnosed with HCC, which may be associated with lead-time bias. In a prospective cohort study in Europe, hepatic resection performed under strict intraoperative ultrasonographic guidance had low mortality and acceptable morbidity, even in patients with intermediate and advanced HCC [50].

### IMPROVING TREATMENT OPTIONS

There remains a considerable number of unanswered questions in the recommendations for treatment of early-stage HCC, many of which require a definitive answer to be provided through robust data from RCTs. Key areas for consideration include: the use of neoadjuvant or adjuvant therapy to decrease or delay recurrence after resection or ablation, chemoprevention after resection or ablation, and the use of molecular profiling of HCC to provide additional tools to define those patients most at risk for recurrence following resection. Indeed, a number of clinical trials are ongoing in these areas. Three ongoing phase IV trials are investigating radiotherapy (ClinicalTrials.gov identifier, NCT00557024), TACE (ClinicalTrials.gov identifier, NCT00556803), and lamivudine or entecavir (ClinicalTrials.gov identifier, NCT00555334) as adjuvant therapies after RFA, and are due to complete in 2010. Furthermore, sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ; Bayer Schering Pharma AG, Berlin, Germany) is being investigated as adjuvant treatment in the prevention of recurrence of HCC following either surgical resection or local ablation, in the large phase III randomized, double-blind, placebo-controlled Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carci-

noma (STORM) trial (ClinicalTrials.gov identifier, NCT00692770), due to complete in 2011. With regard to liver transplantation, bridging therapy before transplantation, including the questions of which treatment to give and when [7], and prospective analysis of outcomes of living donor compared with deceased donor transplantation are areas that warrant further study.

Important considerations in future trials include analysis of the cost-effectiveness of the treatments under investigation and also the use of genomics- and proteomics-based technologies [51], in order to add to the body of information on the biologic behavior and natural history of HCC, which should help guide the diagnosis and management of HCC.

### CONCLUSIONS

Early diagnosis remains a key goal in order to improve the prognosis of HCC patients. Surgical resection and liver transplantation are usually considered as first-line options because they offer the possibility of prolonged survival in patients with early disease and have excellent outcomes in well-selected patients. Local ablation therapy, using RFA or PEI, also has a role to play. Further improvements in the outcome of patients with early HCC may be achieved once outstanding questions have been answered by prospective RCTs.

### ACKNOWLEDGMENTS

The authors take full responsibility for the scope, direction, and content of the manuscript and have approved the submitted manuscript. They would like to thank Karen Brayshaw, PhD, at Complete HealthVizion for her assistance in the preparation and revision of the draft manuscript, based on detailed discussion and feedback from all the authors. Editorial assistance was supported by a grant from Bayer HealthCare Pharmaceuticals.

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