Radioembolisation with Y90-resin microspheres followed by nivolumab for advanced hepatocellular carcinoma (CA 209-678): a single arm, single centre, phase 2 trial

David Tai, Kelvin Loke, Apoorva Gogna, Neslihan Arife Kaya, Sze Huey Tan, Tiffany Hennedige, David Ng, Farah Irani, Joycelyn Lee, Jia Qi Lim, Chow Wei Too, Matthew C H Ng, Chee Kian Tham, Justina Lam, Si Lin Koo, Hui Shan Chong, George Boon-Bee Goh, Hian Liang Huang, Nanda Venkatanarasimha, Richard Lo, Pierce K H Chow, Brian K P Goh, Alexander Chung, Han Chong Toh, Choon Hua Thng, Tony K H Lim, Joe Yeong, Weiwei Zhai, Chung Yip Chan, Su Pin Choo

Summary

Background Therapeutic synergism between radiotherapy and immune checkpoint blockade has been observed in preclinical models of hepatocellular carcinoma. We aimed to study the safety and efficacy of sequential radioembolisation with yttrium-90-resin microspheres (Y90-radioembolisation) followed by nivolumab in patients with advanced hepatocellular carcinoma.

Methods Patients with Child-Pugh A cirrhosis and advanced hepatocellular carcinoma not suitable for curative surgery were treated with Y90-radioembolisation followed by intravenous nivolumab 240 mg 21 days after Y90-radioembolisation and every 2 weeks thereafter. The primary endpoint, assessed in the per-protocol population, was the objective response rate, determined by RECIST version 1.1, defined as the proportion of patients with a confirmed complete or partial response observed for lesions both within and outside the Y90-radioembolisation field. This study is registered with ClinicalTrials.gov, NCT03033446 and has been completed.

Findings 40 patients were enrolled, of whom 36 received Y90-radioembolisation followed by nivolumab. One (3%) patient had a complete response and ten (28%) had a partial response; the objective response rate was 30·6% (95% CI 16·4–48·1). The most common treatment-related adverse events of any grade were pruritus (18 [50%] of 36 patients) and maculopapular rash (13 [36%]). Two (6%) patients experienced grade 3–4 treatment-related adverse events: one patient had a grade 3 increase in alanine aminotransferase levels, grade 3 bilirubin increase, and grade 4 increase in aspartate aminotransferase levels, while the other had a grade 3 maculopapular rash. Five (14%) patients had a treatment-related serious adverse event (Steven-Johnson syndrome, hepatitis E infection, fever, liver abscesses, and ascites).

Interpretation Y90-radioembolisation followed by nivolumab resulted in an encouraging objective response rate in patients with advanced hepatocellular carcinoma, although the activity observed was not as high as the study was powered for. This strategy should be further evaluated in patients with Barcelona Clinic Liver Clinic (BCLC) stage B hepatocellular carcinoma that is ineligible or refractory to transarterial chemoembolisation and patients with BCLC C disease without extrahepatic spread.

Funding National Medical Research Council Singapore, Bristol-Myers Squibb, Sirtex.

Introduction

Hepatocellular carcinoma is the sixth most common cancer worldwide and second most common cause of cancer-related death.[1,2] Most patients are diagnosed when surgical resection is not possible, rendering locoregional therapies or systemic therapies the mainstay of treatment.[1,2] Radioembolisation has emerged as a locoregional option for unresectable hepatocellular carcinoma. Radioembolisation with yttrium-90 resin microspheres (Y90-radioembolisation) demonstrated similar disease control and median overall survival to sorafenib, whilst offering higher response rates and fewer treatment-related toxicities.[3,4] Immune checkpoint blockade monotherapy has demonstrated clinical benefit in the first-line setting in patients with advanced hepatocellular carcinoma (median overall survival 16·4 months).[5] Despite these encouraging results, objective response rates with single-agent anti-PD-1 drugs are modest, at 15%.[5]

Dose-dependent upregulation of PD-L1 expression following irradiation of hepatocellular carcinoma cell lines has been described.[6] Therapeutic synergism has been observed with combination radiotherapy and immune checkpoint blockade in preclinical models of hepatocellular carcinoma.[6] Post-radiotherapy upregulation of PD-1 expression by CD8 T cells and PD-L1 expression by tumour cells has also been reported in a clinical study.[7] Thus combination radiotherapy and immune checkpoint

Lancet Gastroenterol Hepatol 2021

Published Online October 22, 2021 https://doi.org/10.1016/S2468-1253(21)00305-8

See Online/Comment https://doi.org/10.1016/S2468-1253(21)00388-5

Division of Medical Oncology (D Tai MD, J Lee MD, M C H Ng MD, C K Tham MD, J Lam MD, S L Koo MD, H C Toh MD, S P Choo MD), **Division of Clinical Trials and Epidemiological Sciences** (S H Tan PhD, H S Chong BSc), **Division of Oncologic Imaging** (T Hennedige MD, Prof C H Thng MD), **Division of Surgery and Surgical Oncology** (Prof P K H Chow MD), **National Cancer Centre, Singapore; Nuclear Medicine and Molecular Imaging** (K Loke MD, D Ng MD, H L Huang MRCP), **Vascular and Interventional Radiology** (A Gogna MD, F Irani MD, C W Too MD, N Venkatanarasimha MD, R Lo MD), **Hepatopancreatobiliary and Transplant Surgery** (Prof P K H Chow, Prof B K P Goh MD, Prof A Chung MD, C Y Chan MD), **Anatomical Pathology** (Prof T K H Lim FRCPath, J Yeong PhD), **Department of Gastroenterology and Hepatology** (G B-B Goh), **Singapore General Hospital, Singapore; Duke NUS Medical School, Singapore** (D Tai, K Loke, A Gogna, S H Tan, T Hennedige, D Ng, F Irani, J Lee, C W Too, M C H Ng, C K Tham, J Lam, S L Koo, G B B Goh MD, H L Huang, Prof P K H Chow, Prof B K P Goh, Prof A Chung, H C Toh, Prof C H Thing, Prof T K H Lim, C Y Chan, S P Choo); **Genome Institute of Singapore, A*STAR, Singapore** (N A Kaya PhD, J Q Lim BSc,

W Zhai PhD); **Key Laboratory of Zoological Systematics and Evolution, Institute of Zoology, Chinese Academy of Sciences, Beijing, China** (W Zhai); **Center for Excellence in Animal Evolution and Genetics, Chinese Academy of Sciences, Kunming, China** (W Zhai); **School of Biological Sciences, Nanyang Technological University, Singapore** (N A Kaya)

Correspondence to:
Dr David Tai,
Division of Medical Oncology,
National Cancer Centre
Singapore, 11 Hospital Crescent,
Singapore 169610
david.tai.w.m@singhealth.com.sg

Research in context

Evidence before this study

Immunotherapy with PD-1 inhibitors can result in notable and durable responses in patients with hepatocellular carcinoma. While combination radiotherapy and immunotherapy is expected to be synergistic, its safety and efficacy have not been prospectively explored in hepatocellular carcinoma. We searched PubMed from Jan 1, 2010, to Sept 20, 2020, with the following terms: "HCC", "Y90", and "PD-1 OR PD-L1". We found two case reports showing activity using this combination. The only prospective data were from interim reports from the current study and NASIR-HCC, which showed preliminary evidence of activity of Y90-radioembolisation followed by nivolumab with good tolerability.

Added value of this study

Our CA 209-678 study reports results of Y90-radioembolisation followed by nivolumab in patients with advanced hepatocellular carcinoma. Safety data indicate that this treatment is well tolerated with no new safety concerns in this patient population. Promising anti-tumour activity was also noted, although not as high as the study was powered for.

Implications of all the available evidence

Y90-radioembolisation followed by nivolumab was safe and associated with an objective response rate of 30·6%. The objective response rate when analysed only in patients without extrahepatic spread was 43·5%. Of note, 81% of patients experienced intrahepatic tumour regression. Further studies exploring combination immunotherapy strategies with Y90-radioembolisation in patients with BCLC B disease and those with BCLC C disease with no extrahepatic spread are necessary to confirm its efficacy.

blockade warrants further evaluation. Therefore, we conducted a phase 2 study evaluating the safety and activity of Y90-radioembolisation followed by nivolumab in patients with advanced hepatocellular carcinoma.

Methods

Study design and participants

CA 209-678 was a single-arm, single-centre, two-stage phase 2 trial designed to investigate the activity and safety of Y90-radioembolisation followed by nivolumab in patients with advanced hepatocellular carcinoma, conducted at the National Cancer Centre Singapore/Singapore General Hospital, Singapore. Patients aged 21 years or older with Child-Pugh A cirrhosis and hepatocellular carcinoma not suitable for curative surgery and planned for Y90-radioembolisation were eligible for inclusion. Major inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0–2, adequate end organ function (haemoglobin ≥8·5 g/dL, white blood cell count ≥2000/μL, platelets $\geq 50 \times 10^9$ per L, bilirubin <3 mg/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤3×the upper limit of normal [ULN], creatinine ≤1·5×ULN). Prior locoregional or systemic therapy other than Y90-radioembolisation or immunotherapy was allowed; patients with 50% or greater liver involvement or main portal vein involvement were also eligible for enrolment. Patients with hepatitis B virus infection had to be on concurrent antiviral therapy to be eligible. Patients were not required to have a measurable lesion outside the intended Y90-radioembolisation field. A full list of eligibility criteria can be found in the appendix (pp 1–2).

See Online for appendix

All patients provided written informed consent and the institutional review board committee approved the protocol (Singhealth IRB Ref No. 2016/2613). The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice.

Procedures

All patients underwent intrahepatic arterial Y90-radioembolisation (SIR-Spheres Y90 resin microspheres, Sirtex, Singapore). The administered activity of Y90-resin microspheres was determined by the nuclear medicine physician using either the artery-specific partition model or body surface area calculation within the limits of radiation safety, taking into account treatment variables such as the patient's body surface area, tumour-to-normal liver ratio, and size of the tumour within the liver. Where possible, personalised dosimetry using the partition model was the default methodology to facilitate selective administration of Y90-radioembolisation avoiding toxicities to the normal liver parenchyma (details of the partition model can be found in the appendix [p 3]). Dose activity modifications were made for patients with lung shunting between 10–20% on Tc-99m macro-aggregated albumin scan.

Patients received their dose of intravenous nivolumab 240 mg 21 days (±3 days) after Y90-radioembolisation. Intravenous nivolumab 240 mg was then given every 2 weeks until development of severe toxicities, progression, death, physician discretion, or withdrawal of consent. Dose interruption, but not reduction, was allowed.

Tumours were assessed centrally by independent radiology review of CT or MRI at baseline, before cycle 4, 8, and 12 of intravenous nivolumab and every 12 weeks thereafter (±7 days) using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), mRECIST, and iRECIST. Two experienced radiologists with no direct involvement in patient care reviewed all images in the study. Safety assessments were conducted throughout the treatment period, including physical

examination, vital signs, ECGs, and laboratory and radiological investigations. Adverse events were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.01. The frequency, duration, and severity of adverse events were recorded.

For biomarker analyses, pre-treatment and on-treatment biopsies were taken from liver lesions before Y90-radioembolisation and after one dose of intravenous nivolumab. RNA-seq analysis involved mapping,[8] counting gene expression level,[9] and normalisation.[10] Using the method described by Danaher and colleagues,[11] we deconvoluted gene expression profiles into the abundance of 14 cell types. Patients were subsequently classified into two groups as hot and cold by clustering cellular abundance values using k-means algorithm (k=2, see appendix p 4).

Outcomes

The primary endpoint was the objective response rate, defined as the proportion of patients with a confirmed complete or partial response observed for lesions both within and outside the Y90-radioembolisation field per RECIST version 1.1 in patients who received both Y90-radioembolisation and nivolumab. Secondary endpoints were progression-free survival, defined as time from Y90-radioembolisation to first documented disease progression per RECIST version 1.1 or death from any cause; time to progression, defined as time from Y90-radioembolisation to first documented disease progression per RECIST version 1.1; overall survival, defined as time from Y90-radioembolisation to date of death from any cause; time to response, defined as time from Y90-radioembolisation to first date of documented response (complete or partial response per RECIST version 1.1); duration of response, defined as the time from first documented evidence of complete or partial response until the first documented sign of disease progression or death from any cause; pattern of disease progression (intrahepatic or extrahepatic) per RECIST version 1.1; safety and tolerability; and quality-of-life measurement using the FACT-Hep score and EORTC QLQ-C30.

Statistical analysis

The sample size for this trial was determined using the Simon two-stage optimal design. This two-stage trial aimed to investigate whether the confirmed objective response rate in the per-protocol population was at least 41% compared with a historical control rate of 21%.[4] At 80% power and 5% significance level, a total of 36 patients would be recruited, with 11 patients enrolled in the first stage. An additional 25 patients would be enrolled in the second stage if three or more patients had an objective response in the first stage. If 12 or more patients among a total of 36 patients had a complete or partial response, the treatment combination would be considered worthy of further study. Patients who received Y90-radioembolisation and at least one full dose of nivolumab followed by appropriate restaging assessment were considered evaluable (per-protocol population).

The objective response rate and corresponding 95% CI were estimated using the Clopper-Pearson method. For each time-to-event endpoint, the survival distributions were estimated using the Kaplan-Meier product-limit method. The median time and corresponding 95% CI were estimated using the Brookmeyer and Crowley method. All quality-of-life scores were calculated using the EORTC and FACT-Hep methods. Mean quality of life with SD at each time point were tabulated. All quality-of-life scores were plotted and examined graphically. Exploratory mRNA sequencing statistical analysis methods are described in the appendix (p 4). All statistical analyses were performed with SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT03033446 and has been completed.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

40 patients were enrolled between Jan 18, 2017, and June 6, 2019. Four patients were excluded from the efficacy analyses: one patient was screened and deemed ineligible (due to recent variceal bleeding), three patients did not receive treatment combination (one patient deteriorated before Y90-radioembolisation and was not suitable for study, one patient deteriorated after Y90-radioembolisation and was not suitable for nivolumab, and one patient developed grade 3 infusional reaction moments into nivolumab treatment and did not continue on study). Thus 36 patients received Y90-radioembolisation followed by at least one full dose of nivolumab and were included in the safety and efficacy endpoint analyses (figure 1).

The baseline characteristics of the per-protocol population are shown in table 1. Most patients were male and had Child-Pugh score A5 and Barcelona Clinic Liver Cancer (BCLC) C disease. Demographics and clinical characteristics of individual patients are presented in the appendix (pp 7–8). Y90-radioembolisation dosimetry was personalised for 26 (72%) patients and not personalised for ten (28%).

Five patients had intrahepatic disease that was not entirely treated by a single Y90-radioembolisation before administration of nivolumab. One of these patients was lost to follow-up, one had intrahepatic progression at first radiological assessment (outside the Y90-radioembolisation field) and died shortly after, two patients had extrahepatic progression, and one had both intrahepatic and extrahepatic progression.

As of the data cutoff date (Jan 31, 2021), 31 patients had completed study treatment and five patients continued on

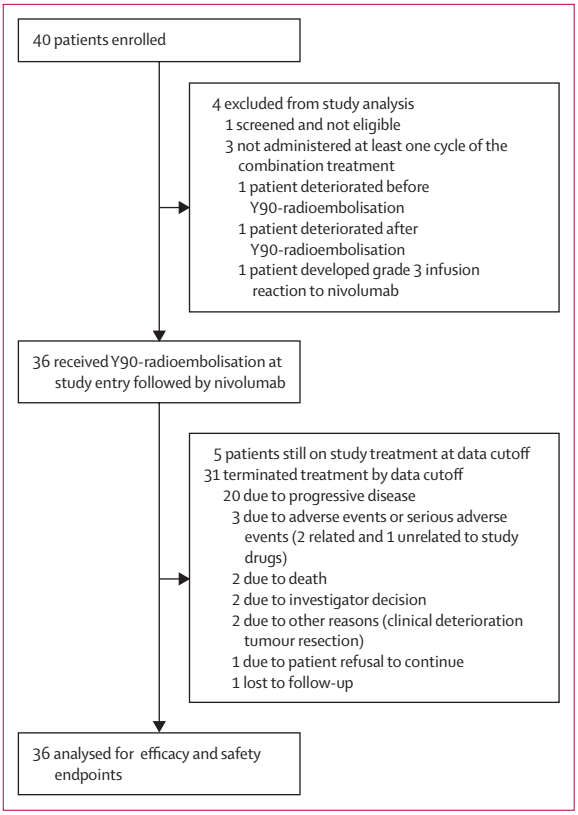

Figure 1: **Trial profile**

	Characteristic (N=36)
Age, years	
Median (IQR)	64 (59·7 to 70·9; 23·3 to 78·7)
Sex	
Male	28 (78%)
Female	8 (22%)
Ethnicity	
Chinese	25 (69%)
Indian	2 (6%)
Other	9 (25%)
ECOG performance status	
0	26 (72%)
1	9 (25%)
2	1 (3%)
Child-Pugh score	
A5	27 (75%)
A6	9 (25%)
Aetiology	
Hepatitis B	21 (58%)
Hepatitis C	3 (8%)
Hepatitis B and hepatitis C	1 (3%)
Non-viral	11 (33%)
Alpha-fetoprotein	
≤400 ng/mL	18 (50%)
>400 ng/mL	18 (50%)
BCLC staging	
A	1 (3%)
B1*	1 (3%)
B2*	10 (28%)
C	24 (67%)
Macrovascular invasion	
No	20 (56%)
Yes	16 (44%)
Extrahepatic spread	
Yes	13 (36%)
No	23 (64%)

(Table 1 continues on next page)

study treatment (appendix p 17). The median number of cycles of nivolumab received was 7 (IQR 4–23). A summary of Y90-radioembolisation treatment received by patients is presented in the appendix (p 9) together with a list of subsequent treatment received by patients following progression (appendix pp 7–8).

In the stage one cohort, four (36%) of 11 patients had a partial response and the trial proceeded to recruit another 25 patients into stage two. Of the total 36 patients, one had a complete response (2·8%, 95% CI 0·07–14·5), ten had a partial response (27·8%, 14·2–45·2), 11 had stable disease (30·6%, 16·4–48·1), and 11 had progressive disease (30·6%, 16·4–48·1) according to RECIST version 1.1. Three patients were non-evaluable (one died before staging re-assessment, one had a non-contrasted CT re-assessment due to development of severe contrast allergy which limited interpretation, and one was lost to follow-up). Thus, the objective response rate was 30·6% (95% CI 16·4–48·1), and the study did not meet its primary endpoint. Data for the objective response rate determined by mRECIST and iRECIST are shown in table 2. Objective response rates within Y90-radioembolisation fields, determined by RECIST version 1.1 and mRECIST, were higher than objective response rates outside Y90-radioembolisation fields (appendix p 10).

The objective response rate among the 13 patients with extrahepatic spread was 7·7% (95% CI 0·2–36·0), 7·7% (0·2–36·0), and 23·1% (5·0–53·8) when determined by RECIST version 1.1, mRECIST, and iRECIST, respectively. By contrast, objective response rates among the 23 patients without extrahepatic spread were 43·5% (95% CI 23·2–65·5), 60·9% (38·5–80·3), and 43·5% (23·2–65·5), respectively (appendix p 11). Objective response rates by BCLC stage are shown in the appendix (p 12).

Spider plots of patients' composite tumour changes from baseline are presented in figure 2A. Waterfall plots of patients' tumour changes from pre-treatment within the Y90-radioembolisation field are presented in figure 2B; target lesions within the Y90-radioembolisation field regressed in 29 (81%) of 36 patients. Waterfall plots of patients' tumour changes from pre-treatment outside the Y90-radioembolisation field are shown in figure 2C.

Median time to response was 3·8 months (95% CI

	Characteristic (N=36)
(Continued from previous column)	
Disease outside Y90-radioembolisation fields	
Yes	16 (44%)
No	20 (67%)
Prior treatment	
Liver resection	9 (25%)
Locoregional therapy	14 (36%)
Microwave ablation	1 (2%)
RFA	5 (11%)
TACE	11 (25%)
TACE + RFA	1 (2%)
Systemic therapy (sorafenib/lenvatinib)	5 (11%)
Albumin bilirubin score (ALBI)	–2·4 (–2·7 to –2·2; –3·0 to –1·6)
Liver lesions, n†	5 (4 to 9; 1 to >20)
Size of largest liver lesion, mm	78·5 (40·5 to 110·5; 14 to 177)
Tumour invasion in liver above 50%	
No	26 (72%)
Yes	10 (28%)

RFA=radiofrequency ablation. TACE=transarterial chemoembolisation. Data are median (IQR; range) or n (%). *Clinical characteristics of BCLC B1 and BCLC B2 patients can be found in the appendix (pp 5–6). †Five patients had >10 lesions at study entry.

Table 1: **Demographics and clinical characteristics**

	RECIST 1.1	mRECIST	iRECIST
Objective response			
Complete response	1 (3%)	4 (11%)	1 (3%)
Partial response	10 (28%)	11 (31%)	12 (33%)
Stable disease	11 (31%)	6 (17%)	11 (31%)
Progressive disease	11 (31%)	11 (31%)	iUPD 3 (8%); iCPD 6 (17%)
Not evaluable	3 (8%)	4 (11%)	3 (8%)
Confirmed objective response (95% CI)	30·6% (16·4–48·1)	41·7% (25·5–59·2)	36·1% (20·8–53·8)
Disease control rate (95% CI)	61·1% (43·5–76·9)	58·3% (40·8–74·5)	66·7% (49·0–81·4)

Table 2: **Objective response determined by RECIST 1.1, mRECIST, and iRECIST**

1·97–3·95). Of the 11 patients who had an objective response, eight patients had not progressed as of data cutoff. Thus, data to assess median duration of response are immature.

After a median follow-up of 24·8 months (IQR 20·3–38·2), median progression-free survival was 5·6 months (95% CI 2·1–8·8; figure 3A), median time to treatment progression was 5·6 months (95% CI 2·1–8·8), and median overall survival was 16·9 months (95% CI 8·1–27·6; figure 3B). 6-month, 12-month, and 24-month progression-free survival was 48·6% (95% CI 31·5–63·8), 33·0% (18·0–48·9), and 14·1% (3·3–32·3), respectively. 6-month, 12-month, and 24-month overall survival was 82·9% (95% CI 65·9–91·9), 62·3% (44·0–76·1), and 37·9% (20·9–54·8), respectively.

Median progression-free survival among patients with extrahepatic spread was 2·1 months (95% CI 1·8 to 3·7) and was 15·1 months (3·8–20·2) for those without extrahepatic spread (figure 3A). Median overall survival among patients with extrahepatic spread was 7·1 months (95% CI 2·4–21·3) and was 20·2 months (11·4–32·1) for those without extrahepatic spread (figure 3B). Corresponding data by BCLC stage are shown in the appendix (p 12).

Median progression-free survival for patients who had an overall response was 20·2 months (95% CI 8·4–not evaluable [NE]) and median overall survival was 27·6 months (95% CI 14·0–NE). Median progression-free survival for patients who had stable disease was 7·3 months (95% CI 3·0–19·6) and median overall survival was 17·1 months (95% CI 8·1–32·1). Median progression-free survival for patients who had progressive disease was 1·9 months (95% CI 1·8–2·1) and median overall survival was 7·1 months (95% CI 3·2–NE; appendix p 18).

First disease progression was intrahepatic in 15 (42%) of 36 patients and extrahepatic in ten (28%; appendix p 13). Among the 23 patients with no extrahepatic spread, five (22%) developed new intrahepatic lesions, of whom four developed new lesions within previous Y90-radioembolisation fields. Thus, only one patient might have benefited from further locoregional therapy at the point of first progression.

29 (81%) patients experienced treatment-related adverse events (table 3). The most common treatment-related adverse events were pruritus (18 [50%]) and maculopapular rash (13 [36%]). Five (14%) patients experienced grade 3–4 treatment-related adverse events or serious adverse events. Two (6%) patients experienced grade 3–4 treatment-related adverse events: one patient had a grade 3 ALT elevation, grade 3 bilirubin elevation, and grade 4 AST elevation (subsequently diagnosed as hepatitis E virus [HEV] infection), while the other had grade 3 maculopapular rash (subsequently diagnosed as Steven–Johnson syndrome). Serious adverse events were reported in 20 (56%) patients, of which five events in five patients were deemed to be treatment related (table 3). One of these was the patient with Stevens–Johnson syndrome, which was related to nivolumab; the patient subsequently withdrew from the study. The patient who was diagnosed with HEV infection was also deemed to have had a serious adverse event possibly related to nivolumab, and the other three serious adverse events (fever, liver abscesses, and ascites) were deemed to be related to Y90-radioembolisation. Five (14%) patients had any-grade treatment-related adverse events that were treated with steroids (grade 1 pneumonitis, grade 2 infusional reaction, grade 2 rash, grade 3 Steven–Johnson syndrome, and grade 3–4 elevation of bilirubin, AST, and ALT [the patient was subsequently diagnosed with HEV infection and steroids ceased]). No radiation-induced liver disease or treatment-related deaths were noted. Two (6%) of 36 patients discontinued the study because of treatment-

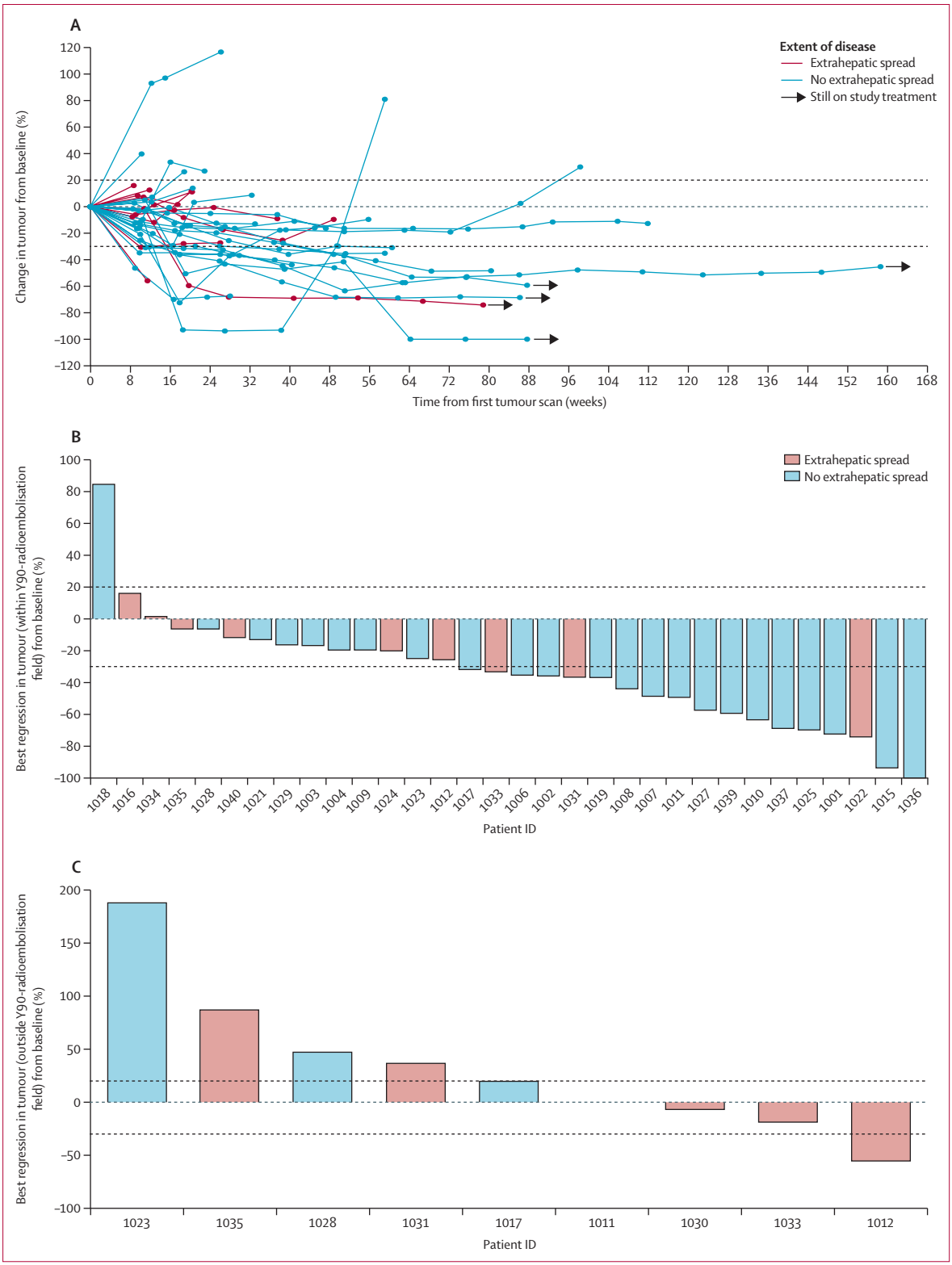

Figure 2: **Tumour responses**
(A) Spider plots of patients' composite tumour changes (summation of all target lesions within and outside Y90-radioembolisation fields) from baseline. (B) Waterfall plot of patients' tumour changes from pre-treatment within the Y90-radioembolisation field; four patients were not evaluable for this analysis. (C) Waterfall plot of patients' tumour changes from pre-treatment outside the Y90-radioembolisation field.

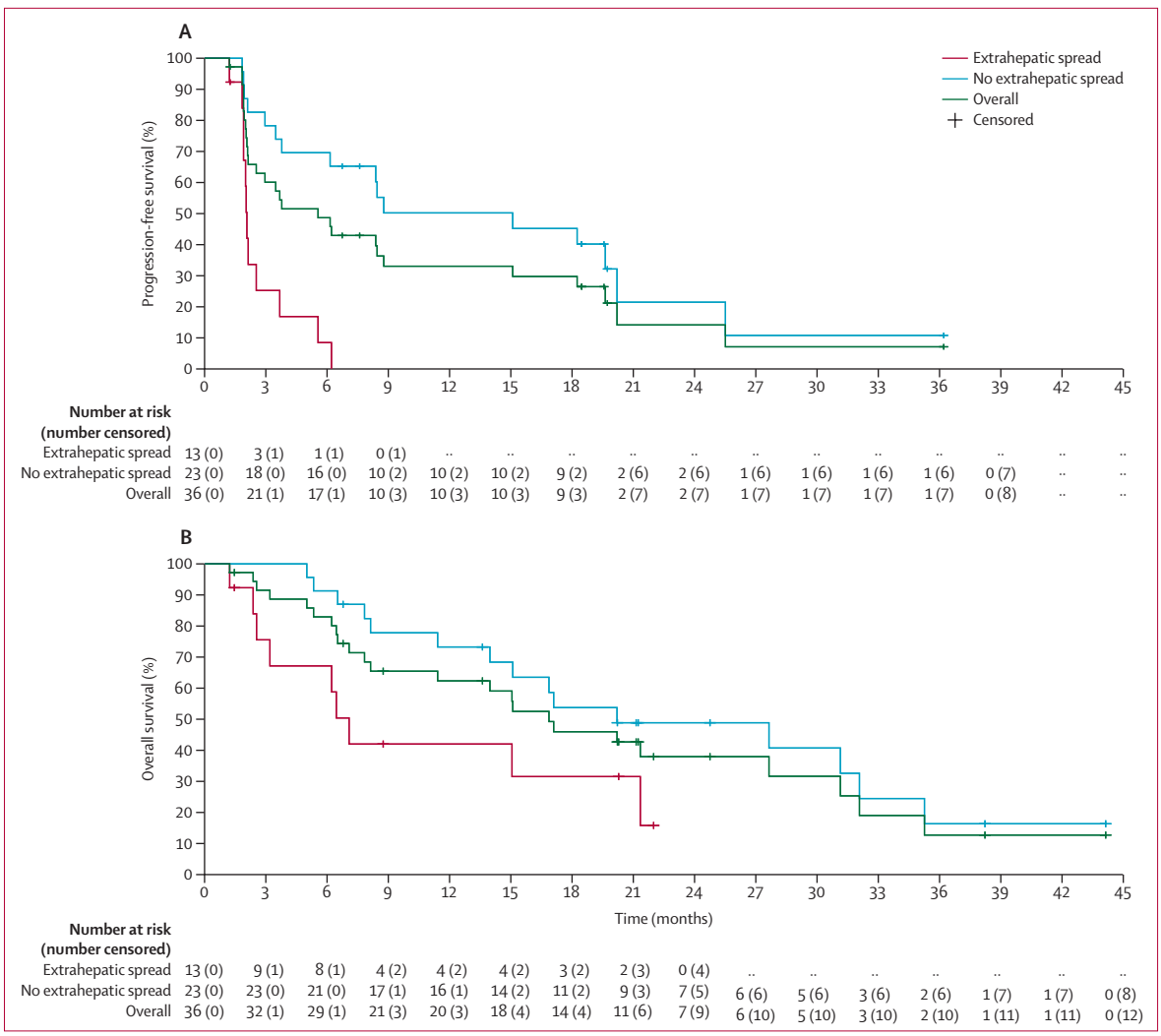

Figure 3: **Survival analyses in the per-protocol set**
(A) Progression-free survival. (B) Overall survival.

related toxicities. All adverse events that were related to nivolumab are presented in the appendix (p 14) as are those related to Y90-radioembolisation (appendix p 15).

mRNA was sequenced from 62 biopsies (31 pre-treatment and 31 on-treatment (after Y90-radioembolisation and one dose of nivolumab) taken from 28 patients. We clustered the samples into immunologically hot and cold tumours. Patients with multiple biopsies (n=4) often had concordant immune class across sectors except for one of the patients who responded (mixed subtypes). Although the proportion of samples deemed hot or mixed immune class among patients with a response was not significantly higher than among patients without a response before treatment (p=0·35, appendix p 19), all on-treatment samples from patients who had a response became immunologically hot or mixed, while the level of immune activation in patients who did not have a response stayed similar and were significantly different from patients who had a response post-treatment (p=0·03, appendix p 19). This observation was consistent when we compared the overall levels of immune infiltration between responders and non-responders (appendix p 19). An inflammation gene signature score that predicts response to immunotherapy in hepatocellular carcinoma[12] was significantly increased with treatment in responders (p=0·035), but was not significant in non-responders (p=0·22, appendix p 19).

EORTC QLQ-C30 and FACT-Hep quality-of-life scores are shown in the appendix (pp 16, 20–21). There was no significant deterioration in quality-of-life scores while receiving study treatment.

Discussion

In this study of Y90-radioembolisation followed by nivolumab in patients with advanced hepatocellular carcinoma, the observed objective response rate of 30·6% compares favourably with an objective response rate

	Grade 1–2	Grade 3	Grade 4	Grade 5
Any treatment-related AE/SAE	24 (67%)	4 (11%)	1 (3%)	0
Treatment-related SAE				
Ascites	0	1 (3%)*	0	0
Fever	0	1 (3%)*	0	0
Hepatitis E infection	0	1 (3%)†	0	0
Liver abscess	0	1 (3%)*	0	0
Steven–Johnson syndrome	0	1 (3%)†	0	0
Treatment-related AE				
Gastrointestinal				
Abdominal pain	5 (14%)	0	0	0
Bloating	1 (3%)	0	0	0
Constipation	1 (3%)	0	0	0
Diarrhoea	3 (8%)	0	0	0
Dry mouth	3 (8%)	0	0	0
Epigastric pain	1 (3%)	0	0	0
Gastro-oesophageal reflux disease	1 (3%)	0	0	0
Oral mucositis	1 (3%)	0	0	0
Nausea	2 (6%)	0	0	0
Parotid gland swelling	1 (3%)	0	0	0
Vomiting	1 (3%)	0	0	0
Investigations				
ALT increased	3 (8%)	1 (3%)	0	0
AST increased	2 (6%)	0	1 (3%)	0
Blood bilirubin increased	4 (11%)	1 (3%)	0	0
Creatinine increased	1 (3%)	0	0	0
Platelet count decreased	5 (14%)	0	0	0
White blood cell decreased	2 (6%)	0	0	0
Metabolism and nutrition disorders				
Anorexia	4 (11%)	0	0	0
Neurological				
Dysesthesia	1 (3%)	0	0	0
Dysgeusia	1 (3%)	0	0	0
Headache	1 (3%)	0	0	0
Lethargy	1 (3%)	0	0	0
Ocular				
Dry eye	1 (3%)	0	0	0
Psychiatric				
Insomnia	1 (3%)	0	0	0

(Table 3 continues on next page)

of approximately 20% noted with Y90-radioembolisation alone[3,4] and 15–23% reported with anti-PD-1 agents alone.[5,13] However, it should be noted that the study did not achieve the prespecified objective response rate of 41% that the study was powered for.

Of note, the objective response rate in patients without extrahepatic spread was 43·5%, suggesting that Y90-radioembolisation followed by nivolumab should be further evaluated in patients with BCLC B or BCLC C hepatocellular carcinoma with no extrahepatic spread. The objective response rate reported in the NASIR-HCC study, which combined Y90-radioembolisation and nivolumab in Spanish patients with hepatocellular carcinoma with no extrahepatic spread, was a comparable 38·1%.[14] It is noteworthy that 81% of in-field target lesions regressed, especially given the significant intrahepatic disease burden in our patient cohort. The median number of liver lesions was five (range one to >20 lesions), the median size of the largest liver lesion was 78·5 mm (range 14–177), more than a quarter of patients had an intrahepatic disease burden of more than 50% of their total liver volume, and almost half had macrovascular invasion.

Significant downsizing or downstaging of hepatocellular carcinoma could allow subsequent surgical interventions. Two (9%) of the 23 patients with no extrahepatic spread pursued curative resection and liver transplantation. One patient underwent curative resection and had a complete pathological response. The patient planned for liver transplantation was noted to have radiological complete response according to mRECIST 1·5 years after their last dose of nivolumab and remained in this condition a further 1·5 years later at the time of data cutoff. Liver transplantation was never performed. This compares favourably with liver resection rates reported in the NASIR-HCC study (n=3; 7·1%).[14] Aggressive multimodal treatment could potentially alter the clinical trajectory of this subset of patients with hepatocellular carcinoma.

The median overall survival of 16·9 months reported here is similar to that seen in the CheckMate 459 study nivolumab arm (16·4 months), in which patients with advanced hepatocellular carcinoma were treated with either nivolumab or sorafenib.[5] Direct comparison is difficult, however, since 11% of patients in our study had received previous systemic therapy (by contrast, CheckMate 459 only enrolled patients with no previous systemic therapy), together with inherent differences in patients' characteristics between the two studies. The median time to response in our study was 3·8 months, similar to that reported in CheckMate 459 (3·3 months).[5]

No new safety concerns were noted in our study compared with either Y90-radioembolisation alone or nivolumab monotherapy. However, rates of grade 1–2 pruritus in this study (50%) were higher than in larger studies using nivolumab monotherapy (13–21%).[5,13] Grade 1–2 pruritus occurred in 26% of Asian patients treated with nivolumab in the CA 209-040 trial.[15] Rates of all-grade pruritus with Y90-radioembolisation alone are low (eg, 4% in the SARAH trial).[4] It is unclear whether the higher rate of pruritus is due to a combinational effect, a chance occurrence due to small sample size, or a reflection of ethnic or geographic variations in toxicity.

There were no treatment-related deaths in our study. Any grade treatment-related adverse events or serious adverse events in this study were reported by 81% of patients, with grade 3–4 treatment-related adverse events reported in 6%. Any grade treatment-related adverse events in the Y90-radioembolisation treated group in SIRveNIB were reported by 60% of patients, with grade 3 or higher treatment-related adverse events reported by 27·7%.[3] Any grade treatment-related

adverse events occurred in 77% of patients in the Y90-radioembolisation treated group in SARAH, and grade 3 or higher treatment-related adverse events in 41%.[4] 9% of patients in the Y90-radioembolisation group in SARAH had grade 3–4 increased laboratory liver values, compared with one (3%) patient in this study. Our strict inclusion criteria, enrolling only patients with Child-Pugh A disease with AST and ALT levels of less than three times the upper limit of normal could explain the low incidence of hepatic toxicities observed. Any grade treatment-related adverse events were reported by 83% of patients in CheckMate 459 study treated with nivolumab monotherapy, and grade 3–4 events were reported in 25%.[5] Thus, no apparent additive side-effects were noted when Y90-radioembolisation was followed by nivolumab in our study.

While combination systemic therapies have revolutionised treatment of patients with advanced hepatocellular carcinoma with encouraging objective response rates (13·6–36·0%), the incidence of grade 3–4 toxicities noted in these trials are of concern (grade 3–4 treatment-related adverse events in 35·1–64·4% of patients).[16–20] In this context, the objective response rates and incidences of grade 3–4 treatment-related adverse events in our trial suggest the potential value of our strategy in selected patients with hepatocellular carcinoma.

Combination radiotherapy and immunotherapy has been postulated to have a synergistic effect and improved response rates.[21–23] Radiotherapy increases tumour-infiltrating lymphocytes through alterations in the endothelium, chemokines enhancing immune-cell extravasation,[23] and via tumour DNA damage and cell death. The latter mechanism increases the release of tumour-associated antigens and damage-associated molecular patterns (DAMPs),[24] which in turn increases the antigen presentation capacity of dendritic cells, thus promoting immune cell infiltration.[25–28] In addition, DAMPs also activate the STING pathway, which increases the production of type I interferons, promoting downstream immune activation of infiltrated lymphocytes.[22] Y90-radioembolisation has been shown to increase immune activation in the treated tumour, systemically rendering a sustained clinical response.[7]

We compared immune classes and inflammation scores calculated from RNA-seq data between patients with and without a response and also between pre-treatment and post-treatment samples. Previous studies involving other tumour types have reported that immunologically hot tumours were predictive of response to immune checkpoint inhibitors.[29] This phenomenon was not observed in our cohort based on transcriptomic data. We did not observe a significant difference in hot tumour proportions between patients who had a response and those who did not nor in total tumour-infiltrating lymphocytes and inflammation scores in pre-treatment samples between those who responded and those who did not. However, the small sample size of our cohort limits definitive conclusions. Nonetheless, we observed that patients who had a response showed an increase in inflammation compared with those without a response in paired tumour samples taken 4 weeks after treatment initiation.

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)				
Respiratory disorders				
Cough	1 (3%)	0	0	0
Pneumonitis	1 (3%)	0	0	0
Skin				
Dry skin	5 (14%)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	1 (3%)	0	0	0
Pruritus	18 (50%)	0	0	0
Maculopaplular rash	13 (36%)	1 (3%)	0	0
General disorders and administration site conditions				
Oedema, limbs	1 (3%)	0	0	0
Localised oedema	1 (3%)	0	0	0
Fatigue	8 (22%)	0	0	0
Infusion-related reaction	2 (6%)	0	0	0

Data are number of patients with event (%). AE=adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. SAE=serious adverse event. *Y90 radioembolisation-related SAE. †Nivolumab-related SAE.

Table 3: **Treatment-related adverse events and serious adverse events**

Predictive biomarkers of response to immunotherapy in prospective trials in hepatocellular carcinoma have thus far been limited to an inflammatory gene signature (n=37)[12] and early expansion of CD8+Ki67+ lymphocytes (n=125).[17] The inflammatory gene signature score was significantly increased in on-treatment biopsy samples from patients who responded to Y90-radioembolisation followed by nivolumab (p=0·035), but was not significantly increased in patients who did not have a response (p=0·22).

Patient and treatment heterogeneity were the main weaknesses of our study. We included one patient with BCLC A disease, 11 with BCLC B1/B2, 11 with BCLC C with no extrahepatic spread, and 13 with BCLC C with extrahepatic spread. 11 (31%) patients had transarterial chemoembolisation at some point in their disease course before enrolment (three [8%] of those with BCLC B), and five (14%) patients had received systemic therapy. Personalised dosimetry was not used in ten (28%) of the 36 patients. These factors could have diluted the true efficacy of Y90-radioembolisation followed by nivolumab. Other limitations included this being a single-arm study conducted in a single centre.

However, inclusion of 13 patients with extrahepatic spread allowed evaluation of extrahepatic disease control. The objective response rate for this group of patients was 7·7%. The objective response rate of Y90-radioembolisation treated lesions was 15·4% while progressive disease was noted in 53·9% of lesions not treated with Y90-radioembolisation (appendix p 11) not dissimilar to nivolumab monotherapy,[5,13] suggesting

absence of an abscopal effect with Y90-radioembolisation in this small cohort of patients with advanced hepatocellular carcinoma. It remains to be seen whether an abscopal effect can be achieved with different sequences of radiotherapy and immunotherapy, or with variations in radiotherapy delivery, dose, and fractionation.

In conclusion, Y90-radioembolisation followed by nivolumab resulted in an encouraging objective response rate of 30·6% in patients with advanced hepatocellular carcinoma, and of 43·5% for patients without extrahepatic spread. 81% of target lesions within the Y90-radioembolisation field regressed. This combination is safe and tolerable with grade 3–4 treatment related adverse events or serious adverse events noted in 14% of patients. This strategy should be further evaluated in patients with BCLC B disease that is refractory to or ineligible for transarterial chemoembolisation and patients with BCLC C disease without extrahepatic spread, and compared with systemic therapy alone in a randomised study.

Contributors

DT, CSP, and TSH designed the study. DT, KL, AG, NKA, TSH, TH, DN, FI, JL, TCW, MN, TCK, JL, KSL, CHS, GGBB, HLH, NK, RL, PC, BG, AC, THC, TCH, TL, JY, ZWW, CCY, and CSP provided the data. DT, CSP, and CHS coordinated the trial at National Cancer Centre Singapore. DT and JL did the literature search. DT, TSH, CSP, and JL analysed the data and designed the figures. DT, TSH, CSP, and JL interpreted the results. DT, TSH, CSP, and JL wrote the manuscript. DT, KL, AG, NKA, TSH, TH, DN, FI, JL, TCW, MN, TCK, JL, KSL, CHS, GGBB, HLH, NK, RL, PC, BG, AC, THC, TCH, TL, JY, ZWW, CCY, and CSP read and reviewed the manuscript. All authors approved the final version of the manuscript. DT, CSP, JL, and TSH verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

DT declares support for the current manuscript from Bristol-Myers Squibb, Sirtex, and NMRC Singapore (CIRG/1470/2017); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Ipsen, Eisai, and Bristol-Myers Squibb; and consulting fees from Novartis, Bristol-Myers Squibb, and Merck Sharpe Dohme. CSP declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, Bristol-Myers Squibb, Ipsen, Lilly, AstraZeneca, and Roche; consulting fees from Bristol-Myers Squibb, Roche, Ipsen, Servier, Eisai, and AstraZeneca; a leadership or fiduciary role for Ministry of Health Singapore Medishield Life Cancer Drug committee; and stock or stock options with Bristol-Myers Squibb. DN declares support for the present manuscript from Sirtex; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sirtex. JL declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bristol-Myers Squibb, Ipsen, and Bayer; and research funding from Bayer. PKHC declares grants or contracts from Sirtex Medical, Ipsen, IQVIA, New B Innovation, Perspectum, AMiLi, MiRXES, Genentech, and Engine Biosciences; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sirtex Medical, Ipsen, Oncosil, Bayer, Roche, New B Innovation, Merck Sharpe Dohme, BTG Plc, Eisai, Abbott, AstraZeneca, IQVIA, Genentech, Worrell Guerbet, LEK Consulting, and COR2ED; and a leadership or fiduciary role, and stock or stock options for AVATAMED. TCW declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events and consulting fees from Sirtex. KL, AG, NKA, TSH, TH, FI, JL, MN, TCK, KSL, CHS, GGBB, HLH, NK, RL, BG, AC, THC, TCH, TL, JY, ZWW, and CCY declared no competing interests.

Data sharing

Data collected for this study can be made available on request to the corresponding author.

Acknowledgments

Funding for this study was acquired from National Medical Research Council Singapore (NMRC/CIRG/1454/2016), Bristol-Myers Squibb, and Sirtex. We thank all patients, their care-givers, treating physicians, and research support staff for contribution to this trial. WZ is supported in part by the National Key R&D program of China grant 2018YFC0910400 and 2018YFC1406902, and National Science Foundation of China (31970566).

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