



## Clinical trial results:

**A multicenter, open-label, phase 2 study of S-588410 as maintenance monotherapy after first-line platinum-containing chemotherapy in patients with advanced and/or metastatic bladder cancer.**

### Summary

EudraCT number	2013-005274-22
Trial protocol	GB BG
Global end of trial date	02 October 2018

### Results information

Result version number	v2 (current)
This version publication date	30 August 2019
First version publication date	28 July 2019
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Correction on the primary endpoint analysis, patients in the observation group were not part of the analysis.

### Trial information

#### Trial identification

Sponsor protocol code	1408P1921
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Shionogi & Co., Ltd
Sponsor organisation address	3-1-8 Doshomachi, Chuo-ku, Osaka, Japan, 541-0045
Public contact	Corporate Communications Department, Shionogi & Co., Ltd, +81 66209 7885, shionogiclintrial588410@shionogi.com
Scientific contact	Corporate Communications Department, Shionogi & Co., Ltd, +81 66209 7885, shionogiclintrial588410@shionogi.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2017
Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the specific cytotoxic T lymphocyte (CTL) response in human leukocyte antigen (HLA)-A\*24:02 positive patients receiving S-588410 for 12 weeks.

Protection of trial subjects:

Prior to initiation of the study, the sponsor discussed the ethical and scientific validity of the study protocol, sample informed consent form/written information for subjects, and other materials at an Ethics Committee on Clinical Trial of Shionogi.

The study was conducted in compliance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) and the guiding principles of the Declaration of Helsinki; and the Japanese Ordinance on GCP in the study sites in Japan.

To maintain subject privacy, the initials and the assigned numbers of the subjects were used but not their names in case report forms (CRFs), study drug accountability records, study reports, and communications. To verify the data gathered on the CRFs and audit the data collection process, only monitors and auditors pre-assigned by the sponsor, and the regulatory authority(ies) could access to the subject's original medical records. The subject's confidentiality has been maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The independent data monitoring committee (IDMC) was to assess the safety and efficacy data in the study and recommend whether or not to continue the study as necessary. The assessment by the IDMC was to be performed at the time when safety data were collected from the first 6 patients treated with S-588410 for 4 weeks and at the time when the study assessments were completed to all patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Japan: 73
Worldwide total number of subjects	81
EEA total number of subjects	8

Notes:

**Subjects enrolled per age group**

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	48
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter study conducted at 62 sites, including 53 sites in Japan, 5 sites in the United Kingdom, 3 sites in France, and 1 site in Bulgaria.

### Pre-assignment

Screening details:

In the Screening Period of 28 days prior to enrollment, potential patients who provided written informed consent were assessed for their eligibility.

### Pre-assignment period milestones

Number of subjects started	81
Number of subjects completed	81

### Period 1

Period 1 title	Treatment/Observation Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	S-588410 group

Arm description:

HLA-A\*24:02 Positive receiving S-588410

Arm type	Experimental
Investigational medicinal product name	S-588410
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients subcutaneously received 1 mL of S-588410 emulsion (1 mg of each peptide), once weekly for 12 weeks and once every 2 weeks thereafter for up to 24 months.

<b>Arm title</b>	Observation group
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Arm description:

HLA-A\*24:02 Negative not receiving S-588410

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	S-588410 group	Observation group
Started	45	36
Completed	8	4
Not completed	37	32
Consent withdrawn by subject	2	3
Adverse event, non-fatal	2	-
Aggravation of target disease	33	29

## Baseline characteristics

### Reporting groups

Reporting group title	S-588410 group
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Reporting group description:

HLA-A\*24:02 Positive receiving S-588410

Reporting group title	Observation group
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Reporting group description:

HLA-A\*24:02 Negative not receiving S-588410

Reporting group values	S-588410 group	Observation group	Total
Number of subjects	45	36	81
Age categorical			
Units: Subjects			
Adults (18-64 years)	22	9	31
From 65-84 years	21	27	48
85 years and over	2	0	2
Age continuous			
Units: years			
arithmetic mean	66.7	67.4	
standard deviation	± 9.0	± 9.3	-
Gender categorical			
Units: Subjects			
Female	9	10	19
Male	36	26	62

## End points

### End points reporting groups

Reporting group title	S-588410 group
Reporting group description: HLA-A*24:02 Positive receiving S-588410	
Reporting group title	Observation group
Reporting group description: HLA-A*24:02 Negative not receiving S-588410	

### Primary: CTL induction

End point title	CTL induction
End point description: CTL induction in HLA-A*24-02-positive patients receiving S-588410 for 12 weeks	
End point type	Primary
End point timeframe: 12 weeks	

End point values	S-588410 group	Observation group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	36 <sup>[1]</sup>		
Units: patients	42	0		

Notes:

[1] - CTL induction in the observation group was not evaluated

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: One-sided binomial test where the null hypothesis was that the CTL induction rate within 12 weeks was equal to 0.5 or less was performed at a significance level of 0.05.	
Comparison groups	S-588410 group v Observation group
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05 <sup>[2]</sup>
Method	one-sided binomial test
Parameter estimate	Clopper-Pearson
Point estimate	93.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.7
upper limit	98.2

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Notes:

[2] - P-value is determined by one-sided binomial test where the null hypothesis that the CTL induction is equal to 0.5 or less



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from screening (up to 28 days before dosing) up to the end of treatment period (104 weeks) or discontinuation.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Treatment Group
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Reporting group description:

HLA-A\*24:02 Positive receiving S-588410

Reporting group title	Observation Group
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Reporting group description:

HLA-A\*24:02 Negative not receiving S-588410

Serious adverse events	Treatment Group	Observation Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 45 (13.33%)	5 / 36 (13.89%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 45 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 45 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Gait disturbance			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial overgrowth	Additional description: Small intestinal bacterial overgrowth		
subjects affected / exposed	0 / 45 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 45 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			
subjects affected / exposed	0 / 45 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	0 / 45 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 45 (2.22%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment Group	Observation Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)	21 / 36 (58.33%)	
Cardiac disorders			

Hypertension subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	2 / 36 (5.56%) 2	
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 36 (5.56%) 2	
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 36 (5.56%) 2	
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	42 / 45 (93.33%) 47	0 / 36 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 18	0 / 36 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4	2 / 36 (5.56%) 2	
Insomnia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	1 / 36 (2.78%) 1	
Malaise subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 5	0 / 36 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 36 (5.56%) 2	
Blood and lymphatic system disorders Haematuria subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	2 / 36 (5.56%) 3	
Gastrointestinal disorders Vomiting			

subjects affected / exposed	3 / 45 (6.67%)	3 / 36 (8.33%)	
occurrences (all)	5	3	
Constipation			
subjects affected / exposed	3 / 45 (6.67%)	1 / 36 (2.78%)	
occurrences (all)	3	2	
Nausea			
subjects affected / exposed	3 / 45 (6.67%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Abdominal pain			
subjects affected / exposed	0 / 45 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	5	
Gingivitis			
subjects affected / exposed	0 / 45 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Dental caries			
subjects affected / exposed	0 / 45 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	0 / 45 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	6 / 45 (13.33%)	2 / 36 (5.56%)	
occurrences (all)	12	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 45 (8.89%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
Dermatitis contact			
subjects affected / exposed	3 / 45 (6.67%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Pruritus			
subjects affected / exposed	3 / 45 (6.67%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			

Dysuria subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	2 / 36 (5.56%) 2	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	4 / 36 (11.11%) 5	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	4 / 36 (11.11%) 4	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 36 (5.56%) 3	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 36 (8.33%) 4	
Infections and infestations			
Helicobacter infection subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 36 (5.56%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2015	<ul style="list-style-type: none"><li>- Inclusion of the expansion of the term bladder cancer.</li><li>- Update of the inclusion and exclusion criteria.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported