

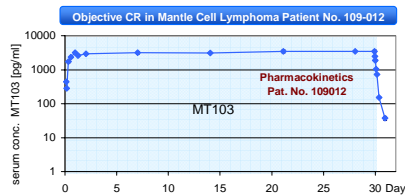
# Feasibility of Subcutaneous Delivery Supports a New Route of Administration for Treating Cancer Patients with EpCAM-specific BiTE Antibody MT110

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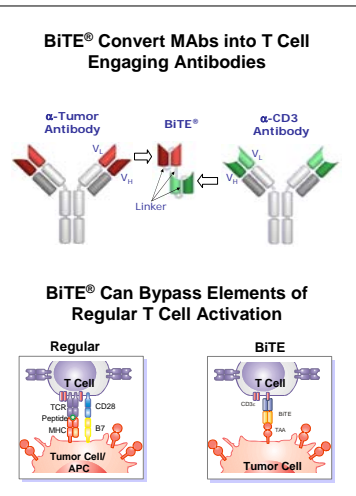
## Introduction

BiTE antibodies are emerging as a new class of therapeutic antibodies with the capability of engaging cytotoxic T-cells for a highly specific redirected lysis of tumor cells. Clinical proof of concept was obtained with CD19-specific BiTE antibody MT103 (MEDI-538) in late-stage lymphoma patients showing clinical complete and partial responses at very low doses of the antibody (0.015 mg/m<sup>2</sup> per day, and higher). Because of its short half life, MT103 is administered by continuous intravenous administration. MT110 is a novel BiTE antibody targeting EpCAM (CD326) for treatment of solid tumors.

The objective of this study was to explore alternative routes of administration for BiTE antibody MT110 in cynomolgus monkeys and to determine its bioavailability after subcutaneous (s.c.) injection. The feasibility of continuous s.c. delivery was tested using a minipump as initially developed for administration of insulin.



Taken from Bargou R. et al., *ASH Annual Meeting (2007)*. Anti-CD19 BiTE Antibody MT103 (MEDI-538) Induces Dose-dependent Objective Complete and Partial Responses in Relapsed Non-Hodgkin Lymphoma (NHL) Patients. Update from Ongoing Phase I Study MT103-104.

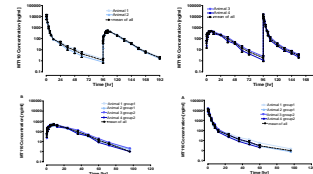


## Study Design

Groups	Route, Dose and Frequency of Administration	Volume [mL/kg b.w.]	No. of Animals	Animal No.
1	Day 1: i.v. bolus injection (0.5 mg/kg b.w.)	1	2	1, 2
	Day 5: s.c. bolus injection (0.5 mg/kg b.w.)	1		
2	Day 1: s.c. bolus injection (0.5 mg/kg b.w.)	1	2	3, 4
	Day 5: i.v. bolus injection (0.5 mg/kg b.w.)	1		
3	Daily s.c. bolus on test days 1 to 6 (0.166 mg/kg b.w.)	1	3	5-7
4	Continuous i.v. infusion on test days 1 to 6 (0.166 mg/kg b.w./24 hr for 6 days)	16	3	8-10
	1st pump: bolus for 20 min (90.58 µg/kg b.w./20 min) on test day 1 and then maintenance (6.945 µg/kg b.w./hr) for 59 hours	Depends on pump setting		
5	2nd pump: maintenance (6.94 µg/kg b.w./hr) for 72 hours (the 2nd pump is filled and prepared for attachment before removing the 1st pump)	Depends on pump setting	3	11-13
	1st pump: maintenance (6.94 µg/kg b.w./hr) for 72 hours starting on test day 1	Depends on pump setting		
6	2nd pump: maintenance (6.94 µg/kg b.w./hr) for 72 hours (the 2nd pump is filled and prepared for attachment before removing the 1st pump)	Depends on pump setting	3	14-16
	1st pump: maintenance (6.94 µg/kg b.w./hr) for 72 hours (the 2nd pump is filled and prepared for attachment before removing the 1st pump)	Depends on pump setting		

## Bolus i.v. + s.c. & vice versa

### Groups 1+2

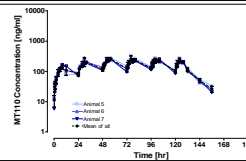


Main pharmacokinetic parameters of MT110 in Cynomolgus monkeys from treatment groups 1 and 2 after bolus i.v. and bolus s.c. injection

Route	T <sub>max</sub> hr	C <sub>max</sub> ng/mL	t <sub>1/2</sub> hr	AUC <sub>last</sub> hr*ng/mL	V <sub>z</sub> mL/kg	CL mL/hr/kg	F %
i.v. (n=4)	0.31 ± 0.46	13381.17 ± 2123.9	11.03 ± 0.5	24215.84 ± 2783.3	331.74 ± 44.682	20.84 ± 2.603	
s.c. (n=4)	9.00 ± 2	485.63 ± 55.21	10.31 ± 0.46	10034.05 ± 1154.56	682.61 ± 56.86	46.00 ± 4.88	45.37 ± 1.91

## Daily s.c.

### Group 3



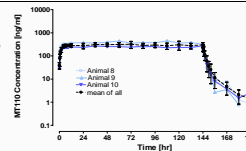
Main pharmacokinetic parameters of MT110 in Cynomolgus monkeys from treatment group 3 after bolus s.c. injection of MT110 for 6 days

Last Dose	T <sub>max</sub> hr	C <sub>max</sub> ng/mL	t <sub>1/2β</sub> hr	AUC <sub>last</sub> hr*ng/mL	V <sub>z</sub> mL/kg	CL <sub>F</sub> mL/hr/kg	F %
Mean (n=3)	5.33 ± 2.31	238.07 ± 33.82	11.28 ± 0.78	3626.3 ± 355.9	668.0 ± 92.8	41.3 ± 4.8	49.8 ± 1.9

based on the last profile

## Continuous i.v.

### Group 4

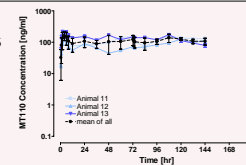


Main pharmacokinetic parameters of MT110 in Cynomolgus monkeys from treatment group 4 after continuous i.v. injection for 6 days

C <sub>max</sub> ng/mL	C <sub>min</sub> ng/mL	t <sub>1/2</sub> hr	AUC <sub>last</sub> hr*ng/mL	V <sub>z</sub> mL/kg	CL mL/hr/kg
Mean (n=3)	344 ± 95.2	291.5 ± 60.3	10.27 ± 1.8	42481 ± 10516	364 ± 121.5

## Continuous s.c.

### Group 5

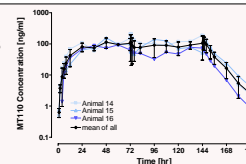


Pharmacokinetic parameters of MT110 in Cynomolgus monkeys from treatment group 5 after bolus s.c. injection followed by continuous s.c. infusion for 6 days

C <sub>min</sub> ng/mL	t <sub>1/2</sub> hr	AUC <sub>last</sub> hr*ng/mL	V <sub>z</sub> mL/kg	CL <sub>F</sub> mL/hr/kg	F %
Mean (n=3)	109.4 ± 21.4	n.c.	15688 ± 4040	n.c.	n.c.

## Continuous s.c.

### Group 6

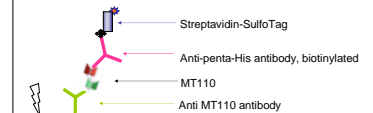


Pharmacokinetic parameters of MT110 in Cynomolgus monkeys from treatment group 6 continuous s.c. injection for 6 days

C <sub>min</sub> ng/mL	t <sub>1/2β</sub> hr	AUC <sub>last</sub> hr*ng/mL	V <sub>z</sub> mL/kg	CL <sub>F</sub> mL/hr/kg	F %
Mean (n=3)	95.3 ± 13.5	8.12 ± 1.2	13206.5 ± 3710.7	932.9 ± 268.8	80.19 ± 25.02

## Analytical Method

- MT110 PK ELISA based on electrochemiluminescence detection (ECL) by Meso Scale Discovery (MSD)
- The assay is based on ELISA sandwich method
- Coating: Anti-MT110 antibody
- Serum samples containing MT110 are added to the plates
- The hexahistidin-tagged MT110 is bound to the coated MT110
- The complex is incubated with biotin-labeled anti-penta-His antibody
- Streptavidin-SulfoTag is added and voltage is impressed on the plate
- Light emitted by the bound SulfoTag is detected by a MSD Sector Imager 2400 device.



- All samples were analyzed in triplicates in one valid measurement
- Data analysis was performed with the pharmacokinetic software package WinNonlin Pro 4.1 (Pharsight Corporation, USA; 2001)

## Conclusions

- Bolus, repeated and continuous s.c. administration of MT110 are feasible
- MT110 is well bioavailable in serum after s.c. administration
- Bioavailability was 30% and 50% for the continuous and bolus s.c. routes of administration, respectively
- Mini-pumps, as used for s.c. delivery of insulin to diabetes patients, achieve very even serum levels of MT110 as seen after continuous i.v. infusion
- Mini-pumps may provide for a very convenient delivery of MT110 and other BiTE antibodies to cancer patients
- The pharmacokinetic parameters after i.v. and s.c. bolus and continuous infusion to cynomolgus monkeys are largely comparable
- The apparent elimination half life was well comparable among the different routes of administration (between 8.1 and 11.03 hr), except for the daily s.c. bolus injection (26.4 hr)
- Subcutaneous delivery of BiTE antibodies by either bolus or mini-pump delivery is worth to be investigated in clinical trials

## References

- Brischwein K. et al. MT110: a novel bispecific single-chain antibody construct with high efficacy in eradicating established tumors. *Mol Immunol* 2006; 43:1129-43.  
 Baeuerle PA, et al. BiTE: A new class of antibodies that recruit T-cells. *Drugs Fut* 2008; 33:137.