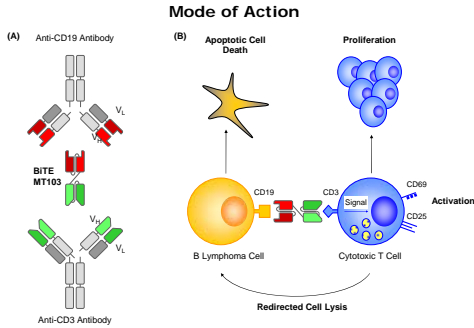


Confirmation of Safety, Efficacy and Response Duration in Non-Hodgkin Lymphoma Patients treated with 60 µg/m²/d of BiTE® Antibody Blinatumomab



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Blinatumomab (MT103), a T Cell-engaging BiTE® Antibody



Safety Profile at 60 µg/m²/d

Most Common Adverse Events

Preferred Term	All Grades N (%)	Grades 3/4 N (%)
Pyrexia	13 (100)	0
Lymphopenia	10 (76.9)	10 (76.9)
Leukopenia	9 (69.2)	2 (15.4)
Headache	9 (69.2)	0
C-reactive protein increase	8 (61.5)	3 (23.1)
Hyperglycaemia	8 (61.5)	3 (23.1)
Thrombocytopenia	7 (53.8)	1 (7.7)
Tremor	6 (46.2)	1 (7.7)
Fatigue	6 (46.2)	0
Diarrhoea	6 (46.2)	0
Weight increased	6 (46.2)	0
Dizziness	5 (38.5)	0
Gamma-GT increased	5 (38.5)	2 (15.4)
Mucosal dryness	5 (38.5)	0
Chills	5 (38.5)	0
Neutropenia	5 (38.5)	2 (15.4)
Nausea	5 (38.5)	0
Haematuria	5 (38.5)	0

Regardless of Relationship, based on 13 patients in data base having received 60µg/m²/d in first treatment cycle. In addition to the above, grade 3/4 events in > 1 patient: three encephalopathies grade 3, two Fibrin D-Dimer increases grade 3.

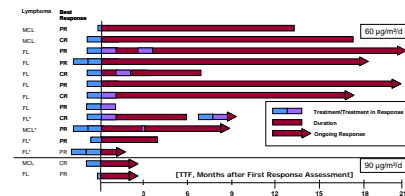
Dose-dependent Clinical Responses Cheson Criteria - Independent Review

Response Rate in Evaluable Patients at 60 µg/m²/ 24 h = 12/12 (100%)

Dose Level	Patients (n=50)	Complete Response	Partial Response	Overall Response Rate
0.5 – 5 µg/m ² /24 h	13	0	0	0/13
15 & 30 µg/m ² /24 h	20	2	2	4/20
60 µg/m²/24 h	9	3	5	8/9*
Step to 60 µg/m²/24 h (starting dose 5 and/or 15)	4	2	2	4/4
90 µg/m ² /24 h	4	1	1	2/4#

* One patient not evaluable due to treatment discontinuation after 2 days.
 # Two patients not evaluable due to DLTs.

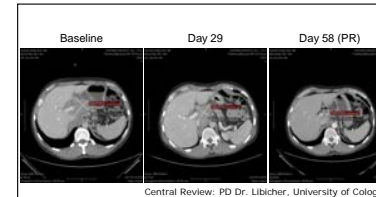
Durability of Responses at 60 and 90 µg Dose Levels



*The last four patients listed at 60 µg/m²/d above had a low B:T cell ratio and, therefore, were treated at a lower dose (5 or 15 or 30 µg/m²/d for the first 2 weeks. TTF = Time to Treatment Failure.

Response in Patient with Bulky Mantle Cell Lymphoma

- Patient with MCL stage IV A, 42 y, male
- Low B:T cell ratio, blinatumomab treatment: 5 → 60 µg/m²/d



Retreatment after Relapse of Follicular Lymphoma

- Patient with follicular lymphoma stage IVBE; 66 y, female
- Prior treatments: Rituximab-CHOP Sep 2006 – Feb. 2007, Rituximab May 2007 –Feb. 2008., Zevalin Nov. 2007 and Jan. 2008
- Start of blinatumomab: Low B:T cell ratio, blinatumomab treatment: 15 → 60 µg/m²/d Patient achieved PR, no neurological adverse events
- Retreatment with blinatumomab at time of relapse: High B:T cell ratio, blinatumomab treatment at 60 µg/m²/d Patient again achieved a PR, no neurological adverse events
- Retreatment possible with re-induction of response

Predictive Biomarker for Neurological Events

- Most adverse events --including neurological events-- are associated with first dosing
- Early adverse events are the consequence of initial T cell activation
- Newly activated T cells --close to blood brain barrier (BBB)-- may have a temporary local bystander effect on BBB
- B target cells in blood enable early adaptation of T cell in blood
- Adapted T cells no longer exert bystander effect on BBB
- This way, B target cells in peripheral blood protect from neurological events

Incidence of Neurological Events Depends on B:T Cell Ratio

Dose Level	Neurological Events Leading to Treatment Discontinuation/Treatment Cycle	
	B:T Cell Ratio in Blood Low (<1:8)	High (≥1:8)
<15 µg/m ² /d	0/3	0/10
15/30 µg/m ² /d	4/8	0/15
60 µg/m ² /d	5/8	0/12
90 µg/m ² /d	1/1	2/3

Based on all 60 treatment cycles in all 50 patients, highest dose level in the respective cycle is considered

Recommended Dosing Algorithm for Blinatumomab

- Patients with high B:T cell ratio (majority): 60 µg/m²/d for 8 weeks → Objective responses in 8 out of 8 evaluable patients
- Patients with low B:T cell ratio (minority): Goal is to prevent dosing interruption due to neurological events. Achieve goal by adapting T cells by step-wise dose increase. Experience with step-wise increase in 4 patients:
 - #1: 15 → 60 µg/m²/d: Late neurological event leading to discontinuation in week 4
 - #2: 15 → 60 µg/m²/d: No neurological event
 - #3: 5 → 60 µg/m²/d: No neurological event
 - #4: 5 → 15 → 60 µg/m²/d: No neurological event
 Objective responses in 4 out of 4 patients
- Recommended algorithm:
 - Low B:T cell ratio → Start with low dose and step up to high dose
 - High B:T cell ratio → Start with high dose

Summary

- 60 µg/m²/d-dose level of blinatumomab in general has a favorable tolerability profile
- Most common adverse events were pyrexia, lymphopenia, headache
- Most common adverse events leading to early discontinuation were neurological events: Mitigation possible by step-up dosing
- Low peripheral B:T cell ratio identified as predictive biomarker for neurological events
 - Low B:T cell ratio → Start with low dose and step up to high dose
 - High B:T cell ratio → Start with high dose
- 100% response rate (12/12) in evaluable patients with high B:T cell ratio starting at 60 µg/m²/d and in patients with low B:T cell ratio using step-wise increase to 60 µg/m²/d
- Response duration up to 20 months (ongoing in 7/12 patients)
- Expedited development of blinatumomab in NHL patients at dose level of 60 µg/m²/d is warranted

Phase I Trial in Advanced B-NHL

Study population

- 50 patients with relapsed non-Hodgkin's lymphoma
- Median age of 66 years; stages: IV 60%, III: 30%, II: 10%
- Most patients with FL* and MCL, ~40% each
- Few patients with MZL, CLL/SLL, MW/PL, DLBCL: total ~20%
- Median of 3 previous regimens (range 1-12)
- 90% of patients pretreated with rituximab, 45% of patients pretreated with fludarabine

Design

- 3+3 dose escalation; 7 dose levels from 0.5 µg/m²/d to 90 µg/m²/d
- Continuous i.v. infusion via port with portable pump over 4-8 weeks (out-patient as of week 3)

Objectives

- Safety and tolerability, PK, PD, anti-tumor activity

*FL: Follicular lymphoma, MCL: Mantle cell lymphoma, CLL: Chronic lymphocytic leukemia., SLL: Small lymphocytic leukemia, PL: plasmocytic lymphoma, WM: Waldenström's macroglobulinemia, MZL: Marginal zone lymphoma, DLBCL: Diffuse large B-cell lymphoma

General Safety Information

Most common adverse events (regardless of relationship, all dose levels):

- Pyrexia (75%), lymphopenia (75%), leukopenia (57%), C-reactive protein increase (53%), headache (45%), thrombocytopenia (39%), weight increase (39%), fatigue (37%), fibrin D dimer increase (37%)

Dose dependency

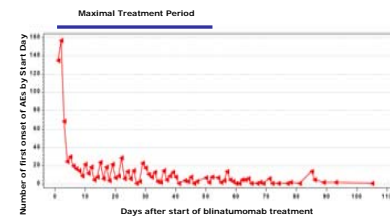
- Possible dose dependency of adverse events seen for pyrexia, lymphopenia, and headache

Maximal dose tested: 90 µg/m²/d

- Neurological events were the dose limiting toxicity

Majority of Adverse Events Occurred During First 3 Days of Treatment

First Dosing Effect with Subsequent Adaptation



Neurological Events Leading to Discontinuation

- Twelve out of 50 patients (total of 60 cycles) discontinued treatment due to neurological events
- Symptoms included encephalopathy, cerebellar syndrome, speech impairment, disorientation
- Most events occurred within 2 days after start of infusion
- No findings by MR imaging: CSF shows disturbance of blood brain barrier in all patients with neurological events
- Evidence for dose dependency
- Five out of 12 affected patients achieved an objective response
- All events were fully reversible within 72 hours after discontinuation; no sequelae