A PHASE I/II STUDY WITH BM7PE IMMUNOTOXIN IN COLORECTAL CANCER PATIENTS WITH METASTATIC DISEASE WHO ARE REFRACTORY TO OR WITH INTOLERANCE TO LAST LINE OF STANDARD CHEMOTHERAPY

Protocol Identification Number: BM7PE

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Protocol ID no:	BM7PE-study

I. Sponsor signatory approval

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II. PI signatory approval

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Geir Olav Hjortland, MD, Ph.D.

Department of Oncology

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PROTOCOL SYNOPSIS

Protocol title: A phase I/II study with immunotoxin BM7PE in colorectal cancer patients with metastatic disease refractory or with intolerance to last line of standard chemotherapy.

Centre:	Oslo University Hospital
Study Period:	Estimated date of first patient enrolled: Q4 2020 Anticipated recruitment period: 4 years Estimated date of last patient completed treatment: Q4 2024
Treatment Duration:	Expected treatment duration pr. patient: 4 weeks.
Follow-up:	Until progressive disease, expected follow-up period pr. patient: 6 months
Endpoints:	Phase I: Primary endpoint: To characterize safety and toxicity of BM7PE. Secondary endpoint: Overall survival, progression free survival, to characterize pharmacokinetics of BM7PE, determine neutralizing anti-immunotoxin antibody response and immunogenic response. Exploratory: quality of life, response rate. Phase II: Primary endpoint: To characterize the safety and toxicity of BM7PE. Secondary endpoint: Overall survival, progression free survival, to characterize pharmacokinetics of BM7PE, determine neutralizing anti-immunotoxin antibody response and immunogenic response, response rate. Exploratory: quality of life. To determine if median OS ≥ 9.3 months is observed. Number of patients obtaining PFS on BM7PE more than 1.3 times PFS on previous line of chemotherapy. N of 1 design.
Study Design:	Open label phase I/II design
Main Inclusion Criteria:	– Metastatic adenocarcinoma of colon or rectum – Patients refractory to or with intolerance to last line of standard chemotherapy
Sample Size:	Phase I up to 30 patients and phase II 30 patients
Safety Criteria:	Measurements done to determine the safety profile of the treatment, ex. safety parameters to include reporting AE, SAE based on clinical findings, biochemistry, hematologyhaematology, vital signs and ECOG performance status.
Efficacy Criteria:	Overall survival, progression free survival, radiological evaluation and quality of life.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CT	Computer tomography
CR	Complete response
CRC	Colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
PR	Partial response
ICF	Informed Consent Form
ICH	International Conference on Harmonization
PD	Progressive disease
PET	Positron Emission Tomography
MRI	Magnetic resonance imaging
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
QoL	Quality of life

1 INTRODUCTION

1.1 Background – Treatment of metastatic colorectal cancer

Colorectal cancer (CRC) is a common disease, with more than 4300 new cases in Norway in 2016 (Cancer Registry of Norway, Norway, 2011). Metastases occur in around 35 % of patients, most commonly in the liver (Nedrebo et al., 2011). The majority of patients with metastases are not candidates for curative resection and are considered for palliative chemotherapy. The median survival for patients treated successively with combination regimens of 5-Fluorouracil, oxaliplatin, irinotecan, and targeted agents such as VEGF or EGFR antibodies, is 20-24 months (Sorbye et al., 2009).

The presence of a *KRAS* mutation in the tumor is a strong negative predictive factor for treatment response to EGFR antibodies (Amado et al., 2008). These patients are therefore not treated with EGFR antibodies. According to the current treatment guidelines, they are eligible for 2 lines of palliative combination chemotherapy. Median overall survival from start of 2nd line chemotherapy is about 10-12 months (Peeters et al., 2010). (*K)RAS* mutations are present in around 40% of patients with metastatic colorectal cancer. Patients with (*K)RAS* wildtype tumors may receive EGFR-antibody as a 3rd line of palliative chemotherapy, provided they have good performance status. Median overall survival from start of 3rd line treatment with EGFR antibodies is about 10 months (Karapetis et al., 2008).

The target for this study is patients with progressive disease after previous treatment with oxaliplatin, irinotecan, 5FU/capecitabine with or without bevacizumab and EGFR-antibodies (i.e. after 3. line in (*K)RAS* wild-type cases and after 2. line in (K)RAS mutant cases). In these cases, the therapeutic options are extremely limited with presently only two alternative drugs, tyrosine kinase regorafenib and the new oral combination therapy TAS-102, which both have poor response rates and considerably toxicity. The median overall survival was 6.4 months when receiving regorafenib in this setting compared to 5.0 months in patients receiving best supportive care (BSC)(Grothey et al., 2013). A median overall survival of 7.1 months was observed with TAS-102 compared to 5.3 months in patients receiving BSC (Mayer et al., 2015). The results correspond well with results from large randomized trials where patients with progressive disease on all lines of standard chemotherapy had a median survival of 5.0 - 5.3 months when receiving BSC.

2 THE BM7PE IMMUNOTOXIN

2.1 BM7PE immunotoxin in cancer treatment

BM7PE immunotoxin is composed of the BM7 monoclonal antibody targeting the mucin 1 surface molecule (Muc1; highly expressed on a range of carcinomas) conjugated to Pseudomonas exotoxin A (PE) (Andersson, Engebraaten, & Fodstad, 2009). The antibody provides target specificity, and the toxin component is the effector molecule (executing the cell killing effect), specifically killing tumor cells and not normal cells (Fig.1) (Andersson et al., 2009; Andersson, Juell, & Fodstad, 2004; Andersson, Le, Juell, & Fodstad, 2006).

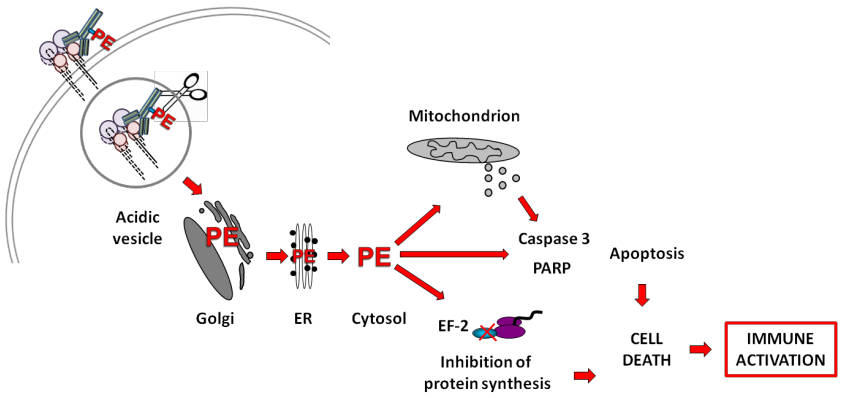

Figure1:
Mechanism of immunotoxin-induced cell death. When internalized into the cancer cells, the toxin effector moiety PE triggers cell death by inhibiting protein synthesis and by directly inducing apoptosis. New evidence points to the mode of cell death being immunogenic, resulting in immune activation that will be exploited in combination with check-point inhibition.

Novel evidence from clinical and preclinical data suggests (manuscript submitted) that immunotoxins kill cells by inducing so-called immunogenic cell death. When cancer cells are killed by immunotoxins, the patient's immune system is activated, and may potentially contribute to inhibit further growth of the tumor. In the era of immunotherapy this is of particular interest, and immunotoxins are interesting candidates for combination with immune check-point inhibitors (ICIs). An effective BM7PE may have a broad clinical field application.

2.2 Preclinical background

We previously showed that administration of another immunotoxin, MOC31PE, induced immune activation and prolonged survival in patients with mCRC (manuscript submitted) with low toxicity to patients (Andersson et al., 2015; Froysnes et al., 2017). The main reason for developing BM7PE as a parallel immunotoxin candidate is that it recognizes a different antigen, Muc1. Muc1 is a particularly well-suited therapeutic target because of its elevated expression and aberrant glycosylation in most carcinomas (including colorectal, ovarian, lung, pancreatic and prostate carcinomas). Importantly, the antibody part of BM7PE recognizes a glycosylated epitope of Muc1 with low expression in normal cells and high expression in cancer cells, explaining the specificity of BM7PE. Comprehensive preclinical studies in cancer cell lines and animal models together with a favorable toxicity profile in monkey studies encourage clinical development of BM7PE.

In the planned clinical trial, BM7PE will be administered intravenously to patients with mCRC to investigate toxicity profile, overall survival, progression free survival and BM7PE-induced immune activation. Only a subgroup of patients with mCRC has so far experienced benefit of ICIs, and current chemotherapy options are disappointingly poor with significant side-effects. The immune-stimulatory mechanisms of our immunotoxins make them attractive candidates for combination with ICIs.

Overexpression of MUC-1 protein expression in colorectal cancer is well known in the literature, and the expression level increases with disease stage and metastasis (Zeng et al, PlosOne, 2015; 10(9), PMID 26367866). Most studies have used immunohistochemical (IHC) detection with different antibodies, but it can be concluded that about 90% of metastatic tumors show overexpression of MUC-1 protein. It is also known that expression levels may differ within a tumor and with time. In our experience we know that even tumor cells with marginal expression levels of target protein may respond well to immunotoxins, indicating that a static assessment of MUC-1 expression may not accurately reflect the sensitivity of the tumor to immunotoxin. Instead of selecting patients for inclusion in the trial based on IHC before treatment, we will examine at a later stage all tumor samples for MUC-1 expression levels and then relate the results to therapy response.

2.3 Clinical experience with immunotoxin treatment

We have recently completed two phase I clinical trials with MOC31PE in metastatic cancer. In the first study the drug was delivered by intravenous injection in 63 patients (Andersson et al., 2015; "ClinicalTrials.gov#NCT01061645: Study of MOC31-PE in Antigen Positive Carcinomas," 2010). Dose limiting toxicity (DLT) was ASAT/ALAT elevation grade 4. DLT was observed at a dose of 8.0 µg/kg body weight. Hepatotoxicity grade 3 was seen from doses of 3 µg/kg. Interestingly, of the 7 patients treated with 8 µg/kg of MOC31PE only 3 of them showed any elevation of ALAT/ASAT. ASAT/ALAT values were normalized within 1-2 weeks after treatment. No other subjective toxicity ≥ grade 3 was reported. In the second study, MOC31PE was administered intraperitoneally in CRC-patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 20 patients ("ClinicalTrials.gov#NCT01061645: Immunotoxin in Peritoneal Carcinomatosis - ImmunoPeCa Trial," 2014; Froysnes et al., 2017). No DLT was observed at any dose level, and the maximum tolerated dose was not reached. Dose escalation was not continued after dose level 4 (10 µg/kg) because a further dose increase was not deemed beneficial.

2.4 Rationale for starting dose

For BM7PE, a 5 times higher dose (150 µg/kg) was safe in the monkey study, compared to that determined for MOC31PE (30 µg/kg) (see section 2.9.1 in IMPD). Similarly, a 5 times higher dose of BM7PE compared to MOC31PE was tolerated in the rodent toxicity study (see table 11 in IMPD). This is in keeping with the immunotoxins being similar in structure and

having similar toxicity profiles (hepatotoxicity) in monkeys and rodents, and it is reasonable to assume that BM7PE can safely be administered to humans. These results suggest that the BM7PE starting dose could be higher than for MOC31-PE. This is further supported by a recent review (Penel & Kramar, 2012) and a recently published paper (Hansen et al., 2015). Here, it is discussed how to select the starting dose for biopharmaceuticals in a first-in-human phase I cancer clinical trial, including when the drug is an antibody-drug-conjugate, i.e. an immunotoxin. According to S9 "Nonclinical evaluation for anticancer pharmaceuticals" when a non-rodent species such as monkeys is used for toxicity testing, the starting dose in humans could be 1/6 of the highest non-severely toxic dose, in this case 1/6 of 150 µg/kg for BM7PE, which equals 25 µg/kg in humans. However, we consider that the starting-dose of BM7PE administered i.v. should at least be lower than the MTD of MOC31-PE (6.5 µg/kg), and to be on the safe side we will start at an even lower dose (2.5 µg/kg).

2.5 Rationale for duration of treatment and observation time

In a previous phase I immunotherapy study (MOC31-PE) with the same toxin, patients received 4 treatments. The only DLT toxicity observed was AST/ALT grade 4. The increase in plasma AST/ALT was highest after the first treatment. Patients developed antibodies against the immunotoxin with increasing levels after the second treatment. Two treatments will therefore probably be safe and the patients will likely not benefit from more than two treatments due to the likelihood of developing antibodies against the immunotoxin with further treatments. The second treatment will not be administered before toxicity is less than grade 2 and/or plasma AST/ALT also has decreased to grade 1 or less.

The chosen observation time is based on previous study MOC31PE were 3 out of 7 patients treated with MOC31PE 8 µg/kg (DLT) showed elevation of ASAT and ALAT. The values were reduced to grade 2 or less within 1-2 weeks after treatment. No other subjective toxicity ≥ grade 3 was reported.

3 RATIONALE FOR THE STUDY

In this study we will include CRC patients that have progressed on or are intolerant to the last line of standard palliative chemotherapy. These patients have a median OS of only 5-6 months. The hypothesis is that treatment with BM7PE immunotoxin will stimulate an immune response and therefore increase OS. The first part of the study is a dose finding study to determine the DLT and recommended dose for the second part of the study (phase II).

3.1 Study hypothesis

The hypothesis is that BM7PE immunotoxin will similar to MOC31-PE immunotoxin cause a dose-dependent short lasting increase in AST and ALT levels that will be the dose limiting toxicity. BM7PE immunotoxin will stimulate an immune response. The hypothesis of the phase-II part of the study is that BM7PE at the recommended dose will result in a median PFS of 1.3 times PFS observed with previous line of treatment. Furthermore, BM7PE will in tCRC patients having progression or intolerance to last line of standard chemotherapy. obtain a median OS that is more than 1.3 times longer than median OS observed in the TAS-102 study (Median OS ≥9.3 months).

4 ENDPOINTS

4.1 Primary, Secondary and Exploratory Endpoints

The endpoints of the phase I and II part of the study are listed in Table 1 and 2 below. The primary endpoint of the dose finding part (phase I) is safety/toxicity. Safety/toxicity will define DLT and recommended dose for the second part (phase II) of the study. Safety and toxicity grade 1-5 toxicity will be reported.

The primary endpoint of the phase II part of the study will also be safety/toxicity.

Table 1 Objectives and related endpoint: Phase I

Objectives	Endpoints	Assessment
Primary:		
To characterize the safety and toxicity of BM7PE	Adverse Events	CTCAE 5.0
Secondary:		
Efficacy	Overall survival (OS)	Death registration
Efficacy	Progression free survival (PFS)	RECIST 1.1
Radiological response to BM7PE	Response rate	
To characterize the pharmacokinetics of BM7PE		
Determine neutralizing anti-immunotoxin antibody response		Blood samples
Determine immunogenic response		
Exploratory:		
Quality of life		EORTC QLQ-C30

Table 2 Objectives and related endpoint: Phase II

Objectives	Endpoints	Assessment
Primary: To characterize the safety and toxicity of BM7PE	Adverse Events	CTCAE 5.0
Secondary: Efficacy	Overall survival (OS)	Death registration
Efficacy Radiological response to BM7PE	Progression free survival (PFS) Respons rate	RECIST 1.1
To characterize the pharmacokinetics of BM7PE Determine neutralizing anti-immunotoxin antibody response Determine immunogenic response		Blood samples
Exploratory: Quality of life		EORTC QLQ-C30
Efficacy	To determine if median OS ≥ 9.3 months is observed.	RECIST 1.1
Efficacy	Number of patients obtaining PFS on BM7PE more than 1.3 times PFS on previous line of chemotherapy. N of 1 design.	
MUC-1 expression	To relate MUC-1 expression to therapy response	

5 OVERALL STUDY DESIGN

The study is a phase I/II trial

Study Period	Estimated date of first patient enrolled: 4.th quarter 2020 Anticipated recruitment period: 4 years Estimated date of last patient completed treatment: 4.th quarter 2024
Treatment Duration:	Expected treatment duration pr. patient is 4 weeks:
Follow-up:	Until progressive disease and collection of survival information
End of study:	Last patients last visit (progressive disease on CT or death).

5.1 N of 1 design

The study is designed to compare patients PFS on BM7PE with previous line of chemotherapy, and there will not be a control group. Number of patients obtaining PFS>1.3 times PFS on last previous line of chemotherapy, N-of-1 design where the patient PFS on BM7PE is compared to previous line of chemotherapy. In general PFS will decrease on each new line of chemotherapy compared to previous line. PFS>1.3 times previous line of chemotherapy may suggest effect of the BM7PE treatment. Furthermore, the longest published median OS in patients having progressive disease on standard 1. and 2. lines of chemotherapy including EGFR-antibodies in RAS-wild type tumors has been 7.1 months compared to 5.3 months with best supportive care (BSC). If patients included in the present study obtain median OS of 1.3 times 7.1 months (9.3 months) this may suggest that BM7PE may have effect in this CRC population.

6 STUDY POPULATION

6.1 Selection of Study Population

Patients with metastatic CRC treated or referred to Oslo University Hospital, who have progressed on all standard lines of chemotherapy or are intolerant to chemotherapy, will be included in the study. Patients may be included also if they have not received Regorafenib and/or TAS- 102 since these drugs only increase OS by 1.4-1.8 months compared to BSC. Due to very limited effects and considerable toxicities and cost, these two drugs are therefore not commonly used in oncological departments in Norway.

6.1.1 Inclusion Criteria

All of the following conditions must apply to the patient at screening prior to receiving study treatment:

- Histologically verified adenocarcinoma of colon or rectum
- Ambulatory with an ECOG performance status 0-1
- At least 18 years of age
- Progressive disease on or last line of standard chemotherapy or intolerance to further chemotherapy
- Laboratory values as the following:
  - ANC $\geq$ 1.5 x 10^9/L
  - Platelets $\geq$ 100 x 10^9/L
  - Hb $\geq$ 9g/dL
  - Creatinine $\leq$ 2x upper limit of normal
  - Bilirubin < 1.5x the upper limit of normal
  - ASAT and ALAT $\leq$ 2.5x the upper limit of normal
  - Albumin levels > 30 g/L
  - INR<1.3
- Signed informed consent and expected cooperation of the patients for the treatment, and follow-up must be obtained and documented according to ICH GCP, and national/local regulations
- Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- WOCBP should be willing to use one highly effective method of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. The majority of WOCBP that are exposed to cancer-targeting IMPs must use highly effective contraception's as standard time in general 4-6 months after last administration.
- Men in sexual relationship with WOCBP must agree to use a condom starting with the first dose of study therapy through 120 days after the last dose of study therapy. In case of female partner of child-bearing potential, the female partner should use one highly effective contraception method as defined in section 6.1.3 Other considerations.

6.1.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- History of prior metastatic disease the last 3 years
- History of CNS or bone metastases
- Significant cardiac or other medical illness that would limit activity or survival, such as severe congestive heart failure, unstable angina, or serious cardiac arrhythmia
- Chemotherapy/radiation therapy or major surgery within the last 4 weeks before start of treatment
- Alcohol or drug abuse
- Any reason why, in the opinion of the investigator, the patient should not participate
- Has a known history of Human Immunodeficiency Virus (HIV)
- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)
- Is pregnant or breastfeeding, or expecting to conceive or father children within the project duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

6.1.3 Other Considerations

The effects of BM7PE on sperm, conception, pregnancy, and lactation are not known. Participation in this study requires patients receiving BM7PE to agree to use one method of highly effective contraception. Methods of contraception must be in successful use from at least 14 days prior to the first dose of BM7PE and until 120 days following the last dose of BM7PE.

Acceptable highly effective methods of contraception in accordance to CTFG guideline:

- Vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm.
- Bilateral tubal ligation performed at least 6 months previously.
- Continuous use of an intrauterine device for at least 90 days previously
- Combined (estrogen and progestin containing) or progestin-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
    - injectable
    - implantable
    - Sexual abstinence is only a highly effextive contraceptive mesure when “it is the usual and preferred lifestyle of the subject”.

NOTE: Hormonal contraceptives can be used as highly effective method of contraception

7 INVESTIGATIONAL MEDICINAL PRODUCT

7.1 Storage and handling

The sterility of the undiluted medical product will be tested according to standard procedure at Department of Cell Therapy/Department of Microbiology. BM7PE immunotoxin is supplied as a liquid solution and is diluted in 0.9% saline to a total volume of 250 ml. The immunotoxin solution for administration to the patients is prepared by the pharmacy department of the hospital according to standard procedure. One vial is equal to one administration and will be given to the patient ambient within maximum 6 hours (ref MOC31-PE). The prepared medical product will be affixed with a clinical label in accordance with regulatory requirements. The study is open-labled, so drug identity (name and strength) is included in the label text.

Drug accountability log in accordance with the standard procedures at Department of Pharmacy, will be used during the course of the study to keep track of which patients have gotten exactly which IMP. Upon completion or termination of the study, all unused and/or partially used Investigational product will be registered according to standard procedure at Department of Pharmacy.

7.2 Administration of BM7PE treatment

The BM7PE treatment will be administered as a 20-minute i.v. infusion. The treatment is repeated after 2 weeks (day 15). The patients will be treated as in-patients, and stay at the hospital at least for a minimum of 24 hours. The Norwegian Radium Hospital, Oslo University Hospital have experience with first in human studies and have trained staff that have conducted immunotoxin studies and also Car T-cell studies.

7.2.1 Dose escalation in phase-I

The dose administered to the patient will be 2.5, 5.0, 7.5, 10.0, 15.0 and 20.0 µg/kg body weight. Dose increments will be made, as described in chapter 2.4, starting on 2.5 µg/kg, with 2.5 µg/kg dose increments until a dose of 10 µg/kg is reached. After this, further dose increments will be made in steps of 5 µg/kg until 20 µg/kg.

The design is a 3+3 design. If there is no dose limiting toxicity (DLT, see section 7.2.3 for definition) observed in the first three patients in the first dose level, three new patients will be added to the next dose level. A total of 3 patients will be treated at each dose level if no DLT is observed. If DLT is observed in one of three patients, up to three more patients are added at that dose level. If only one of six patients have a DLT, then the dose escalation is continued. If two DLT is observed on a dose-level, then up to three more patients will be added to the dose level below. See table 3 for dose escalation rules.

Table 3: Dose Escalation Rules

Number of patients with DLT	Escalation decision rule	
0 out of 3 patients	3 patients will be added at next planned dose level	
1 out of 3 patients	Enter up to 3 patients at same dose level	If only one of six patients have a DLT then the dose escalation is continued
2 out of 2-6 patients	This dose level will be declared maximum tolerated dose (MTD). Enter up to 3 more patients to the dose below	

Patients will be entered sequentially. If no DLT has been observed two weeks after last treatment of the first patient, a second patient can be added on the same dose level. The third patient will be entered two weeks after last treatment of the second if no DLT is encountered. If a DLT is observed a new patient on that dose level may be treated when the patients with DLT has recovered to toxicity grad 2 or less and plasma AST and/or ALT has decreased to grade 3 or less.

A new dose level may be opened two weeks after the last patient on previous dose level has received last treatment, when no DLT is observed. If a DLT is observed in one of six patients a new dose level may be opened when the patient with DLT has been observed for two weeks after the last treatment and the DLT toxicity has decreased to grad 2 or less.

7.2.2 Recommended dose in phase-II

Maximum tolerated dose (MTD) and the recommended dose for the phase II (RPD2) part of the study will be the dose level below were two patients had a DLT. At least six patients will be treated at this dose level. If not two patients experience DLT on any dose levels up to 20 µg/kg, 20 µg/kg will be considered the recommended dose for the phase II part.

Patients may discontinue protocol therapy in the following instances:

- Intercurrent illness which would in the judgment of the investigator effect patient safety, or the ability to deliver treatment according to the protocol
- Request by the patient
- Any reason why, in the opinion of the investigator, the patient should not continue treatment according to the protocol

7.2.3 Dose limiting toxicity (DLT)

A DLT is defined as: Any grade 3 or greater non-laboratory toxicity considered to be related to study drug asses by NCI-CTCAE version 5. Laboratory abnormalities grade 3 or higher except thrombocytopenia and neutropenia.Neutropenia and thrombocytopenia grade 4 lasting more than 7 days or febrile neutropenia will be considered DLT. An incidence of Potential Drug Induced Liver Injury (DILI) will be considered as a DLT.

7.2.4 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. Aminotransferases (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
2. Total bilirubin > 2 times ULN, without initial findings of choleastasis (elevated serum alkaline phosphatase), AND
3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

7.2.5 Schedule Modifications

No dose modifications are planned. The second dose will be administered earliest after 2 weeks or as soon as any drug-related AE has resolved to baseline or CTCAE grade ≤1. The second dose may not be postponed due to late resolution of any drug-related adverse event more than one week (7 days), or any other reason more than two weeks (14 days). If a DLT has occurred after first dose, the second dose should not be administered.

7.3 Concomitant medications.

Prohibited medication during study: Phenytoin, phenobarbital, systemic steroids (equivalent to more than 10mg prednisolone per day), coumarin and alternative/ complementary medicine

8 STUDY PROCEDURES

8.1 Flow Chart

Patients should start the treatment within 4 weeks of signed informed consent. Baseline CT should be taken less than 4 weeks before start of treatment. CT-scan (thorax/abdomen/pelvis) will be performed every 8 weeks from first administration of study medication. All grades of toxicity will be reported, according to the CTCAE version 5.

Table 4: Trial flow chart

	Before treatment	Treatment phase Cycle = 14 days					Follow-up phase		
Cycle		**Cycle 1**		**Cycle 2**			**Safety phone visit[10]**	**Follow-up visit[10]**	**End of study**
Week		**1**	**2**	**3**	**4**	**5**	**7**	**Every 8 week from first dose, until disease progression**	
Day		**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 15**	**30 days after last dose**		
Informed consent	X								
Inclusion/exclusion Evaluation	X								
Medical History	X								
CT/MRI[1]	X							X	
Physical Examination[2]	X	X		X				X	X
Vital signs[3]	X	X	X	X	X	X		X	X
Blood samples[4]	X[5]	X [6, 7]	X	X [7]	X	X [7]		X	X
Treatment		X		X					
Pregnancy test	X (≤ 72 hours prior first dose)				X		Monthly[9]		X
Adverse event[10]	X	X	X	X	X	X	X	X	X
Record of concomitant pain medication	X							X	
QoL	X							X[8]	X
Survival information									X

1. CT/ MRI scans should be taken within 4 weeks of start of treatment.
2. Physical examination at randomization and at evaluation every 8 weeks or more frequently if clinically indicated.
3. Blood pressure, pulse, temperature, weight and ECOG performance status at baseline, time of SIRT and at evaluation every 8 weeks or more frequently if clinically indicated.
4. CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin, bilirubin and CEA.
5. CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin and, bilirubin day 1,3,4 and 5 of each treatments.
6. Pharmacokinetic monitoring. Serum samples will be collected at 0 h, 3 h, 6 h and 24 h after the first BM7PE administration
7. Cytokine monitoring. Serum samples will be collected at 0 h, 24 h, 2 weeks and 4 weeks after the first BM7PE administration
8. Quality of life questionnaire (EORTC QLQ-C30) will be performed every 8 weeks until progressive disease or up to 12 months.
9. For 120 days after last treatment

10. Patients will be followed for AE for 30 days, and for SAEs that are believed to be related to the study drug for 100 days, following their last dose of study drug. The 100 days safety follow-up visit will be covered by the associated scheduled follow-up visit. For patients that discontinue follow up before end study, the safety follow up will be ensured with a phone visit at the required time point.

8.2 Before Treatment Start:

Evaluating patient eligibility, quality of life questionnaire (EORTC QLQ-C30) filled in before treatment, symptom/toxicity registration (NCI-CTCAE version 5), and CT/MR-baseline scan performed within 4 weeks start of treatment. Blood samples: CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin, bilirubin and CEA.

8.3 Follow-up

All patients will have follow-up visits with CT-scans every 8 weeks until progressive disease. See flow chart for details regarding these visits.

Women of child bearing potential will perform monthly pregnancy-tests at home for 4 months after last dosing of BM7PE. The nurse follow-up these patients with monthly phone calls and records the results of the pregnancy tests in the CRFs.

All treatment after end of BM7PE treatment will be collected from medical records from different hospitals. This will include treatments as surgery, radiation therapy, different local treatments, chemotherapy and other medical treatments.

8.3.1 End of Study / Withdrawal Visit

End of Study is defined as last patient last visit (patients will have follow-up until progressive disease on CT scan, death, withdrawal of consent or lost to follow-up).

Quality of life questionnaire (EORTC QLQ-C30), symptom registration, blood samples: CRP, Hb, HCT, WBC (incl.differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALAT, LD, ALP, γGT, INR, albumin, bilirubin and CEA

There will be no study specific follow-up visits after time of progressive disease. Further treatment and follow-up is at the discretion of the responsible physician. Administration of tumour-related treatment (chemotherapy, radiotherapy, invasive radiology, surgery) after treatment and date of death will be recorded.

Quality of life questionnaire (EORTC QLQ-C30) will delivered to the patients at the out-patient clinic or will be mailed to the patients.

8.3.2 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reason as judged by the Principal Investigator
- Severe non-compliance to protocol as judged by the Principal Investigator
- Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant
- Disease progression

8.4 Procedures for Discontinuation

8.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment.

If possible, a final assessment shall be made (end of study visit). The reason for discontinuation shall be recorded.

Patients who withdraw or are withdrawn from the study before start of treatment, will be replaced, to ensure adequate numbers of patients eligible for final analysis.

8.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI in the event of any of the following:

Occurrence of AEs unknown to date in respect of their nature, severity and duration

Medical or ethical reasons affecting the continued performance of the trial

Difficulties in the recruitment of patients

The principal investigator will inform all investigators and the relevant regulatory authorities of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the relevant authorities should be informed within 15 days.

9 ASSESSMENTS

9.1 Safety assessments

9.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

9.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case

should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization. A pre-planned hospitalization admission (i.e., elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

9.1.3 Serious Adverse Reaction

Any untoward medical occurrence or effect that at any dose results in death is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect). The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

9.1.4 Reference Safety Information (RSI)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any serious adverse reaction where the nature or severity is not consistent with the product information mentioned in the Reference Safety Information in the IB. There is no IB for this study as to this date there is limited information of the BM7PE, some clinical experiments are presented in the IMPD. The expected side-effects of the BM7PE are similar to side-effects observed by MOC31PE therapy, temporarily transaminase increase (ASAT and ALAT), with no specific treatment required. But as there are no clinical observations of BM7PE in humans, all SARs that occur in the trial is unexpected, and thus per definition SUSARs.

9.2 Sponsor responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities and investigators in accordance with all applicable national laws and regulations.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Competent Authority according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than 7 days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

SUSARs will be reported using the CIOMS form since Oslo University Hospital (sponsor) is not connected to EudraVigilance.

9.3 Safety Plan

Administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded during the trial until resolved. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined below.

9.3.1 Safety Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory values). Laboratory values must be reviewed prior to each administration of IMP. All grades of toxicity will be reported.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts. During the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection.

The patients will be supplied with a patient card that they can show health personnel in case of hospitalization without investigator`s knowledge. The card will contain emergency contact information to the study team.

Patients will be followed for AE for 30 days, and for SAEs that are believed to be related to the study drug for 100 days, following their last dose of study drug.

Patients who have an ongoing study drug related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the adverse event.

9.4 Procedures in Case of Emergency

The investigator is responsible for assuring that there are procedures and expertize available to cope with emergencies during the study.

9.5 Efficacy

CT-scan of chest/abdomen/pelvis will be obtained and MRI of the liver may be obtained, every 8 weeks according to standard procedure at the Department of Radiology. Assessment of Clinical State including a general physical examination and evaluation of ECOG performance status will be performed every 8 weeks.

9.5.1 Datasets to be analysed

- All patients who enroll and receive and a minimum of one dose of BM7PE immunotoxin will be included in the *Safety Analysis Set*.
- All patients with a repeat assessment of tumor burden on CT/MRI scans will be included in the *Efficacy Analysis Set*.
- OS from start of BM7PE treatment will be calculated.
- Objective response rate (ORR) is defined according to RECIST 1.1, separately. ORR will be calculated for Efficacy Analysis set for all patients.
- Clinical benefit rate is defined as subjects who are not in progression according to RECIST 1.1 at week 8. Patients who discontinue before week 8 are considered to have progressive disease.
- Progression Free Survival (PFS) will be calculated per RECIST 1.1. It is defined as time from start of IMP until progression or death from any cause. If a patient had not had an event (progression or death) before end of trial, then PFS will be censored at the last date known of non-progression.

10 RISK BENEFIT

Colorectal cancer patients included in a previous immunotoxin study with the same toxin (MOC-31PE) had unexpected long overall survival. If patients included in this study will obtain similar survival is unknown. The expected side-effects of the study treatment is significant and transient increase in plasma AST/ALT levels that will last for 3-7 days. A transient increase in AST/ALT will likely not result in any clinical symptoms. If subjects in this clinical trial receive a direct benefit from BM7PE treatment is uncertain, as the primary aim of the clinical trial is to provide information about the safety of the investigational medicinal product. The hypothesis in this study is that treatment with BM7PE immunotoxin will stimulate an immune response and therefore increase OS. The risk of important side effects is limited, and the patients will be carefully monitored for side effects. These patients have no further standard treatment and poor prognosis with median overall survival of 5-6 months. We therefore consider that the potential benefit outweighs the risks associated with the study treatment.

11 RECORDING OF DATA AND SOURCE VERIFICATION

11.1 Case Report Forms (CRFs)

Case report forms (CRF) will be provided for the recording of all data. Data will be recorded directly and legibly onto the record forms, in blue/black ink. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections if applicable, should be made legibly, dated and initialled. Correction fluid is not allowed.

11.2 Source Data

The medical records for each patient should contain information which is important for the patient's safety and continued care and to fulfil the requirement that critical study data should be verifiable. To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- WHO performance status assessments conducted as part of the study;
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice

11.2.1 Source Data Verification

Sponsor's representatives (e.g. monitors, auditors) and/or regulatory authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

11.2.2 Storage of Study Documentation

The investigator shall arrange for the retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by the hospital. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

11.3 Monitoring

The investigator/site will be visited on a regular basis by the Clinical Study Monitor, who will assess compliance with the trial protocol and general principles of Good Clinical Practice. The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required by monitoring plan.

12 STATISTICAL CONSIDERATIONS

Only descriptive statistics will be performed.

12.1 Power Considerations and Determination of Sample Size

No sample size calculation has been performed. Up to 30 patients in Phase 1 (depending on MTD) and 30 in Phase 2 are deemed appropriate for assessment of safety in the new sequential treatment scheme. The number of patients in the Part 1 and Part 2 will be decided by investigators in collaboration with Sponsor based on an overall assessment of available safety and immune activation data available at the time.

13 STUDY MANAGEMENT

13.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

13.2 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Norwegian Medicine Agency (NOMA/SLV) and Ethics Committee according to EU and national regulations.

13.3 Audit and Inspections

Authorised representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the centre to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

13.4 Internal Data and Safety Monitoring Committee (IDSMC)

- Participant safety will be continuously monitored by the internal data and safety committee, which includes safety signal detection at any time during the study.
- In particular, data will be reviewed by the sponsor for identification of the following events on study that would potentially contribute to a requirement to pause or stop the study.
    - Any deaths, regardless of causality
    - Grade 3 fever reported in more than 2 participants
    - Any reason why as decided by the sponsor or the internal IDSMC.
- Enrollment will be paused during the review. If a pausing/stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.

14 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

14.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee and the Norwegian Health Authorities before enrolment of any patients into the study.

The investigator is responsible for informing the Ethics Committee and Norwegian Medicine Agency of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

14.2 Other Regulatory Approvals

The protocol will also be registrated in www.clinicaltrials.gov before inclusion of the first patient.

14.3 Informed Consent

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator File binder and also scanned to be part of the patient's electronic medical record at the hospital.

14.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient numbers, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth.

15 TRIAL SPONSORSHIP AND FINANCING

The study has no external sponsorship.

16 PUBLICATION POLICY

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

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