Potential novel immuno-oncology mechanism revealed during translational phase I immuno-blood profiling of experimental ADC medicine OBT076 in a gastric cancer patient.

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Abstract

Background: CD205 is a type I transmembrane glycoprotein, with unique characteristics that make it an ideal target for Antibody Drug Conjugate (ADC) therapy. Here we report on a potential novel immuno- oncology mechanism revealed during the Translational Phase I (NCT04064359) immuno-blood profiling of a chemo-refractory patient treated with OBT076, an experimental CD205-directed ADC.
Methods: A chemo-refractory advanced gastric cancer (GC) patient with 60% CD205 expression in the primary tumor via IHC and having previously undergone 2 lines of chemotherapy treatment (Docetaxel/cisplatin/5FU and ramucirumab/Paclitaxel), received five 21-day cycles of OBT076 (one at 2.5mg/kg and four cycles at 2.0 mg/kg) followed by 1 cycle of pembrolizumab (PZ; 200mg) ~4 weeks later. Clinical response was evaluated and immunological markers (CD45, CD205, CD4, CD8, and PD1) in peripheral blood cells were quantified using flow cytometry.
Results: After 2 OBT076 cycles at 2.0 mg/kg, there was an ~40% shrinkage in the primary gastric tumor size and resolution of ascites and lymph node metastases were observed. Following 2 further cycles and PZ, complete response was achieved for the primary tumor. Flow cytometry showed (1) an initial decrease in the absolute numbers of dendritic cells by day 8, followed by a 2-fold increase in numbers by day 21 after treatment; (2) a near total decrease in the population of CD8+ CD205+ cells by day 8, no recovery in levels were observed; (3) a 3-fold increase in CD4+ and CD8+ T-cell numbers between days 8 and 21 and (4) CD4+ PD1+ and CD8+ PD1+ T-cell numbers followed by an ~4-fold increase between days 8 and 21.
Conclusion: Our results show that increases in PD1+ T-cells, T-cell induction, and decreases in immuno-suppressive CD4+ CD205+ and CD8+ CD205+ cells occur simultaneously; coinciding with rapid resolution of the primary tumor, lymph node metastases and ascites. These findings suggest that OBT076 activates the patient's immune response against the tumor through a potentially novel mechanism: drug-induced depletion of CD8+ CD205+ immuno-suppressive cells and subsequent T-cell activation. Additionally, our data support the use of immune checkpoint inhibitors in conjunction with OBT076 to achieve favorable clinical outcomes.

i. pDC blood levels in GC patient after cycle 1 of OBT076

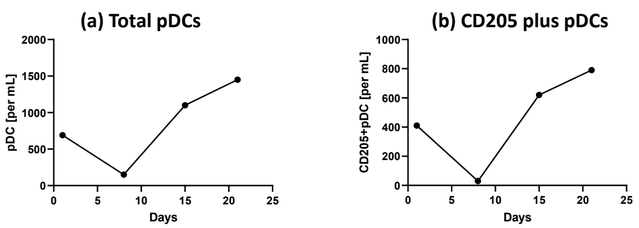


Figure 1. (a) Total pDC levels after cycle 1 of OBT076. (b) CD205 plus pDC levels after cycle 1 of OBT076. pDC: plasmocytic dendritic cells, GC: gastric cancer.

ii. mDC blood levels in GC patient after cycle 1 of OBT076

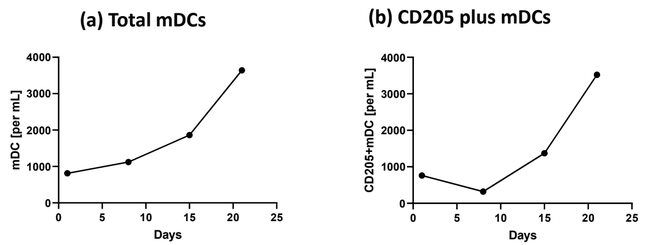


Figure 2. (a) Total mDC levels after cycle 1 of OBT076. (b) CD205 plus mDC levels after cycle 1 of OBT076. mDC: myeloid dendritic cells, GC: gastric cancer.

iii. CD8+, CD4+, PD1+ T-cells and CD205/CD8+, CD205/CD4+ cells in GC patient after cycle 1 of OBT076

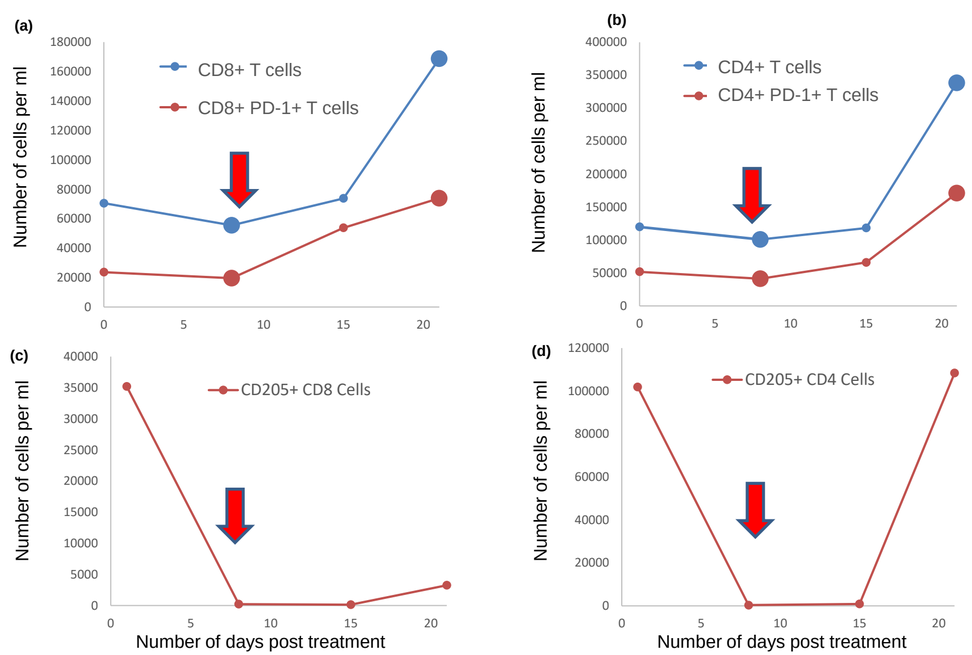


Figure 3 (a) Total CD8+ and CD8+/PD1+ T-cell levels after cycle 1 of OBT076. (b) Total CD4+ and CD4+/PD1+ T-cell levels after cycle 1 of OBT076. (c) Total CD205+/CD8+ cell levels after cycle 1 of OBT076. (d) Total CD205+/CD4+ cell levels after cycle 1 of OBT076.

iv. Impact of pDC presence on OS in gastric cancer

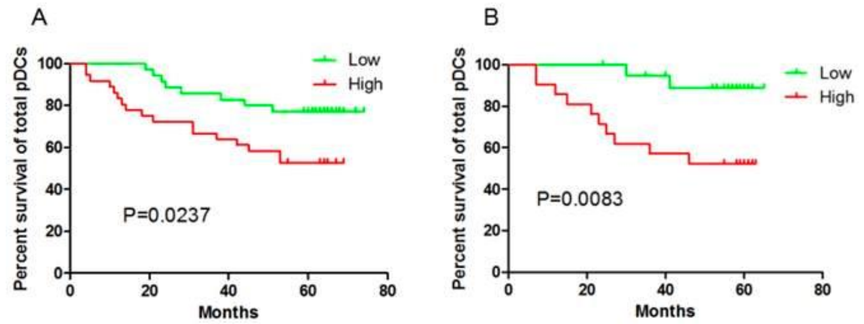


Figure 4 A study by Liu *et al.* revealed that GC patients with elevated pDC levels in the tumor (A) or blood (B) correlated with shorter OS. pDC: plasmocytic dendritic cells, OS: overall survival. Ref: J Cancer 2019; 10(26):6711-6715.

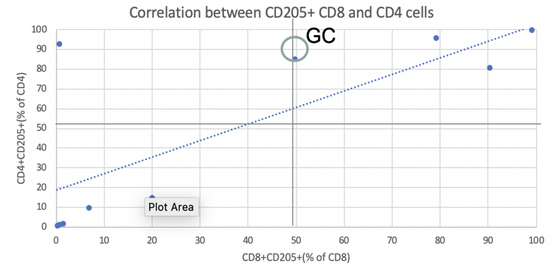
v. a) IHC staining for some of the enrolled subjects

IHC Staining (%)

	1+	2+	3+
Gastric Ca(GEJ)	20	70	0
NSCLC	15	50	0
Esophageal Ca	20	63	2
CRC	0	0	100
TNBC	20	48	2
Gastric Ca	**40**	**60**	**0**
Esophageal Ca	90	0	0
RCC	0	70	30
Thyriod Ca	20	60	20
Endometrial Ca	0	0	100
Epigastric Ca	10	30	60
RCC	50	40	10

Figure 5 (a) Patients selected had a CD205 positive primary tumor in which at least 50% of the tumor cells expressed CD205 at a level of 2+ as measured by immunohistochemistry (IHC) performed with an anti-CD205 antibody from Leica (Cat#: NCL-L-CD205). The tumor of the gastric cancer patients stained 60% 2+ and 40% 1+.

v. b) CD205+/CD8+ blood levels of some of the enrolled subjects



Patient ID	1	2	3	4	5	6	7	8	9	10
CD8+CD205+ (% of CD8)	90.4	19.9	6.77	**49.9**	0.25	0.74	0.69	1.47	99.1	79.2
CD4+CD205+ (% of CD4)	80.6	14.5	9.43	**85**	0.4	0.84	92.4	1.67	99.7	95.4

Figure 5 (b) Percentage of CD205+/CD8+ as % of all CD8+ ranges from 0.25 – 99.1 %.

Patient blood samples were analyzed for the percentage of CD205+/CD8+ cells as the percentage of all CD8+ T-cells: this ranged from 0.25 to 99.1%. The level of CD205+/CD8+ in the GC patient analyzed here was 49.9%.

Conclusions

- The blood analysis of the GC patient showed a biphasic induction of both mDCs and pDCs following an initial depletion of CD205+ pDCs and mDCs.
- The analysis also showed an increase in PD1+ CD4+ and CD8+ T-cells. This coincided with the rapid resolution of the primary tumour, lymph node metastases and ascites.
- While CD205+ pDCs, mDCs and CD205+/CD4+ cells recovered following their initial decrease, a population of CD205+/CD8+ cells remained almost completely depleted throughout the entire 21-day treatment cycle with OBT076. The exact nature of the CD205+/CD8+ cells and their role in tumor regression warrants further investigation.
- These findings suggest that OBT076 activates the patient's immune response against the tumor through a potentially novel mechanism: drug-induced depletion of CD8+ CD205+ immuno-suppressive cells and subsequent T- cell and dendritic cell induction and activation.
- Additionally, our data support the use of immune checkpoint inhibitors in conjunction with OBT076 to achieve favorable clinical outcomes.

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