BioInvent

#EHA-2179, Abstract P1135 | Topic: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Safety and Preliminary Efficacy of BI-1206, an Antibody to CD32b (FcγRIIB), given in Combination with Rituximab in Subjects with Indolent B-Cell Non-Hodgkin Lymphoma

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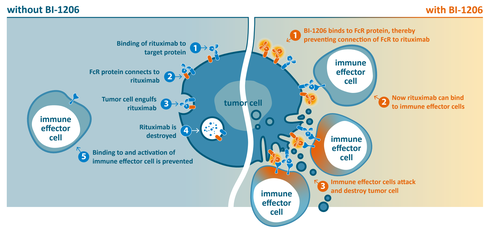
Background

Anti-CD20 antibodies, such as rituximab, are an essential therapy resource in patients with non-Hodgkin's B-cell lymphoma. However, approximately 15% of patients are refractory to treatment, and 25% relapse within 3 years following treatment. Non-clinical and clinical data indicate that the inhibitory Fc receptor CD32b (FcγRIIB) promotes resistance by acting both on tumor and immune effector cells. CD32b triggers rituximab internalization, and tumor CD32b expression correlate inversely with response to rituximab in MCL, FL, and DLBCL. BI-1206 is an anti-CD32b IgG1 antibody that blocks rituximab internalization and in non-clinical experimental models enhances efficacy and overcomes rituximab resistance.



Aims

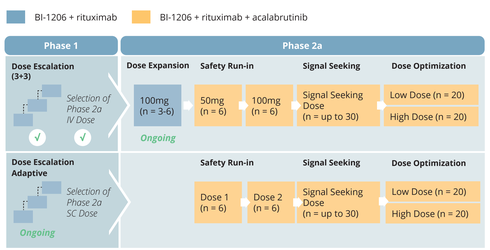
The aim of this study is to characterize the safety profile of BI-1206 in combination with rituximab, and to assess PK, PD and efficacy in relapsed or refractory (R/R) NHL.

Methods

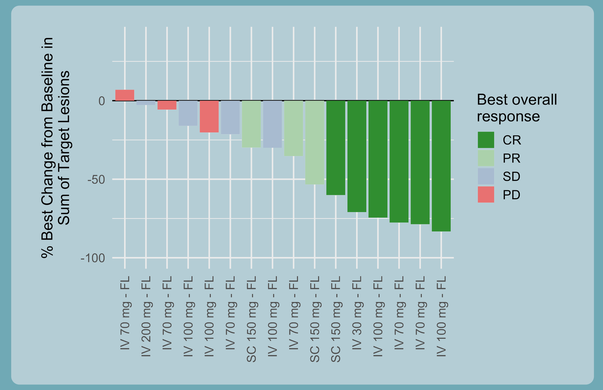
The current phase 1/2a clinical trial includes R/R B-cell NHL; subtypes FL, MZL, and MCL. In this trial, safety and tolerability of both IV and SC BI-1206 in combination with rituximab is evaluated. Corticosteroid pretreatment with two daily doses prior to IV administration was implemented after first three cohorts. IV Phase 2 dose has been established and dose expansion is ongoing. SC BI-1206 dose escalation is ongoing.

During induction therapy, patients receive one dose of single-agent rituximab (375 mg/m²) followed by dosing of BI-1206 with rituximab on weeks 2, 3, and 4. Patients showing clinical benefit at week 6 are eligible for maintenance therapy, with dosing of BI-1206 and rituximab every 8 weeks for up to 6 cycles.

In Phase 2a, BI-1206 will be evaluated in combination with rituximab and acalabrutinib, with a safety run-in followed by an expansion of up to 30 patients.



Co-administration of BI-1206 with rituximab led to high response rates in relapsed/refactory FL patients



Best response in tumor burden in FL patients.
(Color indicate Lugano criteria response)

Conclusions

- Addition of BI-1206 to rituximab treatment shows promising efficacy in R/R FL, with CRR of 38% and ORR of 56%.
- BI-1206 + rituximab appears to be safe and adverse drug reactions are manageable. Implementation of premedication with corticosteroids minimized risk and TEAEs after IV administration.
- Subcutaneous administration shows great potential to mitigate TEAEs further, and to provide prolonged target engagement with increased patient convenience.
- The combination will be further explored in Phase 2a with the addition of acalabrutinib.

Results

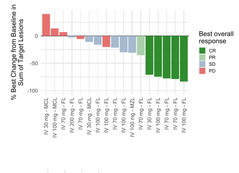
As of May 1, 2024, the most frequent related treatment-emergent adverse events after BI-1206 IV were thrombocytopenia and elevated transaminases. Thrombocytopenia ≥G3 occurred in 4 out of 10 subjects without premedication, and in 6 out of 13 subjects with premedication. No associated bleeding occurred. All events were resolved with a median duration of 5 days. Elevated liver enzymes ≥G3 occurred in 4 out of 10 subjects without premedication and 3 out of 13 subjects with premedication. Events were resolved with a median duration of 4 days without any clinical complication. DLTs occurred at IV dose levels of 70 and 100 mg but were not observed after introduction of two days steroid pretreatment. IV doses up to 200 mg were tested.

Safety findings	BI-1206 + Rituximab						
TEAEs	**IV**				**SC**		**Total**
Dose	30 mg	70 mg	100 mg	200 mg	150 mg	300 mg	
Number of subjects	N=3	N=8	N=8	N=4	N=5	N=2	N=30
Subjects with at least 1 TEAE any grade	3 (100%)	8 (100%)	7 (88%)	4 (100%)	5 (100%)	2 (100%)	29 (97%)
Subjects with ≥Grade 3 TEAEs	3 (100%)	7 (88%)	7 (88%)	3 (75%)	3 (60%)	2 (100%)	26 (87%)
Subjects with TEAEs related to rituximab	3 (100%)	7 (88%)	7 (88%)	2 (50%)	3 (60%)	1 (50%)	23 (77%)
Subjects with ≥Grade 3 TEAEs related to rituximab	2 (67%)	5 (63%)	5 (63%)	0	1 (20%)	1 (50%)	14 (47%)
Subjects with TEAEs related to BI-1206	3 (100%)	8 (100%)	7 (88%)	4 (100%)	3 (60%)	2 (100%)	28 (93%)
Subjects with ≥Grade 3 TEAEs related to BI-1206	1 (33%)	7 (88%)	7 (88%)	3 (75%)	3 (60%)	2 (100%)	23 (77%)
Subjects with serious TEAEs related to BI-1206	1 (33%)	1 (13%)	0	2 (50%)	1 (20%)	1 (50%)	6 (20%)
Subjects with treatment related AE:s that led to discontinuation	2 (67%)	2 (25%)	2 (25%)	3 (75%)	0	2 (100%)	11 (37%)
TEAEs of interest related to BI-1206							
Subjects with any grade Infusion/injection related reaction (IRR)	2 (75%)	8 (100%)	7 (88%)	3 (75%)	1 (20%)	2 (100%)	23 (77%)
Subjects with ≥Grade 3 Infusion/injection related reaction (IRR)	0	2 (25%)	2 (25%)	1 (25%)	0	1 (50%)	6 (20%)
Subjects with any grade Thrombocytopenia	0	4 (50%)	5 (63%)	2 (50%)	3 (60%)	1 (50%)	15 (50%)
Subjects with ≥Grade 3 Thrombocytopenia	0	3 (38%)	4 (50%)	2 (50%)	2 (40%)	1 (50%)	12 (40%)
Subjects with any grade Increased ALT/AST	0	6 (75%)	4 (50%)	2 (50%)	1 (20%)	2 (100%)	15 (50%)
Subjects with ≥Grade 3 Increased ALT/AST	0	4 (50%)	2 (25%)	1 (25%)	0	2 (50%)	9 (30%)

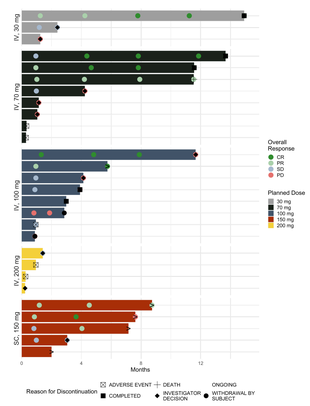
Baseline Demographics

Number of patients	**31**
Age	
Median (range)	71 (53-87)
Sex	
Female	14
Male	17
Disease type	
Relapsed	28
Refractory	3
Indication	
FL	26
MCL	3
MZL	2
Prior Lines of Therapy	
Median (range)	2.5 (1-8)
1	8
2	11
3	7
4	2
≥5	2
Prior aCD20	31 (100%)
Allogeneic transplant	0

- After IV treatment, objective response, complete response, and disease control rates (ORR, CRR and DCR) of 35%, 29% and 71% was seen as best response in 17 evaluable patients.
- SC administration has been shown to improve tolerability of BI-1206, and dose escalation is currently ongoing in the Phase 1 of this trial.
- In the SC arm, 6 patients have been treated to date with 1 CR, 2 PR, 1 SD out of 4 evaluable patients.
- In the subset of 16 FL patients, an ORR of 56% and a CRR of 38% was observed.



Best response in tumor burden in IV (top panel) and SC (bottom panel) patients.
(Color indicate Lugano criteria response)



Swimmer plot showing time on treatment for patients in Study 17-BI-1206-02

Forward looking

In the ROSEWOOD trial[1], addition of the BTK-inhibitor zanubrutinib to the anti-CD20 mAb obinituzumab increased the CRR in R/R FL patients from 19% to 39% and ORR from 46% to 69%. A smaller study from 2018 showed that acalabrutinib, alone and combined with rituximab, was well-tolerated and yielded promising response rates in FL[2].

With promising efficacy signal of BI-1206 + rituximab observed in Phase 1, development will proceed into a Phase 2a setting. Given the promising results of combinatory inhibition of CD20 and BTK in R/R FL patients, addition of acalabrutinib to treatment will be explored.

References:
[1] Zinzani *et al*, JCO 2023, **41** (33), "ROSEWOOD: A Phase II Randomized Study of Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab Monotherapy in Patients With Relapsed or Refractory Follicular Lymphoma"
[2] Fowler *et al*, JCO 2018, **36** (15s). " Acalabrutinib alone or in combination with rituximab (R) in follicular lymphoma (FL)"

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Study identifier: ClinicalTrials.gov ID: NCT03571568

Acalabrutinib is provided by AstraZeneca (LSE/STO/Nasdaq: AZN)