Phase 1 study of OBT076, first in class anti-DEC205 ADC, in patients with advanced/metastatic solid tumors: Safety, efficacy and PK/PD results.

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Background

- OBT076 is a novel Antibody Drug Conjugate (ADC) consisting of a fully human IgG1/k antibody, conjugated via a cleavable linker SPDB to the derivative microtubule inhibitor, DM4.
- The ADC has specificity for CD205/Ly75 protein, which is an endocytic receptor, highly expressed on myeloid dendritic cells and low levels on other lymphocytes. Its main function is antigen uptake and subsequent presentation to CD4+ and CD8+ T cells.
- CD205 is expressed on the cell surface of many solid (Figure1a) and liquid tumors (Figure1b), and immunosuppressive dendritic cells.

Figure 1a: Expression of CD205 in solid tumors

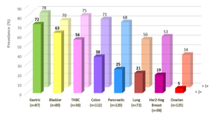


Figure 1b: Expression of CD205 in hematological tumors

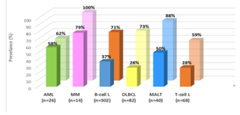


Figure 1. (a) IHC survey of solid tumors indications showing high prevalence of CD205 expression. Gastric, bladder, and triple-negative breast cancer show the highest prevalence by IHC staining 2+ or greater. (b) In liquid tumors CD205 is prevalent in MM, AML, MALT, B-/T-cell lymphoma

Objectives and Study Design

Open labelled, two parts trial in patients with metastatic CD205+ve solid tumors who progressed on standard therapy

- Part A of the study consisted in dose escalation from 1.6 mg/kg to 3.5 mg/kg.
- An mTPI design was used to guide dose escalation and to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) (Figure 2).
- Part B is an ongoing expansion basket phase 1 trial enriched in indications where preliminary efficacy has been seen in part A (Figure 3).

Figure 2: Dose Escalation Phase (Part A)

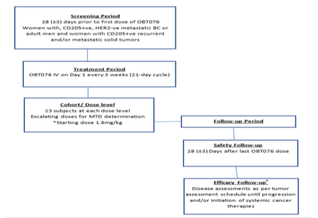


Figure 2. Part A of the study consisted in dose escalation from 1.6 mg/kg to 3.5 mg/kg for all comers with high (> or= to 2+) CD205 expression as detected by IHC test.

Figure 3: Single Agent Expansion Phase (Part B)

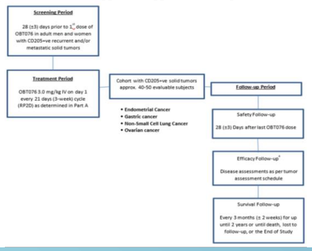


Figure 3. Part B is an expansion single agent basket trial.

Results

- Data cut off is May 16, 2022.
- Typical phase 1 patients with advanced metastatic disease and progressed on all standard treatments.

Table 1: Patient Demographics and Disease Characteristics

Demography	Cohort 1 1.6 mg/kg N=3	Cohort 2 2.5 mg/kg N=4	Cohort 2b 2.5 mg/kg N=5	Cohort 3 3.5mg/kg N=3	Cohort 4 3.0mg/kg N=3	Part B 3.0mg/kg N=9	All N=27
Age	61 (33-77)	63 (32-74)	45 (29-64)	71 (61-78)	55 (22-72)	61 (42-72)	59 (22 -78)
Gender							
Male	1	1	2	2	2	5	13
Female	2	3	3	1	1	4	14
Primary Tumor type							
Bladder	1	-	-	-	-	2	3
Breast	1	1	1	-	-	-	3
Endometrial	-	-	-	-	1	1	2
Esophageal	-	1	-	1	-	-	2
Colorectal	-	-	1	-	-	-	1
Gastric	-	-	1	-	1	-	2
GEJ	-	-	-	-	-	3	3
Lung	1	-	-	1	-	-	2
Ovarian	-	1	-	-	-	2	3
Renal	-	1	2	-	-	1	4
Thyroid	-	-	-	1	-	-	1
Thymic	-	-	-	-	1	-	1
Met Sites							
Bladder	-	1	-	-	-	-	1
Bone	3	1	3	-	1	1	8
Brain	1	-	-	-	-	-	1
Chest Wall	-	-	-	-	1	-	1
Liver	2	-	2	1	2	-	7
LN	2	3	5	1	3	4	18
Lung	1	1	3	1	1	4	11
Peritoneum	1	-	1	-	1	3	6
Rectum	1	-	-	-	-	-	1
Kidney	-	-	1	-	-	-	1
Other	-	-	-	-	1	-	1

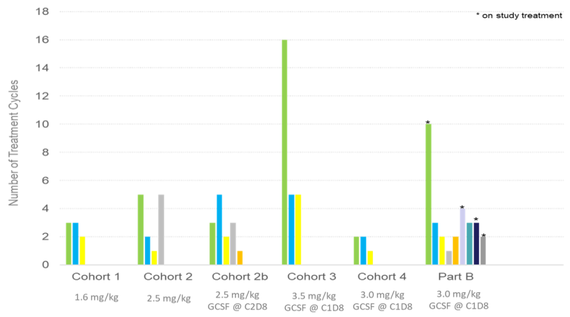
Table 2: Patient Demographics and Characteristics

Demography	Cohort 1 1.6 mg/kg N=3	Cohort 2 2.5 mg/kg N=4	Cohort 2b 2.5 mg/kg N=5	Cohort 3 3.5mg/kg N=3	Cohort 4 3.0mg/kg N=3	Part B 3.0mg/kg N=9	All N=27
No. Prior Metastatic Chemotherapy Regiments:							
0	-	-	2	1	1	1	5
1	-	1	2	-	1	-	4
2	2	1	1	2	-	6	12
3	1	1	-	-	1	-	3
>3	-	1	-	-	-	2	3
Prior Radiation:							
Yes	1	2	2	2	0	2	9
No	2	2	3	1	3	7	18
UNK	-	-	-	-			-
ECOG PS:							
0	2	2	1	2	1	4	12
1	1	2	4	1	2	5	15
ANC at C1D1:							
<1.5	-	-	-	-	-	-	0
1.5 to 2.5	-	-	-	-	-	-	0
2.5 to 4	-	1	1	1	-	4	7
>4	3	3	4	2	3	5	20

Drug Activity and Treatment Duration for all Patients

- Tumor evaluation was performed every 3 cycles and patients assessed according to RECIST criteria.
- One patient had major objective response despite progressing on all prior treatments.
- In addition, six patients had long lasting stable disease and received between 5-to 16 cycles (Figure 5).
- Enrolment in part B is ongoing to further assess safety and efficacy of OBT076 as single agent in several solid tumors.
- Furthermore, two patients with no or low PD-L-1 expression received checkpoint inhibitor treatment with Pembrolizumab after 2 and 5 cycles of OBT076 respectively, and both patients experienced near complete response after only one to two cycles of Pembrolizumab.

Figure 5: Treatment Duration



Immune-profiling of the blood samples to identify populations of Dendritic cells and T cells (Figure 6 and 7)

The observed early decrease in CD205+ cells, at least in part,

- Due to depletion of CD205 expressing cells
- OBT076 induced internalization of CD205 expressed on the cell surface. Internalization of receptor

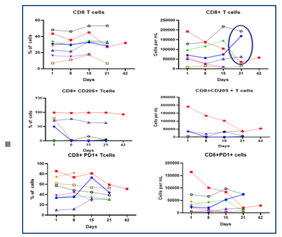


Figure 6: In three of all patients in cohort 2, CD8+ T cells show proliferation and in 2 of these patients, PD1 positive cell numbers also increased.

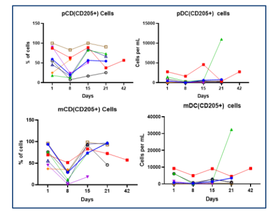


Figure 7: CD205 positive pDCs and mDCs are depleted by day 8 in cohort 2 for all patients and recovered.

Safety: Most Common AEs (Tables 3 and 4)

- All patients have at least one AE.
- The main AE is neutropenia, nadir between days 10 and 15, lasting between 3-5 days.
- Neutropenia is well managed by G-CSF administered at day 8.
- Treatment is well tolerated without any other safety concern.

Table 3: Hematological AEs

	Cohort 1: 1.6 mg/kg N=3		Cohort 2 : 2.5 mg/kg N=4		Cohort 2b: 2.5 mg/kg N=5		Cohort 3: 3.5mg/kg N=3		Cohort 4: 3.0mg/kg N=3		Part B: 3.0 m/kg N=9		All N=27	
Grade	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4
Anaemia	1	1	1	-	3	-	2	-	1	1	1	1	9	3
Neutropenia	2	2	4	4	4	4	3	3	2	1	5	5	20	19
Febrile neutropenia	-	-	-	-	1	1	1	1	1	1	2	2	5	5
Lymphocyte Decrease	-	-	-	-	4	3	1	1	2	1	-	-	7	5
Decreased WBC	-	-	2	2	5	4	3	2	2	1	1	1	13	10
Decrease Platelets		-	1		1	1	1	1		-	-	-	3	2

Table 4: Other related AEs

	Cohort 1: 1.6 mg/kg N=3		Cohort 2 : 2.5 mg/kg N=4		Cohort 2b: 2.5 mg/kg N=5		Cohort 3: 3.5mg/kg N=3		Cohort 4: 3.0mg/kg N=3		Part B: 3.0 m/kg N=9		All N=27	
Grade	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4	all	3/4
Diarrhea	1	-	2	-	1	-	2	-	1	-	-	-	7	-
Dry Mouth	1	-	1	-	-	-	-	-	-	-	1	-	2	-
Nausea/Vomiting	1	-	1	-	1	-	2	-	-	-	1	-	6	-
Dysphagia	-	-	2	-	1	1	-	-	-	-	-	-	3	1
Fatigue	2	-	2	-	1	-	2	1	2	1	1	-	10	2
Fever/pyrexia	-	-	2	-	-	-	1	-	1	-	1	-	5	-
Decreased Appetite	3	1	-	-	-	-	2	1	-	-	1	-	6	2
Weight loss	2	-	1	-	1	1	2	-	1	-	-	-	7	1
Infections/UTI*	-	-	-	-	-	-	1	1	-	-	1	-	2	1
Peripheral sensory neuropathy	-	-	1	-	-	-	1	-	-	-	-	-	2	-
Rash/pruritus	1	-	2	1	2	1	1	-	-	-	-	-	6	2
Arthralgia	1	-	1	-	1	-	-	-	-	-	-	-	3	-

*Events suspected to be related to OBT076

Clinical Pharmacokinetics and ADA

- OBT076 exposure (Cmax) increase is proportional to increasing doses.
- Cmax of 40.000-90.000ng/ml was achieved between 2.5 and 3.5mg/kg dose and is comparable to the therapeutic dose in mouse models.
- No drug accumulation following repeated-dose administration was evident in any dose range
- Three out 18 patients tested are confirmed to have ADA in dose escalation phase (Part A) of the study.

Figure 8: PK parameters

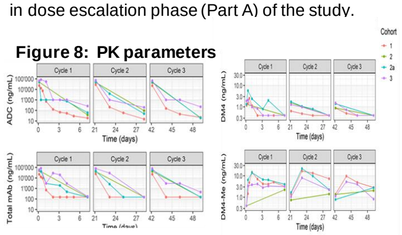


Figure 8: Overall, OBT076 serum concentrations increases with increasing doses and accumulation of metabolite of DM4 was not observed in the PK Samples.

Conclusions

- OBT076 at 3.0mg/kg has shown favorable safety profile with manageable neutropenia. The preliminary efficacy has suggested single agent antitumoral activity in gastric, ovarian, endometrial and lung cancer.
- The two patients who received a sequential administration of pembrolizumab after OBT076 showed considerable tumor activity and is also supported by PD marker analysis in the whole blood samples.
- The use of immune checkpoint inhibitors in conjunction with OBT076 is being studied in a randomized basket cohort within the same study.

Acknowledgments

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