3. SYNOPSIS

Name of Sponsor: AIO-Studien-gGmbH

Name of Finished Product/Active Ingredient: Bintrafusp alfa
Name of Manufacturer: Merck Healthcare KGaA

Title of Study: **Neoadjuvant Bintrafusp alfa in patients with resectable biliary tract cancer**

Coordinating Investigator: Prof. Dr. Oliver Waidmann, Universitätsklinikum Frankfurt

Study centers:
Three study sites were initiated in Germany, two of which enrolled patients into the study.

Publication: n/a

Studied period	**Phase of development**: II
First Patient In: 08-Jul-2021 Recruitment halted due to Sponsor decision: 29-Sep-2021 Study termination: 05-Jan-2022	

Primary Objective: To explore the efficacy of preoperative Bintrafusp alfa (M7824, MSB0011359C) in inducing a major pathological response in biliary tract cancer patients

Secondary Objectives:
Secondary objectives were exploratory, and included accumulation of further feasibility data (i.e., safety data, additional efficacy data) as well as a translational research part investigating changes in a subjects' immune activation determined by blood tests and tissue analysis before and after treatment with Bintrafusp alfa

Single arm, multi-center, open-label, therapeutic exploratory

Number of patients

Planned: 24

Enrolled: 3

Diagnosis: Treatment-naïve, resectable biliary tract cancer, confirmed by histopathology
Main criteria for inclusion:

- Adult patients (≥ 18 years of age)
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Resectable biliary tract cancer, confirmed by histopathology, limited to the liver assessed by an interdisciplinary tumor board involving a hepatobiliary surgeon; No prior systemic therapy
- Normal organ and bone marrow function
- Subject willing and able to comply with the protocol and written informed consent granted

Test product, dose and mode of administration, batch number:
Bintrafusp alfa at 1200 mg q2w for two cycles from batch BF73705.

Duration of treatment:
Subject participation consisted of two treatment cycles which were administered q2w, followed by surgery and an EoT visit six weeks post surgery.
Safety follow-up was until 90 days post surgery.

Reference therapy, dose and mode of administration, batch number: N/A

ENDPOINTS
Efficacy:
Primary endpoint: Major Pathologic Response measured in the surgically resected tumor
Secondary endpoints:

- Tumor response according to RECIST1.1
- Rate of resectability

Safety:

- Adverse events according to CTCAE V5
- Adverse events of special interest (postoperative wound infections, impaired wound healing, wound dehiscence, prolongation of post-op hospitalization beyond 14 days)

Statistical methods:

The study was terminated prematurely with only 3 patients enrolled. No statistical methods were used. Results are only reported descriptively.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:
The study was terminated prematurely with only 3 of 24 patients enrolled following the discontinuation of the phase 2/3 trial INTR@PID BTC 055 by the manufacturer of bintrafusp alfa, Merck. This trial investigated bintrafusp alfa in frontline treatment of patients with locally advanced or metastatic biliary tract cancer, and the trial's IDMC concluded that the trial was unlikely to achieve its primary objective of overall survival. This development, as well as additional clinical data, led to the joint decision by the Sponsor and the Coordinating Investigator to halt study recruitment after enrollment of three patients. All patients had finished study treatment at this point.
All subjects were male Caucasians, ranging in age between 57 and 76 and had a diagnosis of histologically confirmed resectable biliary tract cancer and an ECOG of 0 (two patients) or 1 (one patient). All subjects received study treatment as per protocol and subsequently underwent tumor surgery. Central review analysis of the resected tumor samples for the primary endpoint resulted in Becker grade 3 for all three samples, corresponding to > 50% residual tumor/tumor bed. The result for the secondary efficacy endpoint of tumor response according to RECIST 1.1 is 'stable disease' for all three subjects. Resectability rate was 100%.

SAFETY RESULTS:
Each patient was affected by 2 adverse events. Three of the total of 6 adverse events were serious. Two adverse events were assessed as causally related to study treatment; their maximum severity grade was reported as 1.
Two of the SAEs were of severity grade 3 and were reported as recovered/resolved within 8 days of occurrence.
One SAE, a case of myocardial infarction, which occurred in a 76-year old male patient three days after tumor resection, was fatal.
The following table gives a summary of all adverse events:

System organ class (SOC) Preferred term (PT)	**AEs**	**SAEs**
Cardiac disorders	**1**	**1**
Myocardial infarction	1	1
Gastrointestinal disorders	**2**	**1**
Nausea	1	0
Pancreatic fistula	1	1
General disorders and administration site conditions	**1**	**0**
Fatigue	1	0
Hepatobiliary disorders	**1**	**1**
Cholangitis	1	1
Respiratory, thoracic and mediastinal disorders	**1**	**0**
Epistaxis	1	0
SUM	**6**	**3**

CONCLUSION:
While the treated patient cohort is small, strongly limiting the significance of the observations, no promising efficacy signals were detected. Tumors of all three subjects were stable according to RECIST 1.1 criteria and maintained resectability during study treatment, but no response according to RECIST or to Becker criteria was observed. Therefore, no manifestation of the desired effect of improving tumor resectability is conceivable.
Safety results are inconspicuous, but, like the efficacy results, the generated data set is too small for any meaningful conclusion.

This report is based on the only approved protocol version V3.0 dated 03-May-2021.

Date of the report: 07-July-2022