



Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study

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Summary

Background This study aimed to assess the safety and tolerability of the immune checkpoint inhibitor nivolumab, as monotherapy or combined with chemotherapy, in Japanese patients with biliary tract cancer.

Methods This multicentre, open-label, phase 1 trial was done at four cancer centres in Japan. Eligible patients were aged 20–79 years, had biliary tract adenocarcinoma (intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, or ampullary cancer), Eastern Cooperative Oncology Group performance status 0 or 1, adequate hepatic, renal, and haematological function, and tumour tissue samples for PD-L1 expression analysis. Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens received nivolumab monotherapy (240 mg every 2 weeks [monotherapy cohort]). Chemotherapy-naïve patients with unresectable or recurrent biliary tract cancer received nivolumab (240 mg every 2 weeks) and cisplatin (25 mg/m²) plus gemcitabine (1000 mg/m²) chemotherapy (combined therapy cohort). The primary objective was to assess tolerability and safety. The primary objective was assessed in the safety population of all patients who had received at least one dose of nivolumab. This study is registered with www.clinicaltrials.jp, number JapicCTI-153098, and follow-up is ongoing.

Findings 30 patients were enrolled into each cohort between Jan 13, 2016, and April 19, 2017. Data cutoff was Aug 31, 2017. In the monotherapy cohort, the most frequently reported treatment-related adverse events were decreased appetite (five [17%]), malaise (four [13%]), and pruritus (four [13%]). Grade 3–4 treatment-related adverse events were reported by three (10%) patients (rash, maculopapular rash, and amylase increase) and treatment-related serious adverse events were reported by one (3%) patient (pleurisy). In the combined therapy cohort, the most frequently reported treatment-related adverse events were neutrophil count decrease (any grade 25 [83%]; grade 3–4 in 23 [77%] patients) and platelet count decrease (any grade 25 [83%] of 30; grade 3–4 in 15 [50%] patients). Six (20%) patients reported 11 treatment-related serious adverse events (platelet count decrease [three patients], febrile neutropenia [two patients], neutrophil count decrease, anaemia, anaphylactic reaction, decreased appetite, pyrexia, and myocarditis [one patient each]). In the monotherapy cohort, median overall survival was 5·2 months (90% CI 4·5–5·8), median progression-free survival was 1·4 months (90% CI 1·4–1·4), and one of 30 patients had an objective response. In the combined therapy cohort, median overall survival was 15·4 months (90% CI 11·8–not estimable), median progression-free survival was 4·2 months (90% CI 2·8–5·6), and 11 of 30 patients had an objective response.

Interpretation Nivolumab had a manageable safety profile and signs of clinical activity in patients with unresectable or recurrent biliary tract cancer. This initial assessment of nivolumab for the treatment of advanced biliary tract cancer provides supportive evidence for future larger randomised studies of nivolumab in this difficult to treat cancer.

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Introduction

Biliary tract cancer is a heterogeneous group of cancers including intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, and ampullary cancer.¹ Incidence of biliary tract cancer varies worldwide, with high incidences in east Asia, including Japan, and Latin America.² In Japan in 2013, 22 102 cases of biliary tract cancer were diagnosed³ and 18 225 deaths were attributed

to the disease.⁴ 5-year survival is generally poor.⁵ Treatment of biliary tract cancer is challenging because complete surgical resection is not feasible in most patients and recurrence is common.^{1,6} Furthermore, treatment options for patients with unresectable disease are scarce.¹ Combination chemotherapy with cisplatin plus gemcitabine was the first regimen to show a survival benefit in a randomised phase 3 study (ABC-02)⁷ in

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Research in context

Evidence before this study

We searched PubMed and American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) conference abstracts with combinations of the search terms “biliary tract cancer”, “nivolumab”, “pembrolizumab”, and “immunotherapy”, with no publication date or language restrictions. We found few clinical trials of immunotherapy in patients with advanced biliary tract cancer. Nivolumab was reported to be well tolerated with promising efficacy in a phase 2 study of previously treated patients with advanced biliary tract cancer. The anti-PD-1 antibody pembrolizumab was also reported to have manageable toxicity, and durable antitumour activity in a subset of patients in the biliary tract cancer cohort of the KEYNOTE-158 and KEYNOTE-028 studies (KEYNOTE-028 was done in patients with PD-L1 expression in $\geq 1\%$ of tumour cells or tumour-infiltrating lymphocytes). The randomised phase 3 ABC-02 study established combination chemotherapy with cisplatin plus gemcitabine as a standard of care for first-line treatment of unresectable or recurrent biliary tract cancer. However, no established second-line treatment is available.

Added value of this study

In this study, we assessed the safety and efficacy of nivolumab monotherapy in treated patients and, for the first time to the

best of our knowledge, nivolumab in combination with chemotherapy in chemotherapy-naïve patients.

Nivolumab was well tolerated and had a manageable safety profile when given as monotherapy in previously treated patients with advanced biliary tract cancer and when combined with cisplatin plus gemcitabine chemotherapy in chemotherapy-naïve patients.

Implications of all the available evidence

This initial assessment of nivolumab in the treatment of unresectable or recurrent biliary tract cancer, which demonstrated a manageable safety profile and signs of antitumour activity, provides the basis for larger, randomised studies in this difficult-to-treat cancer. The finding that PD-L1 expression status might be associated with longer overall survival suggests that it might be possible to identify patients with advanced biliary tract cancer who would benefit from nivolumab treatment. However, further investigation is required, including whether PD-L1 expression is associated with response to nivolumab when it is given in combination with chemotherapy. Biomarker analyses should be included in future studies to help establish the role of nivolumab in the first-line and second-line settings.

patients with advanced biliary tract cancer, leading to this regimen becoming a standard of care.⁸ However, the benefit of traditional chemotherapy seems to have reached a limit and, therefore, new effective treatment options for biliary tract cancer, with different mechanisms of action, are needed.¹ Additionally, no established second-line treatment regimen is available for patients with biliary tract cancer.^{8,9}

PD-1 is an immune checkpoint receptor expressed by activated T cells.¹⁰ The PD-1 ligands, PD-L1 and PD-L2, are expressed by tumour cells and tumour-infiltrating immune cells.¹⁰ Binding of PD-L1 or PD-L2 to PD-1 inhibits T-cell activation, which promotes immune tolerance, allowing tumour cells to proliferate undetected by immunosurveillance.¹⁰ Nivolumab is a human monoclonal antibody against PD-1 that inhibits binding of PD-L1 and PD-L2 to PD-1 and therefore enhances the immune response to tumours.¹¹ Nivolumab has been shown to have antitumour activity in a wide range of tumours, including metastatic melanoma, squamous non-small-cell lung cancer, and renal cell carcinoma.¹¹ Studies of PD-L1 expression have reported PD-L1 positivity in tumour cells and tumour-infiltrating immune cells in different types of biliary tract cancer,^{12–14} suggesting that biliary tract cancer is potentially responsive to PD-1 or PD-L1 blockade therapy.

This phase 1 study provides an initial assessment of nivolumab as first-line treatment (in combination with chemotherapy) or as second-line or later treatment (as

monotherapy) in Japanese patients with advanced biliary tract cancer.

Methods

Study design

This was a multicentre, open-label, phase 1 trial done at four cancer centres in Japan. We assessed two cohorts: a nivolumab monotherapy cohort of patients with unresectable or recurrent biliary tract cancer refractory or intolerant to gemcitabine-based treatment regimens and a nivolumab with cisplatin plus gemcitabine combination therapy cohort of patients with unresectable or recurrent biliary tract cancer who have not previously had chemotherapy. The study protocol was approved by each site's ethics review board and the study was done in accordance with the principles of the Declaration of Helsinki, the Guideline for Good Clinical Practice, and applicable local regulations.

Patients

Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens were eligible for the monotherapy cohort. Patients with unresectable or recurrent biliary tract cancer who had not previously received chemotherapy were eligible for the combination therapy cohort; previous adjuvant therapy was not permitted. The main inclusion criteria for both cohorts were as follows: histologically or cytologically confirmed biliary tract

adenocarcinoma (intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, and ampullary cancer); age 20–79 years; at least one measurable lesion as defined in the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 90 days; adequate hepatic (aspartate aminotransferase and alanine aminotransferase ≤ 150 international units (IU) per L for patients who had had biliary drainage or ≤ 100 IU/L for those who had not; total bilirubin ≤ 3.0 mg/dL for patients who had had biliary drainage or ≤ 2.0 mg/dL for those who had not), renal (creatinine ≤ 1.5 mg/dL for the monotherapy cohort or ≤ 1.2 mg/dL for the combination therapy cohort or creatinine clearance [measured value or estimated value using the Cockcroft-Gault equation] ≥ 45 mL/min for the monotherapy cohort or ≥ 50 mL/min for the combination therapy cohort), haematological (neutrophils ≥ 1500 cells per μL , haemoglobin ≥ 9.0 g/dL), and coagulation (platelets $\geq 100\,000$ per μL) function; and tumour tissue samples for analysis of PD-L1 expression and microsatellite instability status.

The main exclusion criteria for the two cohorts were as follows: previous receipt of nivolumab or antibodies against PD-1, PD-L1, PD-L2, CD137, or CTLA-4, or any other therapeutic antibodies or pharmacotherapies for regulation of T cells; receiving systemic corticosteroids or immunosuppressants in the 28 days before enrolment; concurrent autoimmune disease or a history of chronic or recurrent autoimmune disease; pleurodesis or pericardial adhesion in the 28 days before enrolment; positive test results for HIV antibody, human T-cell leukaemia virus type 1 antibody, hepatitis C virus antibody, hepatitis B surface protein antigen, hepatitis B surface protein antibody, hepatitis B core protein antibody, or any detectable hepatitis B virus DNA; multiple primary cancers (except completely resected basal cell carcinoma, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, and superficial bladder cancer, and any other cancers that have not recurred for at least 5 years); brain or meningeal metastases (unless asymptomatic and requiring no treatment); and uncontrollable or significant cardiovascular disease (appendix). All patients provided written informed consent before enrolling in the study.

Procedures

In both the monotherapy and combined therapy cohorts, nivolumab 240 mg was administered intravenously over 30 min every 2 weeks, with a minimum interval of 10 days between doses. Treatment continued until complete response or progressive disease, unacceptable toxicity, or investigator decision. Dose reduction of nivolumab was not permitted.

Patients in the combination therapy cohort also received cisplatin 25 mg/m² administered intravenously over 60 min followed by gemcitabine 1000 mg/m² administered intravenously over 30 min. Patients

received cisplatin and gemcitabine on day 1 and day 8 of a 3-week cycle (or day 1 of a 2-week cycle if the patient was not able to receive cisplatin plus gemcitabine on day 8 for two consecutive cycles). Cisplatin was given up to 16 times (400 mg/m² in total); after the last dose of cisplatin, cisplatin plus gemcitabine therapy was stopped and gemcitabine monotherapy (1000 mg/m²) was started. The dose of gemcitabine was reduced from 1000 mg/m² to 800 mg/m² in patients who had any of the following events, for which a causal relationship to gemcitabine could not be ruled out: grade 4 or worse neutrophil count decrease; grade 4 or worse platelet count decrease or grade 3 requiring blood transfusion; grade 3 or worse febrile neutropenia; grade 3 or worse infection; grade 3 or worse rash; other grade 3 or worse non-haematological toxicity; or if the dose reduction of gemcitabine was clinically justified in the investigator's or subinvestigator's opinion. The dose of gemcitabine was reduced from 800 mg/m² to 600 mg/m² in patients who had a second of these events. An increase in the dose of gemcitabine was not permitted after it had been reduced. Dose reduction of cisplatin was not permitted.

During the screening period, tumour tissue samples for analysis of PD-L1 expression and microsatellite instability were collected from patients in whom a biopsy could be safely done; preserved samples were used for patients who were unable to undergo biopsy. Tumour tissue samples were stained for PD-L1 and assessed by a pathologist at the central laboratory. PD-L1 expression was analysed with the pharmDx 28–8 assay (Dako, Carpinteria, CA, USA) with positivity defined as expression in 1% or more of tumour cells, 1% or more of tumour-associated immune cells, or 1% or more of tumour cells or tumour-associated immune cells (or both). The 1% cutoff for the PD-L1 analyses was not prespecified; this cutoff was chosen because it is commonly used in the assessment of efficacy outcomes by PD-L1 expression status.¹⁵ Microsatellite instability status was assessed in tumour tissue and blood samples with the MD1641 MSI Analysis System (Promega, Madison, WI, USA).

Outcomes

The primary safety endpoint was adverse events graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

The secondary efficacy endpoints were overall survival; progression-free survival; best overall response; objective response; disease control; change in tumour diameter; maximum change in tumour diameter; duration of response; and time to response. Overall survival was measured from the start of study treatment to the date of death from any cause. Progression-free survival was measured from the start of study treatment to the date of progressive disease or death from any cause, whichever was earlier. Objective response was defined as a best overall response of complete response or partial response; disease control was defined as a best overall

See Online for appendix

	Monotherapy cohort (n=30)	Combined therapy cohort (n=30)
Sex		
Women	12 (40%)	16 (53%)
Men	18 (60%)	14 (47%)
Age, years	68.0 (60.0–71.0)	67.5 (54.0–75.0)
<65	12 (40%)	14 (47%)
≥65	18 (60%)	16 (53%)
Primary tumour site		
Intrahepatic bile duct	11 (37%)	15 (50%)
Extrahepatic bile duct	7 (23%)	5 (17%)
Gallbladder	10 (33%)	10 (33%)
Ampulla	2 (7%)	0
Extent of disease		
Metastatic	29 (97%)	25 (83%)
Recurrent	11 (37%)	1 (3%)
ECOG performance status		
0	20 (67%)	25 (83%)
1	10 (33%)	5 (17%)
Number of previous treatment regimens		
1	5 (17%)	NA
2	16 (53%)	NA
3	5 (17%)	NA
4	4 (13%)	NA
Microsatellite instability status		
Stable	25 (83%)	26 (87%)
High	0	1 (3%)
Unknown	5 (17%)	3 (10%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. NA=not applicable.

Table 1: Baseline characteristics

response of complete response, partial response, or stable disease. Tumour response was assessed using CT or MRI, according to RECIST, version 1.1, every 6 weeks until discontinuation of treatment. Complete response and partial response were confirmed by two consecutive assessments done at least 28 days apart. Evidence of disease progression was assessed by masked independent central review (central assessment) and by the local investigator (investigator assessment). Other safety endpoints (not reported here) were laboratory tests, vital signs, electrocardiogram, chest x-ray, and ECOG performance status.

Other endpoints included PD-L1 expression and microsatellite instability. Blood subset analysis, serum cytokines, HLA testing, serum microRNA analysis, and genetic testing were other prespecified endpoints and will be reported elsewhere.

Statistical analysis

The sample size was established using a similar calculation to that described by Qureshi and colleagues.¹⁶ Assuming that the true incidence of intolerable adverse events (judged by the investigator and the Data Safety

Monitoring Committee) for which a causal relationship to the study treatment cannot be ruled out is 10%, 15%, or 20%, the probability that such adverse events occur in at least one of 15 patients is estimated to be 79.4%, 91.3%, or 96.5%, respectively. Because these estimates indicate that adverse events required for early safety assessment can be detected at a probability of about 80% or higher, the safety of the study treatment can be assessed. According to these estimates, at least 15 patients were needed for the safety analysis of the study treatment in each cohort; up to an additional 50 patients could be enrolled in the study.

The primary safety endpoints were assessed in the safety population, which consisted of patients who had received at least one dose of nivolumab. The secondary efficacy endpoints were assessed in the full analysis set, which consisted of patients in the safety population who were Good Clinical Practice compliant and met the major eligibility criteria. Adverse events are summarised as the number and proportion of patients reporting each event. Median overall survival and progression-free survival and the associated 90% CIs were estimated using the Kaplan-Meier method. The associated 90% CIs for the objective response were calculated using Wilson's method.

Analyses were done using SAS, version 9.4 (SAS Institute, Cary, NC, USA). This study is registered with www.clinicaltrials.jp, number JapicCTI-153098.

Role of the funding source

The funder was involved in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the article for publication. The trial statistician (SA) had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Patients were enrolled from Jan 13, 2016, to April 19, 2017. Data cutoff was Aug 31, 2017. 30 patients were enrolled in the monotherapy cohort and 30 patients were enrolled in the combined therapy cohort; the safety population and full analysis set comprised 30 patients for each cohort. In the monotherapy cohort, most patients had intrahepatic bile duct cancer (11 [37%] of 30 patients) or gallbladder cancer (ten [33%]), and about half of the patients (16 [53%]) had received two previous treatment regimens for biliary tract cancer (table 1). In the combined therapy cohort, most patients had intrahepatic bile duct cancer (15 [50%] of 30 patients) or gallbladder cancer (ten [33%]; table 1). Across the two cohorts, most patients (51 [85%] of 60 patients) had microsatellite-stable tumours (table 1).

In the monotherapy cohort, 17 (57%) of 30 patients reported any-grade treatment-related adverse events; three (10%) reported grade 3–4 treatment-related adverse events. The most common treatment-related adverse events were decreased appetite (five [17%]), malaise

(four [13%]), pruritus (four [13%]), and rash (three [10%]; table 2). The three grade 3–4 treatment-related adverse events reported in the monotherapy cohort were rash, maculopapular rash, and amylase increase. Serious adverse events were reported by two (7%) patients: depressed level of consciousness and pleurisy. The pleurisy was considered treatment related. No patient discontinued treatment because of a treatment-related adverse event and no intolerable adverse events or treatment-related deaths occurred.

In the combined therapy cohort, all 30 patients reported treatment-related adverse events (related to nivolumab or cisplatin plus gemcitabine); 27 (90%) reported grade 3–4 treatment-related adverse events. The most common treatment-related adverse events were neutrophil count decrease (25 [83%]; grade 3–4 in 23 [77%] patients), platelet count decrease (25 [83%]; grade 3–4 in 15 [50%] patients), and white blood cell count decrease (21 [70%]; grade 3–4 in 14 [47%] patients; table 2). Nine (30%) patients reported 14 serious adverse events; six (20%) reported 11 treatment-related serious adverse events (platelet count decrease [three patients], febrile neutropenia [two patients], and neutrophil count decrease, anaemia, anaphylactic reaction, decreased appetite, pyrexia, and myocarditis [one patient each]; the anaphylactic reaction was reported to be related to cisplatin treatment). Four (13%) patients discontinued treatment because of at least one treatment-related adverse event (neutrophil count decrease [two patients], platelet count decrease, anaemia, anaphylactic reaction, and hypersensitivity [one patient each]). No intolerable adverse events or treatment-related deaths occurred.

In the combined therapy cohort, the median relative dose intensity of cisplatin was 100% (range 50–145) and of gemcitabine was 86% (54–145). 15 (50%) of 30 patients had a reduction in the gemcitabine dose.

In the monotherapy cohort, median follow-up was 5.1 months (IQR 3.4–7.0). Median overall survival was 5.2 months (90% CI 4.5–8.7; figure 1A). Median progression-free survival was 1.4 months (90% CI 1.4–1.4) by central assessment (figure 1B) and 1.4 months (1.4–2.8) by investigator assessment (figure 1C). No patient achieved a complete response; one (3%) of 30 patients achieved a partial response by both central assessment and investigator assessment (objective response 3%; 90% CI 0.7–13.6; table 3). The patient who responded had a durable response, with a duration of response up to data cutoff of 12.7 months, progression-free survival of 14.1 months (central and investigator assessment), and overall survival of 19.2 months; time to response was 43 days (figure 2A). The patient with the durable response had hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) of unknown microsatellite instability status (stable for markers NR21, NR24, and BAT26, and not measurable by PCR for markers BAT25 and MONO27); removing this patient from the analysis did not alter median overall survival for

	Monotherapy cohort (n=30)		Combined therapy cohort (n=30)		
	Grades 1–2	Grade 3	Grades 1–2	Grade 3	Grade 4
Overall	16 (53%)	3 (10%)	30 (100%)	27 (90%)	16 (53%)
Decreased appetite*	5 (17%)	0	10 (33%)	3 (10%)	0
Malaise*	4 (13%)	0	8 (27%)	0	0
Pruritus	4 (13%)	0	4 (13%)	0	0
Rash*	2 (7%)	1 (3%)	5 (17%)	0	0
Pyrexia*	2 (7%)	0	8 (27%)	0	0
Myalgia*	2 (7%)	0	5 (17%)	0	0
Fatigue*	1 (3%)	0	8 (27%)	0	0
Nausea*	1 (3%)	0	11 (37%)	0	0
Vomiting	1 (3%)	0	3 (10%)	0	0
Neutrophil count decrease†	1 (3%)	0	16 (53%)	21 (70%)	13 (43%)
Platelet count decrease‡	0	0	22 (73%)	13 (43%)	6 (20%)
White blood cell count decrease§	1 (3%)	0	18 (60%)	13 (43%)	1 (3%)
Amylase increase	0	1 (3%)	0	0	0
Maculopapular rash*	0	1 (3%)	1 (3%)	0	0
Anaemia	0	0	5 (17%)	14 (47%)	0
Peripheral sensory neuropathy	0	0	6 (20%)	0	0
Alopecia	0	0	5 (17%)	0	0
Stomatitis	0	0	5 (17%)	0	0
Constipation	0	0	3 (10%)	1 (3%)	0
Blood creatinine increase	0	0	3 (10%)	0	0
Dysgeusia	0	0	3 (10%)	0	0
Oedema*	0	0	3 (10%)	0	0
Hiccups	0	0	3 (10%)	0	0
Lymphocyte count decrease	0	0	1 (3%)	1 (3%)	0
Proteinuria*	0	0	1 (3%)	1 (3%)	0
Febrile neutropenia	0	0	0	2 (7%)	0
Anaphylactic reaction	0	0	0	1 (3%)	0
Myocarditis*	0	0	0	1 (3%)	0

Treatment-related adverse events (any grade) occurring in at least 10% of patients in either cohort and all grade 3 and 4 treatment-related adverse events. Patients may be counted in more than one adverse event grade. No treatment-related grade 4 events were reported in the monotherapy cohort. *Treatment-related or immune-related adverse event of interest for nivolumab; other treatment-related adverse events of interest for nivolumab occurring in less than 10% of patients were diarrhoea (two [7%] patients), hypothyroidism (two [7%]), and purpura (one [3%]) in the monotherapy cohort; and diarrhoea (two [7%] patients), proteinuria (two [7%]), purpura (two [7%]), eyelid ptosis (one [3%]), hypothyroidism (one [3%]), pain in extremity (one [3%]), and vasculitis (one [3%]) in the combined therapy cohort. †Includes neutrophil count decreased and neutropenia terms. ‡Includes platelet count decreased and thrombocytopenia terms. §Includes white blood cell count decreased and leukopenia terms.

Table 2: Summary of treatment-related adverse events

the monotherapy cohort (data not shown). A small number of patients maintained a best overall response of stable disease and had a reduction in tumour diameter by RECIST criteria (figure 2A, B). Data for activity by site of disease are shown in the appendix.

In the combined therapy cohort, median follow-up was 8.2 months (IQR 7.0–14.0). Median overall survival was 15.4 months (90% CI 11.8–not estimable; figure 1D). Median progression-free survival was 4.2 months (90% CI 2.8–5.6) by central assessment (figure 1E) and

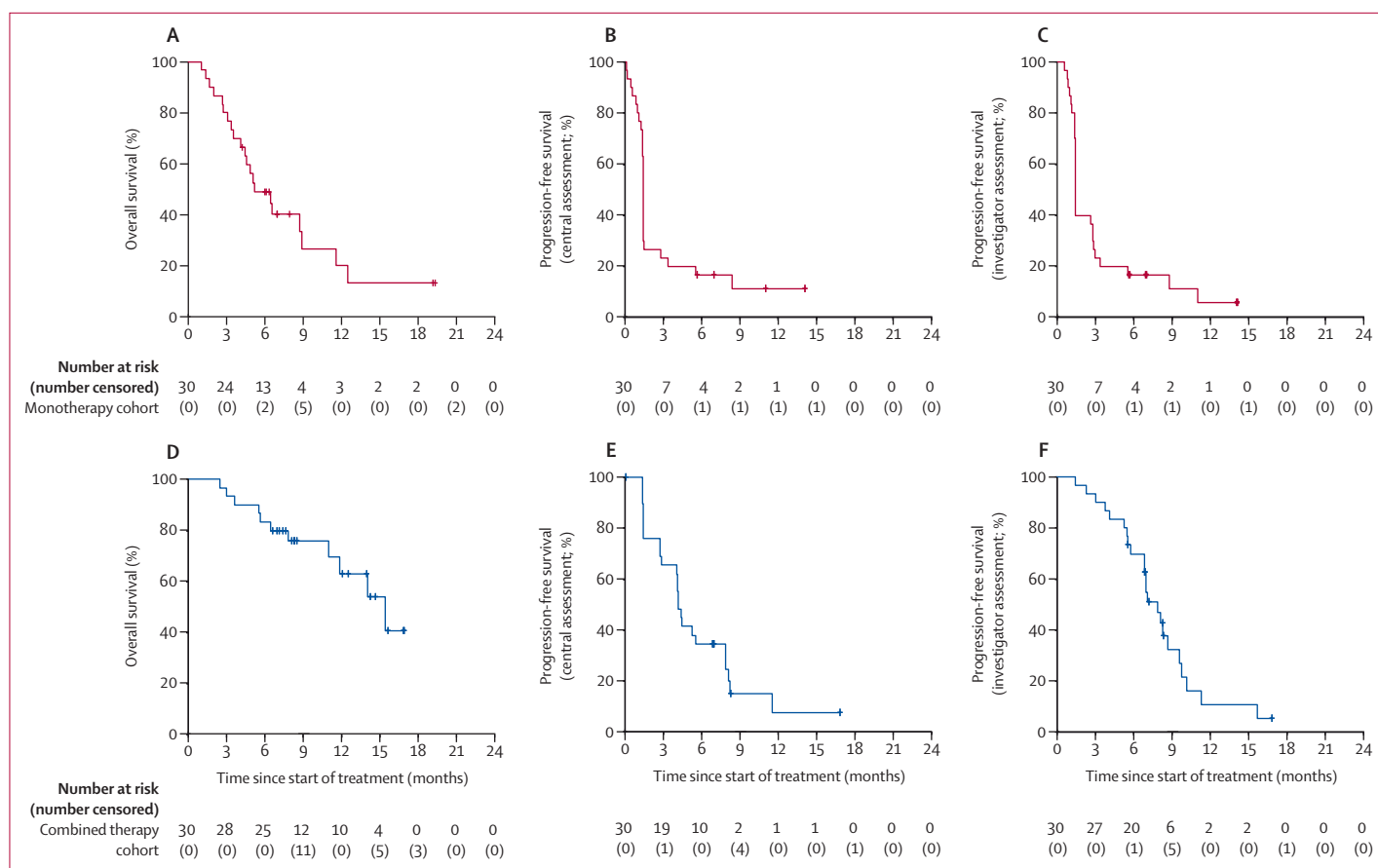


Figure 1: Kaplan-Meier curves of overall and progression-free survival

Overall survival (A), progression-free survival by central assessment (B), and progression-free survival by investigator assessment (C) in the monotherapy group; and overall survival (D), progression-free survival by central assessment (E), and progression-free survival by investigator assessment (F) in the combination therapy group. NE=not estimable.

7.9 months (6.8–8.6) by investigator assessment (figure 1F). No patient achieved a complete response; 11 (37%) of 30 patients achieved a partial response by central assessment (objective response 37% [90% CI 23.9–51.7]); 12 (40%) of 30 patients achieved a partial response by investigator assessment (objective response 40% [26.7–54.9]; table 3). Median duration of response by central assessment was 5.1 months (90% CI 3.7–6.9) and median time to response was 2.8 months (IQR 1.3–5.6; not including patients who discontinued). Several patients maintained a best overall response of stable disease and had a reduction in tumour diameter by RECIST criteria (figure 2C, D). Activity data by site of disease are shown in the appendix.

In both cohorts, most patients had PD-L1 expression in less than 1% of tumour cells and most had PD-L1 expression in 1% or more of tumour-associated immune cells (table 4; appendix).

In the monotherapy cohort, median overall survival and progression-free survival were longer in the five patients with PD-L1 expression in 1% or more of tumour cells (including the patient with a partial response) than in the 23 patients with PD-L1 expression

in less than 1% (table 4). Median overall survival was longer in the 18 patients with PD-L1 expression in 1% or more of tumour-associated immune cells (including the patient with a partial response) than in the ten patients with PD-L1 expression in less than 1% (table 4; appendix).

In the combination cohort, median overall survival was longer in the 21 patients with PD-L1 expression in less than 1% of tumour cells than in the eight patients with PD-L1 expression in 1% or more. Median progression-free survival was also longer in patients with PD-L1 expression in less than 1% of tumour cells by investigator assessment but similar between the two groups of patients by central assessment (table 4). Objective responses were more common in the eight patients with PD-L1 expression in 1% or more tumour cells than in the 21 patients with PD-L1 expression in less than 1%. Objective responses were more common in the 18 patients with PD-L1 expression in 1% or more of tumour-associated immune cells than in the ten patients with PD-L1 expression in less than 1% (table 4). Median overall survival could not be estimated in the patients with PD-L1 expression in 1% or more of tumour-associated immune cells (table 4; appendix).

	Monotherapy cohort (n=30)		Combined therapy cohort (n=30)	
	Central assessment	Investigator assessment	Central assessment	Investigator assessment
Best overall response				
Complete response	0 (0%; 0.0–8.3)	0 (0%; 0.0–8.3)	0 (0%; 0.0–8.3)	0 (0%; 0.0–8.3)
Partial response	1 (3%; 0.7–13.6)	1 (3%; 0.7–13.6)	11 (37%; 23.9–51.7)	12 (40%; 26.7–54.9)
Stable disease	6 (20%; 10.7–34.3)	10 (33%; 21.1–48.3)	8 (27%; 15.7–41.5)	17 (57%; 41.9–70.4)
Progressive disease	22 (73%)	18 (60%)	9 (30%)	1 (3%)
Not evaluable	1 (3%)	1 (3%)	2 (7%)	0
Objective response	1 (3%; 0.7–13.6)	1 (3%; 0.7–13.6)	11 (37%; 23.9–51.7)	12 (40%; 26.7–54.9)
Disease control	7 (23%; 13.2–37.9)	11 (37%; 23.9–51.7)	19 (63%; 48.3–76.1)	29 (97%; 86.4–99.3)

Data are n (%) or n (%; 90% CI). Concordance between central assessment and investigator assessment of best overall response was 87% in the monotherapy cohort and 57% in the combined therapy cohort.

Table 3: Best overall response

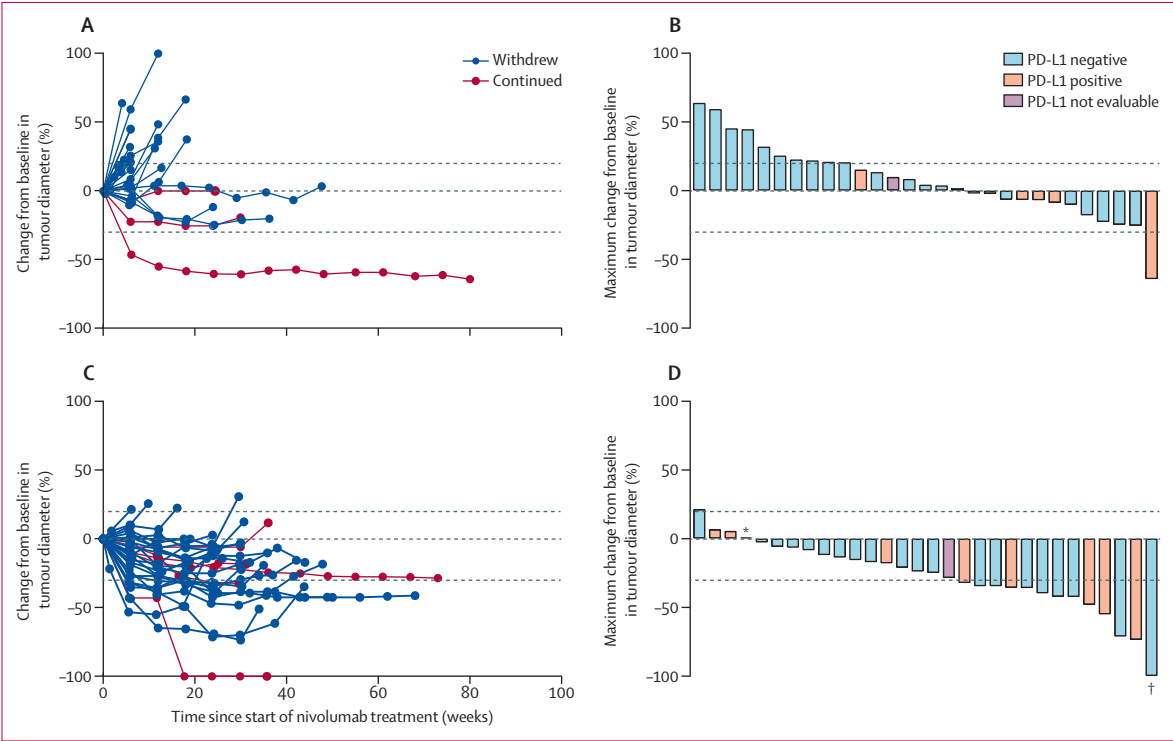


Figure 2: Change in tumour diameter, by investigator assessment
Change over time (A) and maximum change (B) in the monotherapy cohort; and change over time (C) and maximum change (D) in the combined therapy cohort. One patient in the monotherapy cohort was not included in the waterfall plot because they could not be assessed. The dotted line at -30% is the threshold for a partial response and the dotted line at 20% is the threshold for progressive disease, according to RECIST criteria. *No change in tumour diameter. †This patient did not have a best overall response of complete response because a non-target lesion remained.

Efficacy results based on PD-L1 expression in tumour cells and tumour-associated immune cells combined were similar to those observed for PD-L1 expression in tumour-associated immune cells alone, in both cohorts (appendix).

Discussion

Nivolumab as monotherapy or in combination with cisplatin plus gemcitabine chemotherapy was well tolerated in this phase 1 study of patients with unresectable

or recurrent biliary tract cancer; no unexpected safety concerns were reported. Nivolumab monotherapy in previously treated patients and nivolumab with cisplatin plus gemcitabine chemotherapy as first-line treatment were associated with signs of antitumour activity. Taken together, these results provide evidence for future larger randomised studies of nivolumab for the treatment of advanced biliary tract cancer.

Nivolumab monotherapy had a favourable safety profile and was well tolerated in this study, with few patients

	Monotherapy cohort		Combined therapy cohort	
	PD-L1 <1%	PD-L1 ≥1%	PD-L1 <1%	PD-L1 ≥1%
PD-L1 expression in tumour cells				
Total evaluable	23	5	21	8
Overall survival, months	5.2 (4.1–8.7)	11.6 (2.0–NE)	15.4 (11.0–NE)	11.8 (5.5–NE)
Progression-free survival (central assessment), months	1.4 (1.4–1.4)	2.8 (0.2–NE)	4.1 (1.5–5.6)	4.7 (2.8–7.9)
Progression-free survival (investigator assessment), months	1.4 (1.4–2.6)	2.8 (0.8–NE)	8.1 (6.9–9.7)	6.2 (3.8–7.9)
Objective response (central assessment)	0 (0%; 0.0–10.5)	1 (20%; 4.6–56.5)	6 (29%; 15.6–46.5)	4 (50%; 24.9–75.1)
Objective response (investigator assessment)	0 (0%; 0.0–10.5)	1 (20%; 4.6–56.5)	7 (33%; 19.2–51.3)	5 (63%; 34.8–83.9)
PD-L1 expression in tumour-associated immune cells				
Total evaluable	10	18	10	18
Overall survival, months	4.3 (3.1–6.4)	8.7 (4.6–11.6)	15.4 (5.7–15.4)	NE (11.8–NE)
Progression-free survival (central assessment), months	1.4 (1.1–3.4)	1.4 (1.4–1.5)	4.1 (1.4–4.4)	4.3 (2.8–7.9)
Progression-free survival (investigator assessment), months	1.4 (1.1–3.4)	1.4 (1.4–2.8)	6.9 (4.1–10.2)	7.9 (6.8–8.3)
Objective response (central assessment)	0 (0%; 0.0–21.3)	1 (6%; 1.2–21.5)	2 (20%; 6.9–45.9)	8 (44%; 27.2–63.1)
Objective response (investigator assessment)	0 (0%; 0.0–21.3)	1 (6%; 1.2–21.5)	2 (20%; 6.9–45.9)	10 (56%; 36.9–72.8)

Data are median (90% CI) or n (%; 90% CI). NE=not estimable.

Table 4: Efficacy by PD-L1 status

reporting treatment-related grade 3–4 adverse events and no patients discontinuing treatment because of a treatment-related adverse event. The most commonly reported treatment-related adverse events were decreased appetite, malaise, pruritus, and rash, which is consistent with other studies of nivolumab monotherapy.^{17–19} In a pooled dataset of 2578 patients with different tumour types receiving nivolumab monotherapy (3 mg/kg), the most frequent adverse reactions (in ≥10% of patients) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%).²⁰

From a safety perspective, the mild toxicity profile of nivolumab, which does not overlap with the chemotherapy toxicity profile, makes it an attractive option for combination with chemotherapy. In this study, nivolumab in combination with cisplatin plus gemcitabine chemotherapy had a manageable safety profile and was well tolerated. The most common treatment-related grade 3–4 adverse events were haematological toxicities known to be associated with cisplatin and gemcitabine.^{21,22} In particular, these haematological toxicities were reported in patients with advanced biliary tract cancer in the cisplatin plus gemcitabine groups of the ABC-02 randomised phase 3 study⁷ and a randomised phase 2 study comparing cisplatin plus gemcitabine with gemcitabine alone in Japanese patients.²³ Although the frequency of grade 3–4 adverse events was high in the combined therapy cohort, it was offset by the relatively low number of discontinuations because of a treatment-related adverse event.

In this study, some antitumour activity was noted for nivolumab monotherapy in patients with previously treated unresectable or recurrent biliary tract cancer, and the patient who responded was a long-term survivor with

a durable response. The responding patient had Lynch syndrome, which is characterised by high microsatellite instability status. Although microsatellite instability status was not confirmed in this patient, high microsatellite instability status is typically associated with resistance to chemotherapy and responsiveness to immunotherapy.^{24,25} The efficacy results for nivolumab monotherapy in this study are similar to those reported from a phase 1 study of another anti-PD-1 antibody, pembrolizumab, in combination with ramucirumab, an anti-VEGFR2 antibody, in 26 patients with previously treated advanced or metastatic biliary tract cancer.²⁶ Pembrolizumab plus ramucirumab showed low efficacy, with a median overall survival of 6.4 months, median progression-free survival of 1.6 months, objective response in one (4%) of 26 patients, and duration of response of 6 months.²⁶ Because these two phase 1 studies were powered for safety rather than efficacy, assessment of the activity of nivolumab in previously treated patients with advanced biliary tract cancer requires further investigation. In a phase 2 study of nivolumab monotherapy in 34 previously treated patients with advanced biliary tract cancer, five (17%) of 29 evaluable patients had a response (two patients had a duration of response of >12 months) and median progression-free survival was 3.5 months (median overall survival had not been reached).²⁷ The higher proportion of patients with a response than in our study might be attributed to the lower proportion of patients in whom multiple lines of therapy had previously failed (14 [41%] of 34 patients in the phase 2 study vs 25 [83%] of 30 patients in our study; table 1). The phase 2 KEYNOTE-158 study²⁸ of pembrolizumab monotherapy was done in a cohort of 104 previously treated patients with advanced biliary tract cancer, of whom 52% had had

multiple lines of therapy that had failed. Six (6%) of 104 patients achieved a response (median duration of response not reached; range 6.2 to >15.7 months), median progression-free survival was 2.0 months (95% CI 1.9–2.1), and median overall survival was 9.1 months (5.6–10.4). Investigation of treatment options in this setting is of importance because no second-line treatment regimen is established.⁸ A systematic review of second-line chemotherapy for advanced biliary tract cancer that included 761 patients from 14 phase 2 clinical trials and nine retrospective analyses reported a median overall survival of 7.2 months (95% CI 6.2–8.2), a median progression-free survival of 3.2 months (2.7–3.7), and an objective response in 7.7% of patients (4.6–10.9; weighted mean values).⁹ However, the scarcity of phase 3 studies and the large number of retrospective analyses included in this systematic review underline the poor level of evidence available for ascertaining the benefit of second-line treatment for biliary tract cancer.

Combination chemotherapy with cisplatin and gemcitabine is a standard of care for the treatment of advanced biliary tract cancer.⁸ In addition to the potential benefits of combining immunotherapy with chemotherapy from a safety perspective, it has been suggested that chemotherapy might enhance the efficacy of immunotherapy by overcoming immunosuppressive effects of the tumour microenvironment, increasing cross-presentation of tumour antigens, and supporting better penetration of immune cells into the tumour core.²⁹ Cisplatin plus gemcitabine regimens led to a median overall survival of 11.7 months (95% CI 9.5–14.3) in the ABC-02 randomised phase 3 study,⁷ 11.2 months (9.1–12.5) in a randomised phase 2 study in Japan,²³ and 13.4 months and 12.6 months in two recently reported comparative randomised phase 3 studies in chemotherapy-naïve patients with advanced biliary tract cancer.^{30,31} Although cross-study comparisons have many limitations, the longest median overall survival times reported in single-arm phase 2 studies of first-line combination chemotherapy or combination chemotherapy plus targeted therapy in patients with advanced biliary tract cancer are about 15–19 months.³² However, the efficacy of nivolumab plus chemotherapy needs to be compared with chemotherapy alone in randomised controlled trials to assess the contribution of nivolumab to efficacy outcomes in patients with advanced biliary tract cancer.

PD-L1 expression in tumour cells has been associated with increased clinical benefit from nivolumab in some tumour types.^{17,33} More recently, studies of mouse tumour models³⁴ and human tumour samples^{35,36} suggest that PD-L1 expression in tumour-associated immune cells is also associated with response to PD-1 or PD-L1 blockade therapy. In the monotherapy cohort of this study, median overall survival was longer in PD-L1-positive patients than in PD-L1-negative patients, based on PD-L1 expression in both tumour cells and tumour-associated

immune cells, and the one patient who responded was PD-L1 positive in both cell types. These results suggest a possible relationship between PD-L1 expression in tumour or tumour-associated immune cells and response to anti-PD-1 antibody treatment in patients with advanced biliary tract cancer. However, given the exploratory nature of these analyses and the small sample sizes, additional studies are needed to confirm a relationship. Four (17%) of 24 patients with biliary tract cancer achieved a response in the KEYNOTE-28 study of pembrolizumab monotherapy in patients with PD-L1 expression in 1% or more of tumour cells or tumour-infiltrating lymphocytes.³⁷ Because only PD-L1-positive patients were enrolled in the KEYNOTE-28 study, the study does not compare responses between PD-L1-positive patients and PD-L1-negative patients. In the combined therapy cohort of our study, more PD-L1-positive patients than PD-L1-negative patients (tumour cells and tumour-associated immune cells) achieved an objective response, but no clear trends between PD-L1 expression and overall survival were reported, although the small sample sizes need to be taken into consideration. PD-L1 expression might be a useful biomarker for nivolumab monotherapy, but not when nivolumab is combined with chemotherapy, where other factors might affect the efficacy of the treatment regimen. Furthermore, other methods for assessing PD-L1 expression, such as the combined positive score, might better predict benefit from nivolumab monotherapy or nivolumab plus chemotherapy. Our study suggests that limiting enrolment in future studies of nivolumab in advanced biliary tract cancer to patients with PD-L1 expression in 1% or more of tumour-associated immune cells could narrow down the population to a subset of patients with a higher objective response and longer overall survival duration. About 60% of patients in our study had PD-L1 expression in 1% or more of tumour-associated immune cells, suggesting that a large-scale study with enrolment based on PD-L1 expression status is feasible.

Limitations of this study are the non-randomised, single-arm study design and the small sample size for each of the two study cohorts, which are inherent to this phase 1 study design. Given the heterogeneous nature of biliary tract cancer, a possible limitation of the study is the inclusion of patients with different primary tumour locations. For example, the median overall survival of patients with gallbladder cancer has been reported to be shorter than that of patients with other types of biliary tract cancer.³⁸ In this initial assessment of nivolumab in biliary tract cancer, these three types of biliary tract cancer were represented in both the monotherapy and combined therapy cohorts, suggesting that the results were not influenced by a disproportionate inclusion of one type of biliary tract cancer. Future assessment of nivolumab in large randomised studies should take the site of the biliary tract cancer into account in the stratification strategy.

In conclusion, nivolumab was well tolerated, with a manageable safety profile, in this phase 1 study done in Japanese patients with unresectable or recurrent biliary tract cancer. The study results suggest that nivolumab monotherapy might be associated with antitumour activity in previously treated patients, and nivolumab in combination with cisplatin plus gemcitabine chemotherapy might have antitumour activity in chemotherapy-naïve patients. PD-L1 expression status could help to identify patients with advanced biliary tract cancer who are more likely to benefit from nivolumab treatment. Larger randomised studies incorporating biomarker analyses are required to fully elucidate the role of nivolumab in the treatment of advanced biliary tract cancer.

Contributors

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. MU, MI, KK, SA, YN, TO, and JF were involved in the study design. MU, MI, CM, SKob, IO, SKon, NO, TO, and JF were investigators in the study and were involved in the data collection. SA was involved in the data analysis. YN was the medical monitor for the study.

Declaration of interests

MU has received honoraria from Ono Pharmaceutical Co Ltd, AstraZeneca, Eli Lilly, Novartis, Shire, Taiho Pharmaceutical Co Ltd, Teijin Pharma Limited, and Yakult Honsha Co Ltd; has had a consulting or advisory role with Shire; and has received research funding from Ono Pharmaceutical Co Ltd, ASLAN Pharmaceuticals, Daiichi Sankyo Co Ltd, Eisai Co Ltd, Incyte Corporation, Merck Serono, Merck Sharpe and Dohme (MSD), NanoCarrier Co Ltd, Shire, Sumitomo Dainippon Pharma Co Ltd, and Taiho Pharmaceutical Co Ltd. MI has received honoraria from Abbott Japan Co Ltd, Bayer Yakuhin Ltd, Bristol-Myers Squibb (BMS), Daiichi Sankyo Co Ltd, EA Pharma Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, Nobelpharma Co Ltd, Novartis, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma Co Ltd, Taiho Pharmaceutical Co Ltd, Teijin Pharma Limited, and Yakult; has had a consulting or advisory role with Bayer Yakuhin, Ltd, BMS, Daiichi Sankyo Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, Kyowa Hakko Kirin Co Ltd, MSD, NanoCarrier Co Ltd, Novartis, Shire, and Teijin Pharma Limited; and has received research funding from Ono Pharmaceutical Co Ltd, ASLAN Pharmaceuticals, AstraZeneca, Baxalta Japan Ltd, Bayer Yakuhin Ltd, Boehringer Ingelheim, BMS, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, Kowa Company Ltd, Kyowa Hakko Kirin Co Ltd, Merck Serono, NanoCarrier Co Ltd, Novartis, Sumitomo Dainippon Pharma Co Ltd, Taiho Pharmaceutical Co Ltd, Takara Bio, Yakult, and Zeria Pharmaceutical Co Ltd. CM has received honoraria from Eli Lilly, Fujifilm RI Pharma Co Ltd, Nobelpharma Co Ltd, Novartis, Pfizer, Taiho Pharmaceutical Co Ltd, Teijin Pharma Limited, and Yakult Honsha Co Ltd; has had a consulting or advisory role with Novartis, Taiho Pharmaceutical Co Ltd, and Yakult Honsha Co Ltd; and has received research funding from Ono Pharmaceutical Co Ltd, Eisai Co Ltd, Nobelpharma Co Ltd, Pfizer, Taiho Pharmaceutical Co Ltd, and Yakult Honsha Co Ltd. SKob has received honoraria from AstraZeneca, Bayer Yakuhin Ltd, Boston Scientific Japan, Daiichi Sankyo Co Ltd, Kyowa Hakko Kirin Co Ltd, Merck Serono, Nippon Kayaku, Taiho Pharmaceutical Co Ltd, and Teijin Pharma Limited; and has participated in speaker bureaus for Kyowa Hakko Kirin Co Ltd. IO declares no competing interests. SKon has received research funding from ASLAN Pharmaceuticals, AstraZeneca, Bayer, Eli Lilly, MSD, and Pfizer. NO has received honoraria from Ono Pharmaceutical Co Ltd, Eisai Co Ltd, Merck Serono, Takeda Pharmaceutical Company Limited, and Taiho Pharmaceutical Co Ltd; and has received research funding from Ono Pharmaceutical Co Ltd and BMS. KK, SA, and YN are employees of Ono Pharmaceutical Co Ltd. TO has received honoraria from Ono Pharmaceutical Co Ltd, Astellas Pharma Inc, AstraZeneca KK, Baxter, Bayer Yakuhin Ltd, BMS, Celgene KK, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, EA Pharma Co Ltd, Eisai Co Ltd, Eli Lilly

Japan KK, Fujifilm RI Pharma Co Ltd, Merck Serono, MSD KK, Nippon Kayaku, Nipponchemofa, Nobelpharma Co Ltd, Novartis Pharma KK, Pfizer Japan Inc, Shire, Sumitomo Dainippon Pharma Co Ltd, Teijin Pharma Limited, and Yakult Honsha Co Ltd; has had a consulting or advisory role with Ono Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, Eli Lilly Japan KK, NanoCarrier Co Ltd, Nippon Boehringer Ingelheim Co Ltd, Sumitomo Dainippon Pharma Co Ltd, and Zeria Pharmaceutical Co Ltd; and has received research funding from Ono Pharmaceutical Co Ltd, AstraZeneca KK, Baxter, Bayer Yakuhin Ltd, Chugai Pharmaceutical Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, GlaxoSmithKline KK, Kowa Company Ltd, Kyowa Hakko Kirin Co Ltd, Merck Serono, NanoCarrier Co Ltd, Nippon Boehringer Ingelheim Co Ltd, Nobelpharma Co Ltd, Novartis Pharma KK, Pfizer Japan Inc, OncoTherapy Science Inc, Shizuoka Industry, Sumitomo Dainippon Pharma Co Ltd, Takeda Bio Development Center Limited, Yakult Honsha Co Ltd, and Zeria Pharmaceutical Co Ltd. JF has received honoraria from or had a consulting or advisory role with Ono Pharmaceutical Co Ltd, Astellas Pharma Inc, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, EA Pharma Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, Fujifilm RI Pharma Co J-Pharma Co Ltd, Kyowa Hakko Kirin Co Ltd, Mochida Pharmaceutical Co Ltd, Merck Serono, Mitsubishi Tanabe Pharma, MSD, Novartis, Otsuka Pharmaceutical, Pfizer, Sandoz, Sanofi, Sawai Pharmaceutical Co Ltd, Shionogi & Co Ltd, Shire, Sumitomo Dainippon Pharma Co Ltd, Taiho Pharmaceutical Co Ltd, Takeda Pharmaceutical Company Limited, Teijin Pharma Limited, Yakult Honsha Co Ltd, and Zeria Pharmaceutical Co Ltd; and has received research funding from Ono Pharmaceutical Co Ltd, Astellas Pharma Inc, Bayer, BMS, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, Eisai Co Ltd, Eli Lilly Japan KK, Janssen Pharmaceutica, J-Pharma Co Ltd, Kyowa Hakko Kirin Co Ltd, Merck Serono, Mochida Pharmaceutical Co Ltd, MSD, NanoCarrier Co Ltd, Novartis, OncoTherapy Science, Inc, Shionogi & Co Ltd, Sumitomo Dainippon Pharma Co Ltd, Taiho Pharmaceutical Co Ltd, Takeda Pharmaceutical Company Limited, Yakult Honsha Co Ltd, and Zeria Pharmaceutical Co Ltd.

Data sharing

Qualified researchers may request individual patient-level data from clinical studies from Ono Pharmaceutical Co Ltd online from the Clinical Study Data Request website.

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For data requests see <https://clinicalstudydatarequest.com/>

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