CLINICAL STUDY SUMMARY

PROTOCOL NUMBER PHP-HCC-202

EudraCT No. 2014-001585-98

An International Multi-center Phase 2 Study to Evaluate the Efficacy and Safety of Melphalan Hydrochloride for Injection for use with the Hepatic Delivery System Treatment in Patients with Unresectable Hepatocellular Carcinoma or Intra-hepatic Cholangiocarcinoma

SPONSOR APPROVAL PAGE

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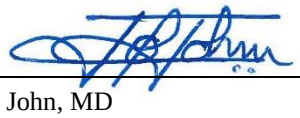

13 Oct 2022

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Date

INTRODUCTION

The purpose of this report is to present the results of study PHP-HCC-202, a Phase 2, multicenter, international study using the Melphalan/Hepatic Delivery System (HDS) to treat patients with unresectable hepatocellular carcinoma (HCC) or intra-hepatic cholangiocarcinoma (ICC).

The study enrolled the first patient 15 Oct 2014 and the last patient was enrolled 05 Jun 2017. Enrollment in the ICC arm was completed 05 Jun 2017 with 12 patients enrolled. Due to insufficient enrollment in the HCC arm, 5 patients, the study was closed prematurely by the Sponsor in October of 2018. The last patient enrolled in the study on 05 Jun 2017 was followed for 10 months after the last dose of study drug. The last date of contact for the survival follow-up period was 24 Sep 2018. The final database lock occurred on 21 Dec 2018.

Melphalan hydrochloride for injection for use with the Hepatic Delivery System (Melphalan/HDS) is a drug/device combination product containing melphalan hydrochloride and the Hepatic Delivery System (HDS). The HDS is used to deliver an intensive local hepatic dose of chemotherapy in which melphalan hydrochloride is delivered intra-arterially to the liver with simultaneous extra-corporeal filtration of the hepatic venous blood return to remove melphalan in the blood before it is returned to the systemic circulation. The procedure by which this is done is known as percutaneous hepatic perfusion (PHP).

Study Rationale

Patients with unresectable HCC or ICC have a poor prognosis. Several loco-regional therapies, such as ablation or embolization are available for these patients, but there are drawbacks associated with them. Generally, there is less information available for the use of these treatments in patients with ICC than HCC.[2]

Percutaneous tumor ablation may be achieved through radiofrequency ablation (RFA), microwave, laser, or cryotherapy, or by the injection of chemicals such as ethanol, acetic acid, or boiling saline. The success of ablation therapies is dependent on the size of the tumor. Necrosis is better achieved in smaller tumors (< 2 cm). Complete necrosis in larger tumors (> 2 to 3 cm) is challenging because of uneven heating (with RFA) due to blood circulation within the tumor, or uneven access (ethanol ablation) due to the presence of intra-tumoral septa. RFA is also associated with a higher rate of adverse reactions such as pleural effusion and peritoneal bleeding. Ethanol ablation requires repeated injections over multiple days. Since ablation therapies also destroy the healthy tissue in the liver, these procedures are limited to being focal treatments and only treat the visible tumor, not the tumorous region; therefore, they are generally available only to patients with a limited number of smaller unresectable tumors. For HCC the recurrence rate after ablation is as high as that seen for resection.[6] The few studies of RFA in patients with ICC have shown less optimal results than findings in patients with HCC.[4]

Transarterial embolization, TACE, radioembolization, and Selective Internal Radiation Therapy (SIRT) represent treatment options for patients ineligible for surgical resection or percutaneous ablation. Although these therapies allow for focal delivery of chemotherapeutic drugs, the drugs cannot be delivered at an escalated dosage level that may be required for an optimal tumor response. These therapies exert their effects partly by cutting off blood supply to the tumor. Furthermore, the treatment is generally applied to specific tumors that can be visualized, and not the entire region of the liver. Multifocal disease involving multiple hepatic lobes is challenging to treat since it may require obstruction of the total hepatic artery blood flow, thus resulting in cutting off blood supply to the healthy liver tissue.[6]

Unlike ablation or embolization therapies that can treat a limited number of visible tumors, Melphalan/HDS, which is designed to perfuse the entire liver with chemotherapeutic agent, permits the treatment of patients with diffuse dominant liver disease (i.e., tumors > 5 cm in diameter and numbering more than 3). More importantly, the procedure does not result in interruption of blood supply to the healthy parts of the liver, thus bypassing the effects of non-target embolization seen in other focal therapies. The direct injection of chemotherapeutic agent into the hepatic artery combined with selective capture and channeling of the venous hepatic flow into a hemofilter prior to its return to the patient allows for the use of high local doses of melphalan while greatly reducing systemic exposure and toxicity. The relatively non-invasive nature of Melphalan/HDS also makes it amenable to be repeated on a regular basis, thus allowing multiple treatments.

In patients with unresectable HCC receiving placebo as evaluated in the randomized sorafenib Phase 3 trials, the time to disease progression was 2.8 months in North America/Europe and 1.4 months in Asia-Pacific. A similarly poor outcome was evident in OS - 7.9 months and 4.2 months for patients in North America/Europe and Asia-Pacific respectively.[7,8] Clearly, the unmet medical need requires an effective new treatment to be included in the armamentarium for the management of a disease representing the third common cause of cancer related death worldwide. The prognosis for patients with cholangiocarcinoma is very poor, with an average 5 year survival rate of 5 to 10%.[1] Similarly, the OS for patients receiving chemotherapy for advanced biliary tract cancer (2197 patients from 82 trials) was 8.2 months.[5]

For HCC, other than sorafenib, no systemic therapy was found to offer a survival benefit over best supportive care as demonstrated by the randomized Phase 3 Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study in North America and Europe, and a similarly designed Phase 3 study in Asia-Pacific.[7,8] In the SHARP study, patients receiving sorafenib had a median time to progression of 5.5 months and OS of 10.7 months. The patients from Asia-Pacific fared worse; the median time to progression was only 2.8 months and OS was 6.8 months. Despite its approval and widespread use as the first line treatment for unresectable HCC, there are challenges and limitations associated with sorafenib. High rates of dermatologic side effects, such as hand-foot skin reaction were reported in the SHARP and Asia-Pacific Phase 3 trials.[7,8] Acute diarrhea has also been described as an early and common side effect of sorafenib treatment.[9] More recently, there have been reports of pancreatic atrophy associated with long-term sorafenib therapy, possibly due to its overall anti angiogenic activity.[10] Resistance to sorafenib despite initial responses has also been reported.[9] Thus, although sorafenib clearly demonstrated survival benefit to HCC patients across geographic regions representing a broad spectrum of disease etiology, substantial toxicities when encountered, often impacted quality of life and led to treatment discontinuation.

Systemic treatment for ICC is limited. Although gemcitabine combined with platinum compounds (especially cisplatin) is current standard therapy,[2,5] its effect on OS seems comparable to other regimens[2,3,4].

There is in vitro evidence to suggest that melphalan is effective in killing HCC cell lines.[11,12] Clinically, melphalan used in IHP to treat isolated liver metastases of primary tumors has been reported to cause partial remission of HCC in a patient with an OS of 14.4 months.[13] However, IHP is invasive and not repeatable. Use of Melphalan/HDS has been reported in different patient populations, including cholangiocarcinoma. The authors reported that in 14 consecutive patients with unresectable hepatic metastases from solid tumors, 1 had cholangiocarcinoma (biliary tract adenocarcinoma) and showed a complete response (CR) to treatment with Melphalan/HDS according to RECIST criteria.[14] In a previous Delcath Phase 2 trial, most of the HCC patients with unresectable disease were able to undergo 3 to 4 Melphalan/HDS treatments, obtaining durable disease control. Their survival appeared longer than anticipated in this disease

population. Only 2 patients with ICC were treated in this study and both withdrew from treatment due to hepatic or extra hepatic disease progression.

This Phase 2 study was designed to evaluate the efficacy and safety of Melphalan/HDS in patients with unresectable HCC or ICC, and to assess the ORR and PFS in these patients. The study was closed by the Sponsor in October of 2018 with 17 patients enrolled, 5 in the HCC arm and 12 in the ICC arm.

ANALYSES

Primary Analysis

- To evaluate the best overall response (BOR) of Melphalan/Hepatic Delivery System (HDS) treatment in patients with unresectable hepatocellular carcinoma (HCC) or intra hepatic cholangiocarcinoma (ICC) confined to the liver.

Secondary Analyses

- To evaluate the safety of melphalan administered by Melphalan/Hepatic Delivery System (HDS)
- To assess overall survival (OS) in patients with unresectable hepatocellular carcinoma (HCC) or intra hepatic cholangiocarcinoma (ICC) confined to the liver.

Methodology

The study had the following phases:

Screening Phase – Screening assessments within 4 weeks of signing informed consent to determine a patient's overall eligibility. These assessments included medical history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), full hematology and biochemistry, radiologic assessments of disease status, and an evaluation of vasculature compatibility for percutaneous hepatic perfusion (PHP).

Melphalan/HDS Phase – Eligible patients received up to 2 Melphalan/HDS treatments. Each treatment cycle had a duration of 6 weeks with an acceptable delay for another 2 weeks before next planned treatment. Tumor response was assessed at the end of Cycle 2. The assessment scan was to be reviewed by an Independent Review Committee. The Melphalan/HDS treatment was terminated in patients with progressive disease (PD) after the 1st treatment and based on safety in patients with > 8 weeks delay of recovery from toxicity irrespective of tumor response. The study endpoint was measured at the conclusion of Melphalan/HDS treatment.

Follow-up Phase – End-of-treatment visit within 30 days following the last Melphalan/HDS treatment. Ongoing adverse events (AEs) at the end-of-treatment were be followed until the severity returned to baseline or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1. Patients were followed for ongoing AEs up to 1 year after the last dose of study treatment until death, consent withdrawal or the patient is lost to follow-up, whichever occurred the earliest.

Clinical and laboratory parameters were obtained to monitor safety and disease status as applicable in all patients. Tumor markers (e.g., α-fetoprotein [AFP]) were monitored; however, disease response or progression was based solely on radiological assessments. Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC was used to evaluate treatment effects on hepatic lesions in patients with HCC and ICC. To evaluate overall treatment effects on intra-hepatic disease and the emergence of extra

hepatic lesions, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was utilized. Safety assessments were performed on all patients at times appropriate to treatment(s) received, including vital signs, complete blood counts, and serum chemistry (including liver function tests [LFTs]). Physical exam, body weight, ECOG PS, and 12-lead electrocardiograms (ECGs) were performed on Day ≤ 14 for screening, Day 1 of each PHP procedure and at the end-of-treatment visit. Echocardiograms (ECHO) were performed on Day ≤ 14 to Day 1 of each Melphalan/HDS cycle. Patients were followed for disease progression. Subsequently, patients were followed every 6 months for the first 2 years and then yearly thereafter for survival status. During the phone call to ascertain survival status, the sponsor will also verify if the Investigator has become aware of the patient developing myelodysplasia or secondary leukemia and document this in the case report form (CRF). Chronic treatment-related toxicities, if any, will also be monitored for up to two years after the last dose of study treatment until death, withdrawal of consent or the patient is lost to follow-up, whichever occurs the earliest. Tumor-related symptoms were assessed at every clinical visit. Tumor response was assessed in both HCC and ICC cohorts every 12 weeks (+/- 2 weeks) until hepatic disease progression.

Test Product, Dose and Mode of Administration, Duration of Treatment

Patients received up to 2 treatments of melphalan 3.0 mg/kg IBW administered by PHP using the HDS. Five (5) patients received 1 cycle of treatment and 12 patients received 2 cycles of treatment.

CRITERIA FOR EVALUATION

Efficacy Outcome Measures

Measures of tumor response were conducted by the investigators. Best Overall Response (BOR), occurring after study treatment as determined by the investigator, was measured using mRECIST to assess hepatic response and progression, and RECIST version 1.1 to assess overall (hepatic and extra-hepatic) response and progression.

Safety Outcome Measures

Safety was assessed by the investigator according to the ICH guideline for GCP. Adverse events included any new or worsening unfavorable and unintended sign, (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, as well the development of an AE that resulted from any protocol-mandated intervention, including those that occurred prior to assignment of study treatment (e.g., invasive screening procedures such as biopsies). Safety was assessed by monitoring AEs and serious adverse events (SAEs); the association with study treatment was assessed, and severity was graded using CTCAE v.4.03.

Hematology, biochemistry, vital signs, including temperature, systolic and diastolic blood pressure, heart rate, respiratory rate and mean arterial pressure (MAP), electrocardiograms (ECGs) and echocardiograms (ECHOs) were evaluated as part of the safety assessments at specified time points in the protocol.

SUMMARY OF RESULTS

Patient Disposition and Demographics/Baseline Characteristics

A total of 17 patients were treated in the study (see Table 1). Of these, 5 received 1 cycle of treatment and 12 received 2 cycles of treatment.

One patient with ICC stopped treatment due to an adverse event. Three patients discontinued for disease progression. One patient was discontinued for both progressive disease and adverse event. For 3 patients, the investigator decided to discontinue the patient from the study (see Table 2).

Table 1: Patient Demographics, Baseline Characteristics, Number of Treatment Cycles

Parameter	Statistics or Category	Overall (N=17)	Hepatocellular Carcinoma (HCC) (N=5)	Intra-hepatic Cholangiocarcinoma (ICC) (N=12)
Age (Years)	n	17	5	12
	Mean (SD)	59.6 (10.15)	63.6 (6.95)	58.0 (11.06)
	Median	61.0	66.0	60.0
	Min, Max	36.0, 75.0	55.0, 72.0	36.0, 75.0
Sex	Female	10 (58.8%)	0	10 (83.3%)
	Male	7 (41.2%)	5 (100.0%)	2 (16.7%)
Height (cm)	n	17	5	12
	Mean (SD)	169.8 (10.34)	178.6 (5.90)	166.2 (9.66)
	Median	169.0	175.0	165.5
	Min, Max	156.0, 190.0	174.0, 186.0	156.0, 190.0
Weight (kg)	n	17	5	12
	Mean (SD)	73.9 (15.55)	86.2 (5.22)	68.8 (15.65)
	Median	77.0	86.0	64.0
	Min, Max	52.0, 98.0	80.0, 94.0	52.0, 98.0
BMI(kg/m2)	n	17	5	12
	Mean (SD)	25.5 (4.64)	27.1 (2.71)	24.9 (5.21)
	Median	24.9	26.4	24.0
	Min, Max	18.6, 36.2	24.6, 31.0	18.6, 36.2
No. of Treatment Cycles	1	5 (29.4%)	2 (40.0%)	3 (25.0%)
	2	12 (70.6%)	3 (60.0%)	9 (75.0%)

Table 2: Patient Disposition

Parameter	Statistics or Category	Overall (N=17)	Hepatocellular Carcinoma (HCC) (N=5)	Intra-hepatic Cholangiocarcinoma (ICC) (N=12)
Reason for Early Treatment Termination or Early Observation Termination	Adverse event	1 (5.9%)	0	1 (8.3%)
	Death	2 (11.8%)	0	2 (16.7%)
	Disease Progression	3 (17.6%)	0	3 (25.0%)
	Disease Progression, Adverse event	1 (5.9%)	1 (20.0%)	0
	Investigator's Decision	3 (17.6%)	1 (20.0%)	2 (16.7%)

Efficacy

End of treatment best overall response (BOR) was evaluated by the investigator in 15 out of 17 patients (see Table 4). In 2 patients, there was no assessment of BOR by the investigator. Two (2) patients with ICC experienced a complete response (CR). In the patients who experienced CR, one was unconfirmed utilizing mRECIST and the second patient experienced a confirmed CR by mRECIST. One (1) patient with HCC was classified by the investigator as a PR. There were 8 patients who experienced stable disease (SD): 2 HCC patients and 6 ICC patients. Four (4) patients were evaluated as having a BOR of progressive disease (PD), 2 in each treatment group.

In 2 patients, the investigator did not complete the response assessment in the case report form.

Survival

Patients had an end-of-treatment visit 6 to 8 weeks following the last Melphalan/HDS treatment. All patients were followed for disease status and chronic toxicity approximately every 12 weeks for up to 2 years after the last dose of study treatment until death, consent withdrawal or the patient was lost to follow-up, whichever occurred the earliest.

The last available date of information was used to document a patient's survival status. This was the date of death if a patient died and the date of death was known, or the date of disease progression if the patient died and the date of death was unknown, or the date of last follow-up if the patient was alive. In 3 patients, the actual date of death was unknown. At the completion of the study, 11 patients had died and 6 were alive (see Table 3).

Table 3: Patient Final Status

Parameter	Statistics or Category	Overall (N=17)	Hepatocellular Carcinoma (HCC) (N=5)	Intra-hepatic Cholangiocarcinoma (ICC) (N=12)
Patient Final Status	Alive	6 (35.3%)	1 (20.0%)	5 (41.7%)
	Dead	11 (64.7%)	4 (80.0%)	7 (58.3%)
End of Study Outcome	Death	2 (11.8%)	1 (20.0%)	1 (8.3%)
	Disease Progression, Alive	6 (35.3%)	1 (20.0%)	5 (41.7%)
	Disease Progression, Death	9 (52.9%)	3 (60.0%)	6 (50.0%)

[1] Treatment cycle 2 related summaries were based on those received 2nd treatment cycle.

Safety

Adverse events are reported as treatment emergent adverse events (TEAE), defined as all adverse events with a start date on or after Treatment Cycle 1 procedure date and up to 30 days after the last treatment date. The last treatment date was defined as Cycle 1 procedure date if a patient only had 1 treatment cycle or the treatment Cycle 2 date if the patient received both cycles of treatment.

A total of 231 adverse events were reported during the study. Nineteen (19) of those events were not considered TEAEs having occurred prior to the start date of study treatment (9) or occurring >30 days after the completion of treatment (10). Two hundred twelve (212) adverse events were considered TEAEs.

The most common TEAEs reported during the study were events related to myelosuppression (59), including leukopenia, thrombocytopenia, neutropenia, and anemia, in 12/17 (70.6%) patients, followed by gastrointestinal disorders (40) including GERD, abdominal pain, and nausea, in 12/17 (70.6%) patients. A summary of all TEAEs considered to be possibly, probably, or definitely related to the study drug can be found in Table 7. Myelosuppresive events of Grades 3 and 4 were reported in 11 (64.7%) patients. A total of 6 treatment-emergent SAEs were reported in 4 patients.

A summary of treatment emergent SAEs can be found in Table 8.

Inclusion Criteria
Patients with HCC

Patients with HCC were required to meet all of the following criteria for study entry:

1 HCC diagnosed by tissue or imaging study.
2 Unresectable HCC without clinically significant extra-hepatic disease (minor lesions [≤ 1 cm and not consistent with metastatic disease] acceptable) based on CT.
3 At least one target lesion based on mRECIST. In patients with prior loco-regional therapy, the target lesion(s) must be located in area(s) outside previous treatment or must have progressed after prior treatment if located within previous treatment field.
4 Child-Pugh Class A.
5 ECOG PS 0-1.

6 No prior radiation therapy to the liver including Y^{90}-, I^{131}-based loco-regional therapy. Prior loco-regional therapy, including resection, based on other technology for HCC, if any, must have been completed at least 4 weeks prior to baseline imaging.
7 Age ≥ 18 years.
8 Signed informed consent.

Patients with ICC

Patients with ICC were required to meet all of the following criteria for study entry:

1 ICC diagnosed by tissue or imaging study.
2 Unresectable ICC without clinically significant extra-hepatic disease (minor lesions [≤ 1 cm and not consistent with metastatic disease] acceptable) based on CT.
3 At least one target lesion based on mRECIST. In patients with prior loco-regional therapy, the target lesion(s) must be located in area(s) outside previous treatment or must have progressed after prior treatment if located within previous treatment field.
4 Child-Pugh Class A.
5 ECOG PS 0-1.
6 No prior radiation therapy to the liver including Y^{90}-, I^{131}-based loco-regional therapy. Prior loco-regional therapy, including resection, based on other technology for ICC, if any, must have been completed at least 4 weeks prior to baseline imaging.
7 Age ≥ 18 years.
8 Signed informed consent.

Exclusion Criteria
Patients with HCC

For the HCC cohort, patients for whom transplantation, RFA, TACE, or systemic treatment with sorafenib are better therapeutic options are to be excluded from study entry.

Patients with HCC or ICC

For both the HCC and ICC cohorts, patients who meet any of following criteria were excluded from the study:

1 Greater than 50% tumor burden in the liver by imaging.
2 History of orthotopic liver transplantation, hepatic vasculature incompatible with perfusion, hepatofugal flow in portal vein or known unresolved venous shunting. Prior Whipple procedure is permitted provided the anatomy is still compatible for perfusion with the Melphalan/HDS system.
3 Evidence of ascites on imaging study, or the use of diuretics for ascites.
4 Clinically significant encephalopathy.
5 History of, or known hypersensitivity to any components of melphalan or the components of the Melphalan/HDS.
6 Known hypersensitivity to heparin or the presence of heparin-induced thrombocytopenia.
7 Received an investigational agent for any indication within 30 days prior to first treatment.
8 Not recovered from side effects of prior therapy to ≤ Grade 1 (according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03). Certain side effects

that are unlikely to develop into serious or life-threatening events (e.g., alopecia) are allowed at > Grade 1.

9 Those with New York Heart Association functional classification II, III or IV; active cardiac conditions including unstable coronary syndromes (unstable or severe angina, recent myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias and severe valvular disease must be evaluated for risks of undergoing general anesthesia.

10 History or evidence of clinically significant pulmonary disease that precludes the use of general anesthesia.

11 Uncontrolled diabetes mellitus, hypothyroidism, or hyperthyroidism.

12 Active infection, including Hepatitis B and Hepatitis C infection. Patients with anti-hepatitis B core antigen (HBc) positive, or hepatitis B surface antigen (HBsAg) but viral deoxyribonucleic acid (DNA) negative are exception(s).

13 History of bleeding disorders.

14 Brain lesions with a propensity to bleed.

15 Known varices at risk of bleeding, including medium or large esophageal or gastric varices or active peptic ulcer.

16 Previous malignancy within 3 years prior to enrollment, except for curatively-treated basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, bladder carcinoma *in situ* or breast cancer *in situ*.

17 Inadequate hematologic function as evidenced by any of the following:
   a) Platelets < 90,000/µL
   b) Hemoglobin < 8 g/dL, independent of transfusion or growth factor support
   c) Neutrophils < 1,500 cells/µL.

18 Serum creatinine > 1.5 mg/dL.

19 Inadequate liver function as evidenced by any of the following:
   a) Total serum bilirubin ≥ 2.0 mg/dL
   b) Prothrombin time (PT)/INR > 1.5
   c) AST > 10 times the upper limit of normal (ULN) or ALT > 5 times ULN
   d) Serum albumin < 3.0 g/dL.

20 Known alcohol abuse.

21 For female subjects of childbearing potential (i.e., having had a menstrual period within the past 12 months): a positive serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) within 7 days prior to enrollment; or unwilling or unable to undergo hormonal suppression to avoid menstruation during treatment. Women who are breastfeeding and are unwilling or unable to stop breastfeeding while on study treatment.

22 Sexually active females of childbearing potential and sexually active males with partners of reproductive potential: unwilling or unable to use appropriate contraception from screening until at least 30 days after last administration of study treatment.

Patients and Treatments

From 5 Nov 2014 through 3 Jul 2017 Melphalan/HDS treatment was administered to 17 (10 female and 7 male) patients, 5 with HCC and 12 with ICC. Patients age ranged from 36 years to 75 years (mean ± SD age 60 ± 10.2 years). Five (5) patients received one cycle and 12 received two cycles of treatment. The overall baseline mean ± SD height and weight were 169.8 ± 10.3 cm and 73.9 ± 15.5 kg respectively, with a mean ± SD body mass index (BMI) of 25.5 ± 4.64 kg/m^2.

Of the 5 patients who had one cycle of treatment, reasons for not receiving the second cycle of treatment included adverse event (1 patient), adverse event and disease progression (1 patient), and investigator's decision (3 patients). Of the 12 patients who had two cycles of treatment, 7 patients completed the initial 6-weeks post treatment observation period (i.e., completed the study) and entered long-term follow-up; 5 patients did not complete the post-treatment observation period: 2 patients died, and 3 patients' disease progressed.

All patients are included in the safety summary and efficacy evaluations. All patients were followed for overall survival until study closure in October 2018.

A summary of demographics and patient disposition can be found in Tables 1 and 2.

Best Overall Response

End of treatment Best overall response (BOR) was evaluated by the investigator in 15 of 17 patients (see Table 4). Two (2) patients with ICC experienced a complete response (CR): one was unconfirmed utilizing mRECIST and the second patient experienced a confirmed CR by mRECIST. One (1) patient with HCC was classified by the investigator as a partial response (PR). There were 8 patients who experienced stable disease (SD): 2 HCC patients and 6 ICC patients. Four (4) patients were evaluated as having a BOR of progressive disease (PD), 2 in each patient group. In 2 patients, the end of treatment response assessment was Not Done: 1 patient died (02-AAA-005) and another (01-AAA-002) did not complete end of treatment due to disease progression.

Table 4: Summary of End of Treatment Overall Best Response

Statistics or Category	Overall (N=17)	Hepatocellular Carcinoma (HCC) (N=5)	Intra-hepatic Cholangiocarcinoma (ICC) (N=12)
1. CR (complete response)	2 (11.8%)	0	2 (16.7%)
2. PR (partial response)	1 (5.9%)	1 (20.0%)	0
3. SD (stable disease)	8 (47.1%)	2 (40.0%)	6 (50.0%)
4. PD (progressive disease)	4 (23.5%)	2 (40.0%)	2 (16.7%)
9. Not Done	2 (11.8%)	0	2 (16.7%)

Overall Survival

At the time of study closure in October 2018, 6 of 17 treated patients were alive although all had documented disease progression. The longest follow-up period was 1167 days (patient 02-AAA-03), and the shortest follow-up period was 297 days (04-BAI-004). Five (5) of the 6 patients had 2 cycles of treatment and all 5 had ICC. Two (2) patients' last follow-up date was more than 1 year prior to study closure in October 2018. Table 5 provides a summary of the surviving patients at study closure.

The overall survival Kaplan-Meier analysis is provided in Table 6. The median survival days ± 95% confidence intervals were 621 ± (250 to 1167) days.

Table 5: Summary of Tumor Type, Treatment, and Follow-up Period in Alive Patients

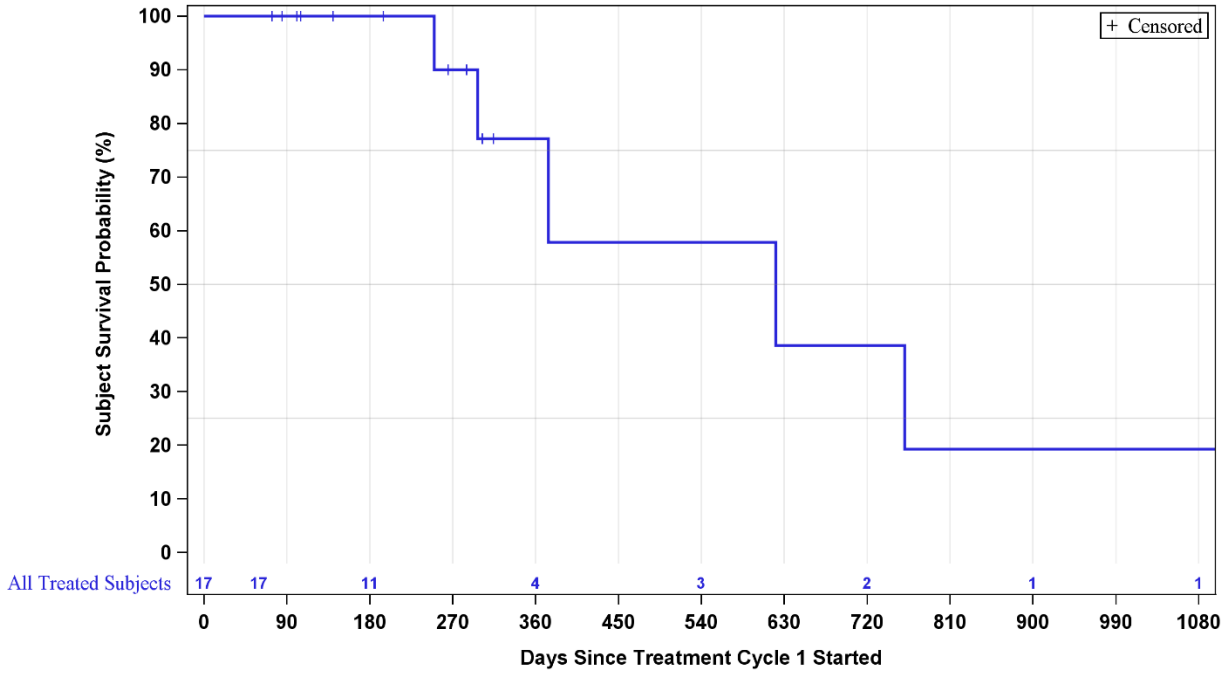
Patient ID	Tumor Type	Number of Treatment Cycles	Date of Treatment Initiation	Date of Last Follow-up	Days Survived
02-AAA-003	HCC	1	13-Jul-2015	21-Sep-2018	1167
02-AAA-009	ICC	2	25-Aug-2016	24-Sep-2018	761
04-BAI-004	ICC	2	4-May-2017	24-Feb-2018	297
04-BE-EL-002	ICC	2	8-Sep-2016	15-May-2017	250
04-BR-FR-003	ICC	2	20-Sep-2016	28-Sep-2017	374
04-DU-RI-001	ICC	2	16-Jun-2016	26-Feb-2018	621

Table 6: Summary of Overall Survival Based on Kaplan-Meier Analysis

Statistics [1]	All Treated Subjects (N=17)
Subjects Survived (%)	6 (35.3%)
Subjects Died (%)	11 (64.7%)
25% tile KM Estimate (95% CI) (Days Survived) [1]	374.0 (250.0, 621.0)
50% tile KM Estimate (95% CI) (Days Survived) [1]	621.0 (250.0, 1167.0)
75% tile KM Estimate (95% CI) (Days Survived) [1]	761.0 (374.0, 1167.0)
KM Estimate Mean (SE) (Days Survived)	626.9 (140.88)

[1] Days survived after treatment cycle 1 started was estimated using Kaplan-Meier product limit method.

Figure 1 Kaplan-Meier Overall Survival Curve – All Treated Patients



Safety Evaluation

The reporting period for safety data was from the initiation of the first dose of Melphalan/HDS until 90 days after the last dose was received. Safety evaluation included analysis of treatment emergent adverse events; and review of graphic profiles of 10 safety laboratory tests of interest.

The Medical Dictionary for Regulatory Activities (Version 21.1) was used to classify all AEs with respect to system organ class and preferred term. However, a few events had partial or missing onset dates; those events were included as TEAEs for the purpose of safety evaluation. Incidence of TEAEs was tabulated for all TEAEs and for serious TEAEs; the summaries provide the overall incidence, incidence by severity and by relationship.

The selected 10 safety laboratory tests of interest included:

1) Hematology tests: Hematocrit, Hemoglobin, Eosinophil, Neutrophil, and Platelets

2) Liver function tests: Albumin, ALT, AST, Direct bilirubin, and Creatinine

Adverse Events

Adverse events are reported as treatment emergent adverse events (TEAE), defined as all adverse events with a start date on or after Treatment Cycle 1 procedure date and up to 30 days after the last treatment date. The last treatment date was defined as Cycle 1 procedure date if a patient only had 1 treatment cycle, if the patient had 2 treatment cycles, the Cycle 2 procedure date was the last treatment date.

The final adverse event dataset included a total of 231 adverse events. Adverse event onset dates were compared with the treatment start date and last treatment date to determine whether they would be included as TEAEs. There were 19 events that were not considered treatment emergent adverse events (TEAE) and these events were excluded from the TEAE summaries, they can however, be found in the individual adverse event data listing:

- 9 events had a start date prior to the start date of the Cycle 1 procedure date
- 10 events had a start date that was > 30 days after the last treatment (ranging from 37-95 days)
- 3 of the 19 events were SAEs, in patients:
    - 02-AAA-006 (AE #23 which the investigator considered as related to the disease)
    - 02-AAA-008 (AE #11 which the investigator considered as related to the procedure, and AE #16 which the investigator considered to have no causal relationship)
- 02-AAA-008 (AE #18) was rated by the investigator as probably related to study drug (>30 days post drug administration)

A total of 212 adverse events were considered TEAEs. Five (5) events are included in the TEAE summary but are excluded from the summary by onset date due to missing start dates:

- 1 adverse event for subject 02-AAA-006 (AE #17) had missing start and stop dates
- 4 adverse events, 3 for subject 02-AAA-05 (AE #11,12,13) and 1 for subject 02-AAA-10 (AE#1) had a missing start date, but the stop date was present.

TEAEs Relative to Treatment Cycles

The cycle 1 procedure was compared with the AE start date and a relative day (AE start date – Cycle 1 procedure date +1) was calculated, hence day 1 = treatment Cycle 1 procedure day. The post procedure period was divided into 2 periods:

- If the relative day is day 1, 2, 3, or 4 then the AE is considered a peri-procedure event for Cycle 1.
- If the relative day is ≥5, then the AE is considered a post-procedure event for Cycle 1.

If a patient received 2 cycles of treatment, the start date was compared to the Cycle 1 procedure date and Cycle 2 procedure date, hence relative days were derived for each AE naming relative Day 1 (per Cycle 1 procedure date) and relative Day 2 (per Cycle 2 procedure date):

- If the relative Daye 1 is Day 1,2, 3 or 4 then the AE is considered a peri-procedure event for Cycle 1.
- If the relative Day 1 is ≥5 and the relative Day 2 is <1 (AE start date is before Cycle 2 procedure date) then the AE is a post-procedure Cycle 1 event.
- If the relative Day 2 is Day 1, 2, 3 or 4 then the AE is a peri-procedure events for Cycle 2.
- If the relative Day 2 is ≥5 then the AE is a post-procedure event for Cycle 2.

Study Drug Relatedness

Investigators were asked to determine whether each adverse event was related to the device, the procedure, the disease, the drug, or none using the following categories: Definitely, Probably, Possibly, Unlikely, or Definitely Not. Events categorized as Definitely, Probably or Possibly were grouped and considered as "Related" Events categorized as Unlikely or Definitely Not were considered as "Not Related.

- One site (Site 01) had an earlier version of the adverse event form which did not include an event relatedness assessment (Definitely, Probably, Possibly, Unlikely, or Definitely Not). These events only had information on whether the event causal relationship was related to the device, procedure, disease, drug, or none.
- A total of 36 events were missing the relatedness assessment and are excluded from the "related" event summaries.
- 15 adverse events were checked for procedure
- 11 adverse events were checked for drug (2 were also checked for procedure)
- 16 adverse events were checked for disease (4 were also checked for procedure or drug)

Treatment Emergent Adverse Event Summaries

Treatment emergent adverse events (TEAEs) were presented in the following table format:

- The summary table included the system organ class (SOC), preferred term (PT) and Onset Phase (peri- or post-procedure)
    - The table included
        - Number (%) of patient with ≥1 incidence within a SOC
        - Number (%) of patients reporting a specific adverse event by PT

- The table also included the total number of events. If a subject had an event more than once (same PT), the patient was counted only once when determining the event rate; all events are included in the total number of events
- The event rate and total number of events were displayed for overall (study) and by onset phase (peri- versus post-procedure)
- 5 events with a missing start date were excluded from the onset phase summary

Summary of Treatment Emergent Adverse Events

Adverse events of any grade were reported in 17 of 17 patients (100%) and investigator-assessed treatment-related adverse events were noted in 16 of 17 patients (94.1%) (see Table 7). The most common drug-related adverse events were blood and lymphatic systems disorders/investigations (myelosuppression) and gastrointestinal disorders. Treatment-related grade 3 or 4 TEAEs were noted in 11 of 17 patients (64.7%). The most common TEAEs observed in the study (see Table 7) were events related to myelosuppression categorized in blood and lymphatic system disorders and investigations reported in 13 of 17 patients (11 in blood and lymphatic disorders and 2 in investigations) for a total of 63 events. Gastrointestinal disorders were reported in 12 patients with the most common events being those related to abdominal discomfort, pain, and nausea. There were 6 patients who experienced decreased appetite. A summary of all TEAEs in all treated patients can be found in Table 7.

Table 7: Summary of all TEAEs

	In Study (N=17)		Peri-Procedure (N=17)		Post-Procedure (N=17)	
System Organ Class Preferred Term (MedDRA 21.1)	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Subjects with >=1 TEAE	17 (100.0)	212	16 (94.1)	75	17 (100.0)	132
Blood and lymphatic system disorders	11 (64.7)	59	5 (29.4)	19	11 (64.7)	40
Anemia	6 (35.3)	17	5 (29.4)	9	5 (29.4)	8
Leukopenia	6 (35.3)	10	0		6 (35.3)	10
Neutropenia	7 (41.2)	11	0		7 (41.2)	11
Thrombocytopenia	6 (35.3)	21	4 (23.5)	10	6 (35.3)	11
Investigations	4 (23.5)	12	2 (11.8)	4	2 (11.8)	8
Platelet count decreased	1 (5.9)	3	0		1 (5.9)	3
White blood cell count decreased	2 (11.8)	4	0		2 (11.8)	4
Gastrointestinal disorders	12 (70.6)	40	8 (47.1)	12	11 (64.7)	26
Abdominal discomfort	1 (5.9)	1	0		1 (5.9)	1
Abdominal distension	2 (11.8)	2	1 (5.9)	1	1 (5.9)	1
Abdominal pain	6 (35.3)	8	3 (17.6)	3	4 (23.5)	5
Abdominal pain upper	4 (23.5)	5	1 (5.9)	1	4 (23.5)	4
Nausea	7 (41.2)	10	3 (17.6)	3	6 (35.3)	7
Metabolism and nutrition disorders	9 (52.9)	11	5 (29.4)	6	5 (29.4)	5
Decreased appetite	6 (35.3)	6	2 (11.8)	2	4 (23.5)	4

Serious Adverse Events

A total of 6 treatment-emergent SAEs were reported in 4 patients. One (1) patient with ICC (02-AAA-010) experienced an SAE of embolism in the cycle 1 peri-operative period. He was treated and the embolism resolved. This event was considered related to the procedure by the investigator. One (1) patient with HCC

(01-AAA-001) experienced 2 study drug related myelosuppressive events: neutropenia and thrombocytopenia. He was hospitalized and treated with neupogen/neulasta and platelet transfusions and the events resolved. One (1) patient with ICC (02-AAA-008) developed hepatic necrosis and acute liver failure post procedure. The patient was treated and study drug treatment was discontinued. This event was considered by the investigator as related to the procedure and possibly related to study drug. This patient also experienced pneumonia which was considered possibly related to the procedure by the investigator. One (1) patient with ICC (02-AAA-005) developed erosive duodenitis and gastritis post procedure. No causal relationship to the study was provided by the investigator.

There were 3 serious adverse events from 2 patients that were classified as not TEAEs:

- Patient 02-AAA-006 with ICC developed severe ascites 37 days after cycle 2 of treatment (82 days after cycle 1 treatment). The investigator considered the event as serious and as probably related to her underlying disease. She was treated with medication and the ascites resolved.
- Patient 02-AAA-008 with ICC developed acute hepatic failure 68 days after treatment; this patient died of pneumonia 95 days after treatment (the patient had 1 cycle of treatment). The investigator considered the event of acute hepatic failure as not related but the event of pneumonia as possibly related to the procedure.

Table 8: Summary of all Serious TEAEs

	In Study (N=17)		Peri-Procedure (N=17)		Post-Procedure (N=17)	
System Organ Class Preferred Term (MedDRA 21.1)	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)	Events
Subjects with >=1 TEAE	4 (23.5)	6	1 (5.9)	1	2 (11.8)	3
Gastrointestinal disorders	1 (5.9)	2	0		0	
Erosive duodenitis	1 (5.9)	1	0		0	
Gastritis erosive	1 (5.9)	1	0		0	
Hepatobiliary disorders	1 (5.9)	1	0		1 (5.9)	1
Hepatic necrosis	1 (5.9)	1	0		1 (5.9)	1
Investigations	1 (5.9)	2	0		1 (5.9)	2
Platelet count decreased	1 (5.9)	1	0		1 (5.9)	1
White blood cell count decreased	1 (5.9)	1	0		1 (5.9)	1
Vascular disorders	1 (5.9)	1	1 (5.9)	1	0	
Embolism	1 (5.9)	1	1 (5.9)	1	0	

Conclusion

The trial included 17 patients with HCC or ICC. Patients received up to two treatments with Melphalan/HDS in four centers in Europe.

The best overall response (BOR) showed that two patients (11.8%) had a complete response (CR) and one patient (5.9%) had a partial response (PR). There were eight patients (47.1%) who had stable disease (SD) as BOR.

For the ICC component of 12 patients, the best overall response (BOR) showed that two patients (16.7%) had a CR, no patients (0%) had a PR, and 6 patients (50%) had SD. There were two patients (16.7%) who had progressive disease (PD) and two patients (16.7%) for whom an end of treatment BOR assessment was not done.

At the time of study closure, 6 patients remained alive and 11 had died. The KM mean estimate of overall survival (OS) was 626.9 days survived (SE: 140.88).

Adverse events in the study were evaluated by CTCAE grading, with the majority of treatment-emergent adverse events (TEAEs) relating to myelosuppression. In the 29 cycles performed during the trial, there were only 6 treatment-emergent serious adverse events that occurred in 4 patients. In the majority of cases, TEAEs were transient in nature and manageable.

Melphalan/HDS is an option for the treatment of patients with unresectable ICC. As the full component of the HCC arm in this study was not enrolled, additional treatment and evaluation of HCC patients will be required to make an overall assessment of the efficacy and safety of Melphalan/HDS in this indication.

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