Phase 2 Study of the Bispecific T-cell Engager (BiTE) Antibody Blinatumomab in relapsed/refractory Diffuse Large B-cell Lymphoma

Objective: To evaluate the efficacy & safety of blinatumomab (Blincyto®) in patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) dosed either stepwise (9-28-112 mcg/day) with weekly dose increases or as a single continuous infusion (112 mcg/day). Both groups used dexamethasone for prophylaxis.

Background: Blinatumomab (Blincyto) is a bispecific, T-cell engaging (BiTE®) is an anti-CD19/CD3, antineoplastic, monoclonal antibody (Appendix 1). Blincyto was awarded breakthrough therapy designation & FDA approved for the treatment of Philadelphia chromosome negative (Ph-), r/r B-cell precursor acute lymphoblastic leukemia (ALL) in 2014.

Trial Registration: www.clinicaltrials.gov # NCT01741792
Sponsors & Collaborators: Supported by research funding from Amgen, Inc.

Trial Design: Multicenter (6 sites, Germany), open-label, single agent, phase 2 study. Enrollment August 2012 to July 2014

Primary Outcomes: Overall Response Rate (ORR) at week 10 after 18 weeks of blinatumomab Based on independent central radiologic assessment Cheson revised response criteria for malignant lymphomas: included contrast enhanced computerized tomography (week 10) & fluorodeoxyglucose positron emission tomography (PET) (week 11)

Secondary Outcomes: Complete Response (CR) & Partial Response (PR) rates, duration of response (DOR), progression free survival (PFS), overall survival, incidence & severity of adverse events.

Inclusion Criteria: Age ≥ 18 years, 1st or subsequent relapse of histologically confirmed DLBCL (WHO classification). Refractory to last treatment (nonresponse or relapse ≤ 6 months, relapse after autologous hematologic stem cell transplant (HSCT) or relapsed an ineligible for autologous HSCT. Life expectancy ≥ 12 weeks, adequate liver, renal & bone marrow function

Exclusion Criteria: CNS involvement, malignancy past 5 years, active infection, active autoimmune disorders or human anti-murine antibodies. Allogenic HSCT at any time, autologous HSCT in prior 6 weeks, chemotherapy in prior 2 weeks or radiotherapy or immunotherapy in prior 4 weeks.

Statistics: Time-to-event variables (Kaplan-Meier method). ORR for evaluable patients (received study drug at target dose for at least 7 days or discontinued due to disease progression)

Table 1: Sample size based on Simon 2-stage design (n=25 total patients)

<table>
<thead>
<tr>
<th>Simon 2-stage design</th>
<th>Stage 1: Dose Finding Phase*</th>
<th>Stage 2: Toxicity &amp; Efficacy</th>
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<tbody>
<tr>
<td>Sequential Cohort Endpoints</td>
<td>Cohort 1 (n=6): Stepwise Dosing 9→28→112 mcg/day Escalation on day 8 &amp; day 15</td>
<td>Assess 1° efficacy &amp; toxicity of each cohort</td>
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<td>Cohort 2 (n=6): flat dose 112 mcg/day</td>
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<td>Cohort 3 (n=+13) dosing based on results from Stage 1: Dosing 9→28→112 mcg/day Escalation on day 8 &amp; day 15</td>
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*All patients received prophylaxis with dexamethasone for each infusion.
Termination point: if 1 or none of 6 patients in cohorts 1 & 2 showed a CR or PR in both cohorts.

Baseline Demographics (n=25)

- Median Age in years (Range) 66.0 (34-85) Women n = 11 (44%)
- Ann Arbor disease stage I & II (%) 5 (20%) III & IV 20 (80%)
- High Risk by IPI 5 (20%) Refractory 16 (64%) Bulky Disease 7 (28%)
- Median # prior treatments (Range) 3 (1-7) Prior autologous HSCT 7 (28%)
- Median months since last treatment (Range) 1.5 (0.2-73.1)
- Median months since last Rituximab (Range) 3.1 (7.8-73.1)
- Transformed disease 10 (40%)
Table 2: Study Results: Cohort II (flat dose) terminated early for safety reasons
Overall median duration of blinatumomab exposure 46.8 days (interquartile range 22.1-76.9 days)

<table>
<thead>
<tr>
<th>Distribution of Patient Outcomes</th>
<th>Treatment Ended in Cycle 1 (induction) (Median exposure to blinatumomab 29.2 days)</th>
<th>17/25 (68%)</th>
<th>Reasons: disease progression (36%), adverse events (20 %), physician decision (12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Ended in Cycle 2 (Consolidation)</td>
<td>7/25 (28%)</td>
<td></td>
<td>Reasons: Adverse events (4%), completion of study (24%)</td>
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<tr>
<td>Retreatment</td>
<td>1/25 (4%)</td>
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Safety & Tolerability

Adverse Events (step wise dosing)
46/47 neurologic events resolved; 1 not considered related to blinatumomab
Median onset to neurologic event: 18 days
Median resolution: 4.5 days
21/23 experienced serious adverse events (8 considered blinatumomab related)

Adverse Events (flat 112 mcg/day dosing), n=2
1 experienced neutropenia (Grade 4), unrelated
1 experienced respiratory failure (Grade 4) considered related to therapy

Neurologic events 16/23 (69.6%); 5 (21.7%) Grade 3 Tremor (47.8%). Speech disorder> dizziness, encephalopathy > aphasia, somnolence, disorientation, confusion, paresthesia

Other Common Adverse Events ( occurring in > 15% of patients): pyrexia, fatigue, edema, thrombocytopenia, pneumonia, diarrhea, device related infection, leukopenia, C-reactive protein increased, hyperglycemia, blood glucose increased, cough, back pain, hypokalemia, rash

Both experienced Grade 3 neurologic events related to therapy
• 1 was able to continue therapy → PR
• 1 patient had CNS DLBCL cells not previously detected

Efficacy based on tumor response in cycle 1 in evaluable patients, n=21; independent radiologic assessment*

- ORR → 9/21 (43%)
- CR → 4/21 (19%)
- Stable disease → 2/21 (9.5%)
- Among the 4 patients not included, 1 remained stable, 3 were not evaluated
- Median DOR → 11.6 months (95% CI 0.9 to not estimable)
- ORR refractory disease → 3/16 (19%) DOR not measurable
- ORR relapsed disease at baseline → 6/9 (67%) DOR → 8.7 months (range 0.7-17.5 months)
- Median PFS → 3.7 months (95% CI 1.4-7.7) ongoing (longest PFS 20.1 months)
- Median overall survival 5.0 months (95% CI 2.3 to not estimable); Median follow up 11.7 months at time of analysis

Figure 1: Tumor size changes during cycle 1 for evaluable patients.

*patients prior autologous HSCT; Δ, bulky disease (>7.5 cm); o, transformed disease baseline. PD, progressive disease; SD, stable
Author’s Conclusions & Comments:

- Results corroborate phase I trial results: 6/11 (55%) patients with r/r DLBCL responded with 4 CR (36%)
  - For patients with r/r Non-Hodgkin’s Lymphoma, maximum tolerated dose (MTD) 60 mcg/m² given in two-step dosing of 5 mcg/m² on days 1-7; 15 mcg/m² on days 8-14; then 60 mcg/m²; median response duration 404 days (95% CI: 201-1129) (ME Goebelner, 2016)
  - At least one week at target dose of 112 mcg/day needed for efficacy (referenced Phase I study, no reference)
  - 39% of patients in step-wise dosing discontinued because of early tumor progression → more rapid dose escalation may have been beneficial
- 3 patients with PR at week 11 later achieved a CR as measured by PET (Used Cheson criteria, 1st time to assess)
-评价时间尺度可能需要扩大
- Blinatumomab efficacy compared to other published r/r DLBCL drugs studied
  - Pinatuzumab bedotin (ORR 39%), Y-ibrutumomab tiuxetan (ORR 53%), lenalidomide (ORR 35%), nivolumab (ORR 36%), inotuzumab ozogamicin (ORR 15%), ibrutinib (ORR 225), buparlisib (ORR 12%)
- Patients in this study were refractory and had short time since last treatment (1.5 months)
  - Response rate was lower (19%) than in patients with later relapse (67%)
- All patients with disease progression leading to discontinuation were refractory (Figure 1)
  - Refractory ORR 19%; Late Relapse ORR 67%
- Side effects are limiting:
  - Grade 3 neurologic events occurred in both phase I & phase II trials; mechanism unknown
  - Short half-life allows for interruption if adverse effects
- Future course: better understanding of minimum treatment duration to achieve response
  - modified dose schedules to achieve target dose earlier
  - use of blinatumomab as consolidation therapy after initial “debulking”

Bibliography


Sentman, N. S. &., 2016. Bispecific T-Cell Engagers (BiTEs) as Treatment of B-Cell Lymphoma. Journal of Clinical Oncology, 1 April, 34(10), pp. 1131-1134.
**Appendix 1: Background Information**: First FDA approved BiTE® antibody & first single-agent immunotherapy.

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**Fig 1. Blinatumomab mechanism of activity**: (A) Blinatumomab is composed of two single-chain variable fragments (Fv) connected by a flexible polypeptide chain linker; one Fv binds CD3 (T-cell, $K_d \sim 10^{-7}$ M); the other Fv bind ($K_d \sim 10^{-9}$ M) CD19 ‘tumor cell (B) or CD19’ cell (C). When both Fv chains bind simultaneously (CD3 and CD19) T-cell activation is triggered, leading to the release of cytokines (eg, interferon gamma, tumor necrosis factor α, interleukin-2), cytotoxic granules & T-cell proliferation. Cell lysis is a result of membrane perforation & subsequent granzyme induced programmed cell death. “BiTEs trigger serial killing by activated T cells. (D)”. (Sentman, 2016) Peripheral B-cell depletion occurs at doses $> 5$ mcg/m$^2$/day; marrow depletion was observed at doses $> 15$ mcg/m$^2$/day. B-cell recovery was not observed during treatment & IgG level recovery took up to 1 year (M Klinger, 2016) Cytokine & granzyme release appear to occur mostly in the first 48 hours of infusion or dose increase and appeared to be reduced by using pentosan polysulfate (PPS) to block T-cell migration into the CNS or dexamethasone (DEX) to decrease cytokine activity. Adverse effects appear to resolve when treatment is discontinued. AE, adverse event; B-ALL, B-cell acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma.” (Sentman, 2016)

Blinatumomab (BLINCYTON™) received breakthrough therapy designation for the treatment of r/r, Ph(-) ALL in December of 2014 based on results from Amgen’s 211 trial; 77/185 patients (41.6%; 95% CI: 34.4-49.1) met the primary endpoint of complete remission or complete remission with partial hematologic recovery. (Amgen, 2014)

**Boxed Warnings**: Cytokine Release Syndrome (CRS) & Neurological Toxicity REMS program @ [http://www.blincytorems.com/](http://www.blincytorems.com/)

**Most common adverse reactions** ($\geq 20\%$): pyrexia (62%), headache (36%), peripheral edema (25%), nausea (25%), hypokalemia (23%), rash (21%), tremor (20%) & constipation (20%). 65% of patients reported serious adverse reactions.

**Administration**: continuous intravenous infusion, 0.2 micron in-line filter, prime line with prepared solution (see insert)

**Storage**: prepared IV Bag 48 hours at room temperature (includes infusion time); 8 days refrigerated; light protected

**Dosing**: 4 weeks of continuous infusion followed by 2-weeks without treatment: Cycle 1: Stepwise Dosing 9 mcg/day on days 1 to 7 then 28 mcg daily on days 8 to 28. Cycle 2 to 5: 28 mcg daily as continuous infusion on days 1 to 28 of 6 week cycle. **Premedicate** with dexamethasone 20 mg IV one hour before the first dose of a cycle, an increase or an interruption $\geq 4$ hours.

**Renal Adjust**: Consider CrCl $< 30$ mL/min **Hepatic**: Interrupt therapy for transaminase $> 5x$ ULN or bilirubin $> 3 x$ ULN

**Monitor**: CBC with differential, liver function test (baseline & throughout), signs & symptoms of CRS, neurotoxicity, infection & TLS tumor lysis syndrome **Low Emesis Potential**

**Drug Interactions**: BCG, Deferiprone, Dipyrone, Natalizumab, Pimecrolimus, Tacrolimus, Tofacitinib, live vaccines

**Size**: $\sim 53$ kDa **Absorption**: linear to dose (28 mcg/day dose Css~ 0.7 ng/mL; 112 mcg/day $\sim 3$ ng/mL) **Distribution**: 4.52 L

**Half-life**: 2.11 hours **Excretion**: expected metabolism via catabolism; minimal urine

**Form**: Solution (reconstituted) 35 mcg (1): $\$3814.28$ Stable in NS only (Lexicomp, 2016)

**Interactions**: transient cytokine elevations may suppress CYP450 enzymes (Amgen, 2014)
Phase I studies showed neurologic events were dose limiting with a maximum tolerated dose of 60 mcg/day continuous infusion (4 to 8 weeks).

Phase II Results (December 2015): BLAST trial Abstracts

- 116 patients with B-cell precursor ALL & persistent or recurrent minimal residual disease (MRD)


Interim analysis showed the primary endpoint of overall survival was met in the TOWER phase III, randomized, open-label study versus standard of care in adults with Philadelphia chromosome negative r/r B-cell precursor acute lymphoblastic lymphoma.

Dosing: continuous IV infusion over 6 weeks with 4 weeks of blinatumomab followed by 2 week treatment free interval. First induction cycle: initial dose 9 mcg/day x 7days then 28 mcg/day starting on day 8 through day 29 (week 4). All subsequent cycles (starting with second induction cycle through consolidation) will be at 28 mcg/day for all 4 weeks.

Epidemiology:

- Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 25 percent of NHL cases. (See 'Epidemiology' above.)
- Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen. Systemic "B" symptoms (ie, fever, weight loss, drenching night sweats) are observed in approximately 30 percent of patients. Bone marrow involvement and extranodal extramedullary disease are seen in up to 30 and 40 percent of cases, respectively. (See 'Clinical presentation' above.)
- DLBCL is a heterogeneous group of tumors consisting of large, transformed B cells with prominent nucleoli and basophilic cytoplasm, a diffuse growth pattern and a high proliferation fraction (picture 2). Tumor cells in DLBCL generally express pan B cell antigens (CD19, CD20, CD22, CD79a). The majority has genetic abnormalities, but there is no single cytogenetic change that is typical or diagnostic. (See 'Pathology' above.)
- The diagnosis of DLBCL is best made based on excisional tissue biopsy, most commonly a lymph node. The diagnosis is based on morphology and immunophenotyping, which is essential to make the diagnosis. (See 'Diagnosis' above.)
- The differential diagnosis of DLBCL includes other large cell malignancies, such as carcinoma, melanoma, and other types of lymphoma (table 2). (See 'Differential diagnosis' above.)
- It is increasingly appreciated that the diagnostic category of "DLBCL" is quite heterogeneous in terms of morphology, genetics, and biologic behavior. A number of clinicopathologic entities are now recognized that are sufficiently distinct to be considered separate diagnostic categories:
  - T cell rich large B cell lymphoma (see 'T cell histocyte rich large B cell lymphoma' above)
  - Primary mediastinal large B cell lymphoma (see 'Primary mediastinal large B cell lymphoma' above)
  - Intravascular lymphoma (see 'Intravascular large B cell lymphoma' above)
  - Lymphomatoid granulomatosis and EBV-positive DLBCL of the elderly (see 'Lymphomatoid granulomatosis' above and 'EBV-positive DLBCL of the elderly' above)

Pathophysiologic: Patients with relapsing ALL have a poor response rate with an OS rate of 3-5 months. (Advani, 2013)
neutrophils 2-5 days, eosinophils 7-12 days, basophils 12-15 days, monocytes 2-5 days, lymphocytes ½ to 1 day, megakaryocytes platelets 9-12 days

Current Treatment: Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up† Tilly et al. 2015 Annals of Oncology 26 (S5): 116-125

Table 3. Recommended treatment strategies in diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>Patients ≤60 years</th>
<th>Patients &gt;60 years</th>
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<tbody>
<tr>
<td>IPI low risk (aIPI = 0) and no bulk</td>
<td>IPI low risk (aIPI = 0) with bulk or IPI low-intermediate risk (aIPI = 1)</td>
</tr>
<tr>
<td>R-CHOP21 × 6 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone)</td>
<td>R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk</td>
</tr>
</tbody>
</table>

Consider CNS prophylaxis in patients at risk for CNS progression (all ages)

<table>
<thead>
<tr>
<th>Elderly &gt;60 years</th>
<th>Fit, 60–80 years</th>
<th>Unfit or frail or &gt;60 years with cardiac dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R</td>
<td>&gt;80 years without cardiac dysfunction</td>
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<tr>
<td>Attenuated regimens: R-miniCHOP21 × 6</td>
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<tr>
<td>Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care</td>
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First relapse/progress

<table>
<thead>
<tr>
<th>Eligible for transplant</th>
<th>Not eligible for transplant</th>
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<tr>
<td>Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, RGDP) as salvage treatment For chemo-sensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse</td>
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<tr>
<td>Platinum- and/or gemcitabine-based regimens Clinical trials with novel drugs</td>
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>2 relapse/progress

<table>
<thead>
<tr>
<th>Eligible for transplant</th>
<th>Not eligible for transplant</th>
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<tbody>
<tr>
<td>Allogeneic transplantation Clinical trials with novel drugs</td>
<td></td>
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<tr>
<td>Clinical trials with novel drugs Palliative care</td>
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IPI, International Prognostic Index; aIPI, age-adjusted IPI; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ACVBP, doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone; IF-RT, involved-field radiotherapy; HDCT, high-dose chemotherapy; ASCT, autologous stem-cell transplantation; DHAP, cisplatin, cytarabine, dexamethasone; ICE, ifosfamide, carboplatin, etoposide; GDP, cisplatin, gemcitabine, dexamethasone; CNS, central nervous system; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone; R-C(X)OP, R-CHOP with substitution of doxorubicin.
Simon 2 stage design Background

In a typical two-stage trial, patients are enrolled in stage I. If the number of responses is fewer than or equal to prespecified, the trial is terminated for lack of efficacy. Otherwise an additional patients are enrolled in stage II. The total number of patients is . If the cumulative number of responses are fewer than or equal to , then lack of efficacy is concluded. Otherwise, it is concluded that the treatment is sufficiently effective for further investigation.

A two-stage design is indexed by four numbers, . These numbers are chosen so that the probability of concluding efficacy when the treatment is not effective is less than and the probability of concluding futility when the treatment is effective is less than .

For a given , there are many designs, i.e., that satisfy and conditions. Following are candidates for good designs among them.

1. The optimal design has the minimum expected sample size under .
2. The minimax design has the smallest .
3. The balanced design has . (reference Ye and Shyr)

There are softwares capable of finding these designs given . One such software is developed and maintained by Fei Ye (ye_fei_cn@yahoo.com) and freely available here. (Vanderbilt-Ingram Cancer Center, Biostatistics Shared Resource)