[P1089] MODELLING THE 10-YEAR COST EFFECTIVENESS OF BENDAMUSTINE AS FIRST LINE TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKAEMIA IN THE NETHERLANDS

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Background. Although promising treatment combinations for chronic lymphocytic leukemia (CLL) like fludarabine, cyclophosphamide and rituximab (FCR) became available in the last decade, a significant proportion of patients is not suitable or eligible for such intensive chemotherapy. In those patients chlorambucil remains a widely used first-line therapy. However, overall and complete response rates with chlorambucil are relatively modest and therefore more effective treatment options are required for this patient group. Bendamustine is a promising drug in this setting, but by being more expensive compared to chlorambucil, it will increase pressure on health care budgets. In this situation, healthcare authorities will require information on cost-effectiveness for regulating reimbursement. *Aims.* The objective of this study was to assess the cost-effectiveness of bendamustine compared to chlorambucil, the current first line treatment for CLL patients with Binet stage B or C disease not eligible for fludarabine combination therapy, from a health care payer perspective in the Netherlands. *Methods.* A Markov model was designed representing the normal evolution of patients with CLL over different treatment lines (Figure 1). Transition probabilities were derived from clinical trials. Healthcare resource utilisation was estimated for each CLL state using clinical guidelines and a Dutch CLL expert panel. Outcomes were life years (LY), quality-adjusted life years (QALYs), progression free life years (PFLY), and CLL related health care costs (e.g. in- and outpatient visits, diagnosis tests, chemotherapy and immunotherapy, costs of best supportive care). The model time horizon was 10 years. *Results.* The mean number of QALYs was 3.77 for bendamustine and 2.21 for chlorambucil. The total average costs amounted to €79,328 for bendamustine, and €67,172 for chlorambucil (2011 values). Compared with chlorambucil, the cost-effectiveness of bendamustine was €7,809 per QALY gained. The costs per LY gained were €7,374 and the costs per PFLY gained were €6,908. The probability is around 95% that bendamustine costs €20,000 per QALY when compared with chlorambucil. *Conclusions.* Bendamustine compared to chlorambucil, in previously untreated CLL patients with Binet stage B or C disease not eligible for fludarabine combination therapy, generated an ICER of €7,809 per QALY gained, indicating

that bendamustine is 10-year cost-effective as first line treatment for CLL in the Netherlands.

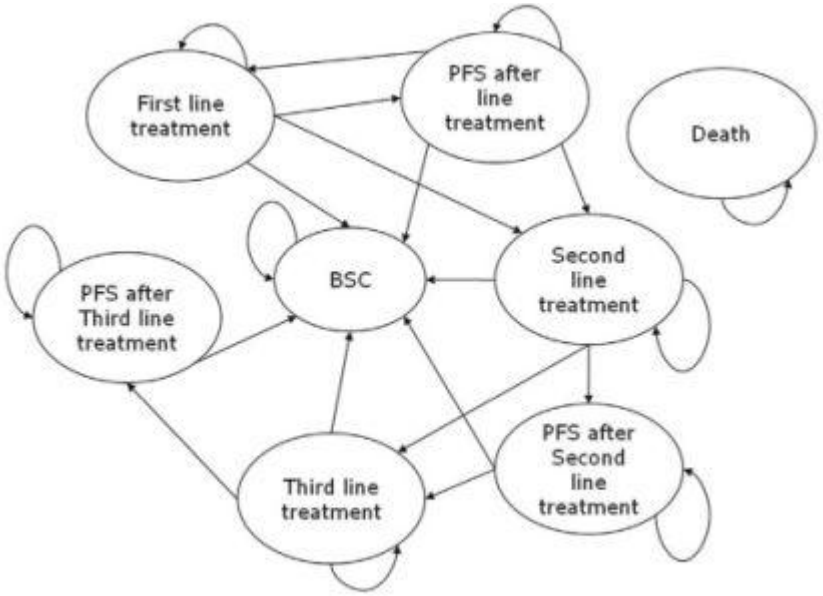

Figure 1: Structure of the Markov model

[P0144] INFLUENCE OF DIFFERENT TREATMENT REGIMENS ON SURVIVAL IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA – A META-ANALYSIS OF THE GERMAN CLL STUDY GROUP (GCLLSG)

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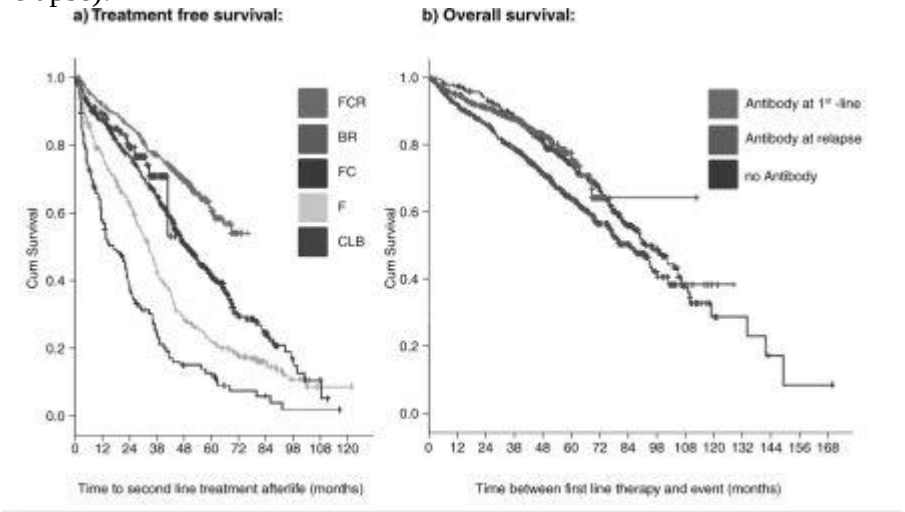
Background. A variety of first-line and relapse therapy regimens for patients with advanced chronic lymphocytic leukemia (CLL) have been established in the past years. Though ESMO guidelines recommend to repeat first-line therapy if relapse occurs later than 24 months after first-line chemoimmunotherapy, these recommendations have not been confirmed by clinical trials so far. However, the most beneficial composition and sequence of regimens (antibody-based, chemoimmunotherapy, CHOP-like regimen) regarding patients' treatment-free and overall survival remains unclear. *Aims.* The aim of this meta-analysis was to evaluate whether special therapeutic regimens have a positive impact on treatment-free and overall survival. *Methods.* From 1659 consecutive patients included in five different study protocols for first-line and relapse of the GCLLSG (CLL4, CLL5, CLL8, CLL2L (Fludarabine + Cyclophosphamide + Alemtuzumab; first-line and in relapse) and CLL2M (Bendamustine + Rituximab; first-line and in relapse) trial) we selected 1558 patients who received at least one therapeutic regimen. 101

patients had to be excluded never having received treatment in one of the trials. Patients were assigned to different treatment categories. For statistical analysis Kaplan-Meier estimators and curves were used including log-rank tests. *Results.* The median age at the beginning of first-line treatment of the whole series (n = 1558, 1113M/425F) was 61 (30-81) years. At first, patients were stratified according to the first-line treatment they received. Comparing the different regimens according to the study generations of the last two decades (first generation: CLL 4 - fludarabine monotherapy vs. fludarabine + cyclophosphamide; CLL 5 - chlorambucil monotherapy vs. fludarabine monotherapy; second generation: CLL 8 - fludarabine + cyclophosphamide vs. fludarabine + cyclophosphamide + Rituximab) treatment-free and overall survival steadily increases along with the advances in clinical CLL research (see figure 1). Thereafter we focused on different treatment regimens that have been administered at any time during the course of disease. Patients who received an antibody-based regimen at least once during their therapeutic course (n = 909) had a significantly longer overall survival than all other patients who had never been treated with antibody-containing therapy (OS after 60 months: 75.7% vs. 64.1%, p = 0.006, see figure 2). This was independent from the time point of administration (first-line or relapse). The CHOP-regimen (Cyclophosphamide, Vincristine, Doxorubicine and Prednisolone), which was often chosen as relapse treatment due to its assumed efficacy especially in high-risk situations (early relapse, unfavourable prognostic markers), was used in 202 patients. The overall survival in the CHOP-collective was significantly shorter than in the comparative group (p < 0.0001) although median observation time was not significantly different. However, this observation might reflect a bias in the selection of high risk patients for this relapse treatment. No influence on survival was observed in patients receiving a mitoxantrone-containing regimen at any time during the treatment course.
Summary/Conclusions. This meta-analysis shows that the advances in the development of strategies for first-line therapies result in prolongation of treatment-free and overall survival for patients with CLL and need of treatment. Chemoimmunotherapies prolong the survival independently of the time point of chemoimmunotherapy administration (for first-line therapy or relapse).



Abstract 0144 – Figure 1: a) Treatment-free survival for patients with different first-line therapies b) OS of pts. with antibody-based regimen vs.pts.with antibody-free regimen

Isfort S, Cramer P, Bahlo J, Busch R, Fischer K, Fink AM, Goede V, Elter T, Bergmann

[P0145] A SINGLE-ARM MULTI-CENTER TRIAL OF BENDAMUSTINE GIVEN WITH OFATUMUMAB (BENDOFA) IN PATIENTS WITH REFRACTORY OR RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA. GIMEMA CLL0809 PROTOCOL

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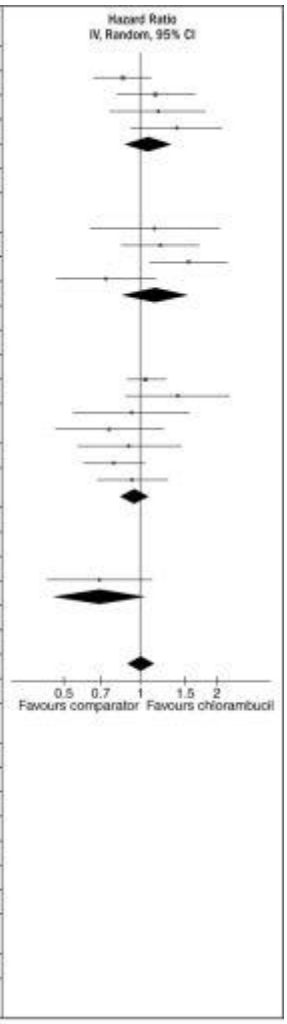
Background. The advent of chemo-immunotherapy associations has substantially improved the overall response rate (ORR), time to progression, and overall survival of chronic lymphocytic leukemia (CLL). However, CLL remains incurable and patients (pts) eventually relapse. The development of an effective therapy that is not cross-resistant with the treatment strategies currently available as front-line treatment is one of the clinical unmet needs in CLL. *Aims.* Within the GIMEMA network, we conducted a phase II, non-comparative, multicenter study (CLL0809) to assess the efficacy and safety of the combination of bendamustine and ofatumumab in relapsed/refractory CLL. *Methods.* Pts with active CLL, pre-treated with no more than two lines of therapy, were eligible. Therapy consisted of bendamustine (70 mg/m^2) for two consecutive days every 28 days and ofatumumab (300 mg on day 1 and 1000 mg on day 8 at the first cycle and 1000 mg on day 1 at the subsequent cycles). Treatment was administered up to 6 cycles. The response was assessed after 3 cycles and at the end of treatment. An extensive biological characterization was performed in all pts. *Results.* Fifty pts have been registered from 14 centers. One patient was ineligible due to active HBV infection. The median age was 66 years (46-81); 71% of pts were in Binet stages B/C and 30%had bulky adenopathy ≥5 cm. FISH analyses detected del(13q), del(11q), +12 or del(17p) in 47%, 12%, 20% and 20% of pts, respectively; 20% of pts carried a p53 mutation and 16% had NOTCH1 mutations; 59% of pts had unmutated IGHV genes, whereas ZAP-70 and CD38 were positive in 65% and 43% of cases. Previous treatments were fludarabine, rituximab or alemtuzumab-based therapy in 71%, 53% and 12% of pts, respectively; 39% of pts were pre-treated with two lines of therapy. The

response was assessable at the 3rd cycle in 35 patients and at the 6th cycle in 18 pts. The ORR was 89% at the 3rd cycle and 79% at the 6th cycle, with respectively 26% and 16% of complete remissions. At the 3rd cycle, pts with 17p- and/or p53 mutation had an ORR of 83%. Hematologic toxicity was the most common adverse event. Grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 65%, 18% and 4% of pts. A total of 3 severe infections were reported, including 2 fatal sepsis. Grade 3 infusion reactions to the first administration of ofatumumab occurred in 4 pts (2 skin rash, 1 sinus bradycardia, 1 hypotension plus dyspnoea). Eight pts went off study: two pts did not start treatment (1 for lack of drug supply and the other for informed consent withdrawal); 3 pts died during therapy (2 deaths were due to sepsis, while 1 patient died owing to a duodenal ulcer hemorrhage); in the remaining 3 pts therapy was stopped because of severe neutropenia, acute myocardial infarction or increased troponine levels. *Conclusions.* This preliminary analysis shows that the combination of ofatumumab and bendamustine is feasible and substantially effective in relapsed/refractory CLL patients with high risk clinical and biological features.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 COP vs. chlorambucil				
Catovsky 1988	-0.16	0.13	9.8%	0.85 [0.66, 1.10]
French cooperative 1990	0.14	0.18	6.8%	1.15 [0.81, 1.64]
Montserat 1985	0.16	0.22	5.1%	1.17 [0.76, 1.81]
Raphael 1991	0.33	0.21	5.5%	1.39 [0.92, 2.10]
Subtotal (95% CI)			27.2%	1.08 [0.86, 1.35]
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.88$, df = 3 (P = 0.18); $I^2 = 39\%$				
Test for overall effect: Z = 0.67 (P = 0.51)				
1.2.2 CHOP vs. chlorambucil				
French cooperative 1994	0.13	0.3	3.2%	1.14 [0.63, 2.05]
Hansen 1991	0.18	0.18	6.8%	1.20 [0.84,1.70]
Jaksic1997	0.44	0.18	6.8%	1.55 [1.09, 2.21]
Kimby 1991	-0.31	0.23	4.8%	0.73 [0.47, 1.15]
Subtotal (95% CI)			21.5%	1.14 [0.83, 1.56]
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.62$, df = 3 (P = 0.09); $I^2 = 55\%$				
Test for overall effect: Z = 0.82 (P = 0.41)				
1.2.3 Purine analogue containing regimen vs. chlorambucil				
Catovsky 2007	0.05	0.09	13.0%	1.05 [0.88 1.25]
Eichhorst 2009	0.34	0.24	4.5%	1.40 [0.88 2.25]
Jaksic 2000	-0.08	0.27	3.8%	0.92 [0.54 1.57]
Karlsson 2007	-0.28	0.25	4.2%	0.76 [0.46 1.23]
Karlsson 2007a	-0.1	0.24	4.5%	0.90 [0.57 1.45]
Rai 2000	-0.24	0.14	9.1%	0.79 [0.60 1.03]
Robak 2000	-0.072	0.163	7.7%	0.93 [0.68 1.28]
Subtotal (95% CI)			46.8%	0.96 [0.84, 1.09]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.59$, df = 6 (P = 0.36); $I^2 = 9\%$				
Test for overall effect: Z= 0.65 (P = 0.51)				
1.2.6 Bendamustine vs. chlorambucil				
Knauf 2009	-0.37	0.24	4.5%	0.69 [0.43, 1.11]
Subtotal (95% CI)			4.5%	0.69 [0.43,1.11]
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.54 (P = 0.12)				
Total (95% CI)			100.0%	1.01 [0.90, 1.13]
Heterogeneity: $Tau^2 = 0.0^2$; $Chi^2 = 23.41$, df = 15 (P = 0.08); $I^2 = 36\%$				
Test for overall effect: Z = 0.17 (P = 0.87)				
Test for subgroup differences: $Chi^2 = 3.84$, df = 3 (P = 0.28), $I^2 = 21.8\%$				



Abstract 0146 - Figure 1: Effect of chlorambucil compared to other chemotherapeutic regimens on overall survival in CLL

[O0545] NAVITOCLAX (ABT-263) PLUS FLUDARABINE/CYCLOPHOSPHAMIDE/RITUXIMAB (FCR) OR BENDAMUSTINE/RITUXIMAB (BR): A PHASE 1 STUDY IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background. Orally bioavailable navitoclax binds with high affinity (Ki ≤1nM) to Bcl-2, Bcl-xL, and Bcl-w, promoting apoptosis. Preclinically, N enhances rituximab (R) efficacy in B-cell lymphoma, alone or combined with chemotherapy. Phase 1 data showed that N monotherapy was well-tolerated and had anti-tumor activity in CLL patients. *Methods*. We treated relapsed/refractory CLL patients in a phase 1 study to evaluate the safety and pharmacokinetics (PK) of escalating doses of navitoclax combined with standard-dose bendamustine (B)-rituximab (R) or a fixed dose of navitoclax (110 mg) with standard-dose fludarabine (F)-cyclophosphamide (C)-R. Secondary objectives were to assess efficacy endpoints (PFS, ORR, TTP, OS, duration of response). Patients required therapy as per iwCLL criteria and had ECOG ≤1. For patients treated with navitoclax-BR, navitoclax was administered once daily (starting dose, 110 mg) on D3-5 of C1 and D1-3 of subsequent cycles, with 6 patients per dose cohort. Dose escalations were via continuous reassessment to identify a dose combined with chemotherapy in which < 33% of patients experienced dose-limiting toxicity (DLTs). We assessed tumor response (NCI-WG 1996 criteria; updated 2008) and adverse events (AE; NCI CTCAE V4). Patients received navitoclax for 1 year or until progressive disease (PD) or intolerable toxicity. *Results*. 26 patients (median age 58 yr [39-80]) enrolled in the BR navitoclax-dose escalation study and 5 patients in the fixed-dose navitoclax-FCR cohort. Median number of prior therapies was 2 (range 1-13). For patients treated with navitoclax-BR 5 had DLTs; 1 elevated liver enzymes (110 mg), 1 grade 4 febrile neutropenia (200 mg), and 3 grade 4 thrombocytopenia (250 mg). 1 patient had a DLT of febrile neutropenia in the navitoclax-FCR cohort. Frequent (> 20%; any grade) AEs were nausea (77%), neutropenia (46%), fatigue (42%), vomiting (31%), pyrexia (31%), headache (31%) and diarrhea (27%). For patients treated with N-FCR, 2 had partial responses (PR) (including 1 with del[11q] CLL), 2 had stable disease (SD) and 1 had incomplete data. Among patients treated with navitoclax-BR, there were 6 complete responses (1 confirmed; 2 with del[17p] and del [11q] CLL), 7 PR (2 confirmed; 2 with del[17p] and del [11q] CLL and 1 with del[17p] CLL), 4 SD, 1 PD, and 8 with incomplete data. The overall response rate of patients treated with navitoclax-BR was 72% (13/18). Preliminary PK results suggest no apparent PK interaction between navitoclax and bendamustine. *Conclusion*. Navitoclax combined with BR appears well-tolerated and shows anti-tumor activity. The maximum tolerated dose (MTD) and recommended phase 2 dose of navitoclax is 250 mg. Navitoclax at 110 mg dose also appears well tolerated when combined with FCR. To date, unacceptable myelotoxicity has not been observed when navitoclax was combined with standard chemo-immunotherapy regimens for treatment of patients with CLL.