Combination therapy with crizotinib and vinblastine for relapsed or refractory pediatric ALK-positive anaplastic large cell lymphoma

Children with early relapsed or refractory ALK-positive anaplastic large cell lymphoma (ALCL) have a high risk of further disease progression during re-induction with intensive chemotherapy as consolidation before allogeneic stem cell transplantation (SCT).[1-3] The intensive re-induction chemotherapy results in considerable treatment-related morbidity and mortality during and after SCT.[3] Based on the efficacy of crizotinib[4-6] and weekly vinblastine[2,7] as monotherapies in relapsed ALK-positive ALCL, a combination of both drugs could offer a potentially less toxic re-induction before SCT, or even allow long-term treatment without SCT. More recently, *in vitro* ALK-positive ALCL models have shown that combination therapy with crizotinib could have a synergistic effect and overcome resistance.[8] We report on 13 patients treated with crizotinib and vinblastine for relapsed ALK-positive ALCL, either enrolled on a clinical trial or treated off-label on an individual basis. Whereas treatment was efficacious with only 2/13 subsequent relapses, severe toxicities occurred in 11/13 patients, including one fatal infection.

We designed a Phase Ib open-label international clinical trial (CRISP, ITCC-053, EudraCT: 2015-005437-53) to assess the recommended Phase II dose (RP2D) for vinblastine in combination with crizotinib. With the trial not yet open in Germany, the combination has been used on an individual basis for patients with a high-risk of relapse in the Non-Hodgkin Lymphoma (NHL)-Berlin-Frankfurt-M□nster (BFM) study group since 2016. Because the individual treatment and the trial treatment were comparable, we analyzed all data together.

In Stratum I of the CRISP trial, patients with relapsed ALK-positive ALCL received a fixed dose of oral crizotinib 2x150 mg/m^2/day (d) per 28-day cycle, based on the responses observed at 2x165 mg/m^2/d in pediatric ALCL patients.[4] Intravenous vinblastine was escalated with three dose levels from 3-6 mg/m^2 per week, using the overdose control method.[9] At the time of trial design, unpublished data from the COG-study ANHL12P1 (clinicaltrials.gov NCT01979536) studying the combination of multi-agent chemotherapy with crizotinib, did not show any elevated risk of toxicities. However, based on considerations for pharmacokinetic interactions[10] and overlapping toxicities, the vinblastine starting dose was set at 4.5 mg/m^2, i.e., 75% of the single-agent dose. Dose-limiting toxicity (DLT) was defined as treatment-related adverse events or abnormal laboratory values during the first cycle, including neutropenia (absolute neutrophil count [ANC] <0.5x10^9/L), thrombocytopenia (platelets <25x10^9/L) lasting >7 days, or platelets <50x10^9/L with significant bleeding). Non-hematologic DLT included any ≥grade 3 treatment-related toxicity despite appropriate management, toxicities of grade ≥2 requiring significant modification, or laboratory abnormalities (grade 4, or grade 3 lasting ≥7 days requiring treatment modification), according to Common Terminology Criteria for Adverse Events v4.03.

We retrospectively identified patients with relapsed or refractory ALK-positive ALCL from the NHL-BFM 2012 registry, treated off-label with the combination therapy. All patients had high-risk relapses and were scheduled to receive consolidation by allogeneic SCT. The recommended dose for oral crizotinib was 2x165 mg/m^2/d. Vinblastine was administered at the discretion of the treating physicians. To prevent central nervous system progression,[11] dexamethasone (10 mg/m^2/d, 5 days every 4 weeks) and intrathecal triple therapy (methotrexate, cytarabine, prednisolone) were also recommended. We collected patients' characteristics and outcomes prospectively; treatment and toxicity data were collected retrospectively. Events were defined as relapse, progressive disease, secondary malignancy, or death from any cause. The prospective trial and the registry were conducted according to the principles of the Declaration of Helsinki and were approved by the institutional ethical committees. All patients or their legal guardians provided written informed consent.

Two CRISP trial patients (TP) and 11 NHL-BFM registry patients (RP) received the combination therapy as second-line treatment. Median age was 11.9 years (range, 2.4-17.9) and 8/13 (62%) were male. All patients had received ALCL99 front-line treatment. Four patients had progressed during front-line treatment and 9 relapsed within one year of diagnosis (mean, 7.6 months). Patients' characteristics and treatment are summarized in Table 1, Figure 1, and *Online Supplementary Table S1*.

TP1 was not evaluable for hematologic DLT due to bone marrow involvement. Vinblastine (4.5 mg/m^2) was administered despite the fact that protocol criteria had not been fulfilled (grade 4 neutropenia) on day 8. On day 11, this patient developed grade 3 nausea, was unresponsive to antiemetics (DLT) and had grade 3 febrile neutropenia. Because of the DLT, treatment was discontinued. The patient died from refractory shock and liver failure 7 days later. Autopsy revealed a systemic fungal infection (*Lich-*

Table 1. Clinical characteristics, treatment, and outcome.

Patient ID	Sex	Age (years)	Type and time of relapse	Total daily dose of crizotinib	Dose of vinblastine per week (N doses)	Concomitant drugs	Severe adverse effects, time to neutropenia, reason for modifications	AlloSCT	Outcome last follow-up
TP1	F	14.3	Relapse (5 mth)	300 mg/m², discontinued	4.5 mg/m², discontinued (N=2)	None	Grade 3 nausea, grade 4 neutropenia (8 d), grade 4 fungal infection, grade 4 anemia, grade 5 liver failure, suspected HLH	No	Died of infection (1 mth)
TP2	F	2.5	Relapse (6.5 mth)	300 mg/m², discontinued	3 mg/m², discontinued (N=3)	None	Grade 4 neutropenia (15 d)	No	FOP (18 mth)
RP1	M	17.7	Progression (2.5 mth)	330 mg/m², paused	6 mg/m², paused (N=5)	None[§]	Grade 4 neutropenia (21 d), ascites (possibly due to progression of lymphoma)	No	Died of lymphoma (2.9 mth)
RP2	M	17.3	Progression (1 mth)	260 mg/m², reduced to 100 mg/m²	5.2 mg/m² (N=10)	DEX, ITT	Grade 4 neutropenia (26 d), grade 4 febrile neutropenia, grade 4 thrombocytopenia with GI hemorrhage, grade 3 hepatotoxicity, grade 3 nausea	Yes	FOP (67.7 mth)
RP3	M	7.7	Relapse (5.5 mth)	420 mg/m²	6 mg/m² (N=9)	DEX	Grade 4 neutropenia (present at initiation of combination treatment)	Yes	FOP after relapse[#] (46.2 mth)
RP4	M	14.3	Relapse (7.6 mth)	280 mg/m² (for 13 days)	5.6 mg/m², reduced last dose 3.6 mg/m² (N=14)	DEX	None reported	Yes	FOP (44.1 mth)
RP5	M	11.4	Progression (5.6 mth)	230 mg/m², paused (4 d)	5 mg/m², discontinued (N=2)	ITT	Grade 4 neutropenia (7 d), grade 4 polyneuropathy	Yes	FOP (41.7 mth)
RP6	F	1.5	Relapse (11 mth)	340 mg/m², paused	6 mg/m², reduced to 4 mg/m², discontinued (N=7)	None	Grade 4 neutropenia (16 d)	Yes	FOP (30.1 mth)
RP7	F	10.7	Relapse (5.8 mth)	320 mg/m², discontinued, switch to ceritinib	5 mg/m², reduced 6 mg/m² (N=8)	DEX, ITT	Grade 4 neutropenia (35 d), febrile neutropenia, colitis, polyneuropathy	Yes	FOP (38.1 mth)
RP8	F	4.0	Relapse (7.1 mth)	560 mg/m², discontinued	6 mg/m², paused and reduced to 5 mg/m² 4 mg/m² (N=11)	DEX, ITT	Polyneuropathy, gastroparesis	Yes	FOP (18.8 mth)
RP9	M	11.8	Relapse (10.1 mth)	370 mg/m², discontinued	6 mg/m², paused and reduced to 4 mg/m² (N=9)	DEX, ITT	Grade 4 neutropenia (13 d), febrile neutropenia, paralytic ileus, peritonitis	Yes	FOP (30.9 mth)
RP10	M	6.5	Progression (3.1 mth)	330 mg/m²	3 mg/m² reduced to biweekly, last dose: 1.5 mg/m² (N=8)	DEX, ITT	Grade 4 neutropenia (20 d), febrile neutropenia	Yes	FOP (23.1 mth)
RP11	M	15.9	Relapse (6.1 mth)	250 mg/m²	3 mg/m² reduced to biweekly (N=7)	DEX, ITT	Grade 4 neutropenia (12 d)	Yes	FOP (19.2 mth)

[§] Patient received one course of BM ALCL99 chemotherapy (5 days dexamethasone, methotrexate 3 g/m², cyclophosphamide 5x200 mg/m², doxorubicin 2x25 mg/m²) after diagnosis of relapse, and brentuximab vedotin after subsequent progression. [#]Patient received 9 courses of brentuximab vedotin after the 2nd relapse. Adverse events were defined according to Common Terminology Criteria for Adverse Events v4.03. Allo SCT: allogeneic stem cell transplantation; mth: month; d: day; M: male; F: female; N: number; TP: trial patient; RP: registry patient; ITT: intrathecal triple therapy; FOP: freedom of progression; DEX: dexamethasone; HLH: hemophagocytic lymphohistiocytosis; GI: gastrointestinal.

theimia species) and suspected secondary hemophagocytic lymphohistiocytosis but no signs of active ALCL.
Due to the severe toxicity observed in TP1, TP2 was assigned to a vinblastine dose of 3.0 mg/m^2. On day 15, vinblastine was administered, despite the fact that the protocol criteria had not been fulfilled (grade 4 neutropenia). The ongoing neutropenia was considered a DLT on day 22, and treatment was discontinued. Neutropenia resolved within 5 days. As per protocol, trial treatment was not resumed. TP2 remained in complete remission (CR) with crizotinib monotherapy (oral 2x100 mg/m^2/d) off-study; at the time of writing, this treatment is ongoing after 23 months. Since DLT had occurred in the first 2 TP included in the study, Stratum I was permanently closed in July 2020.

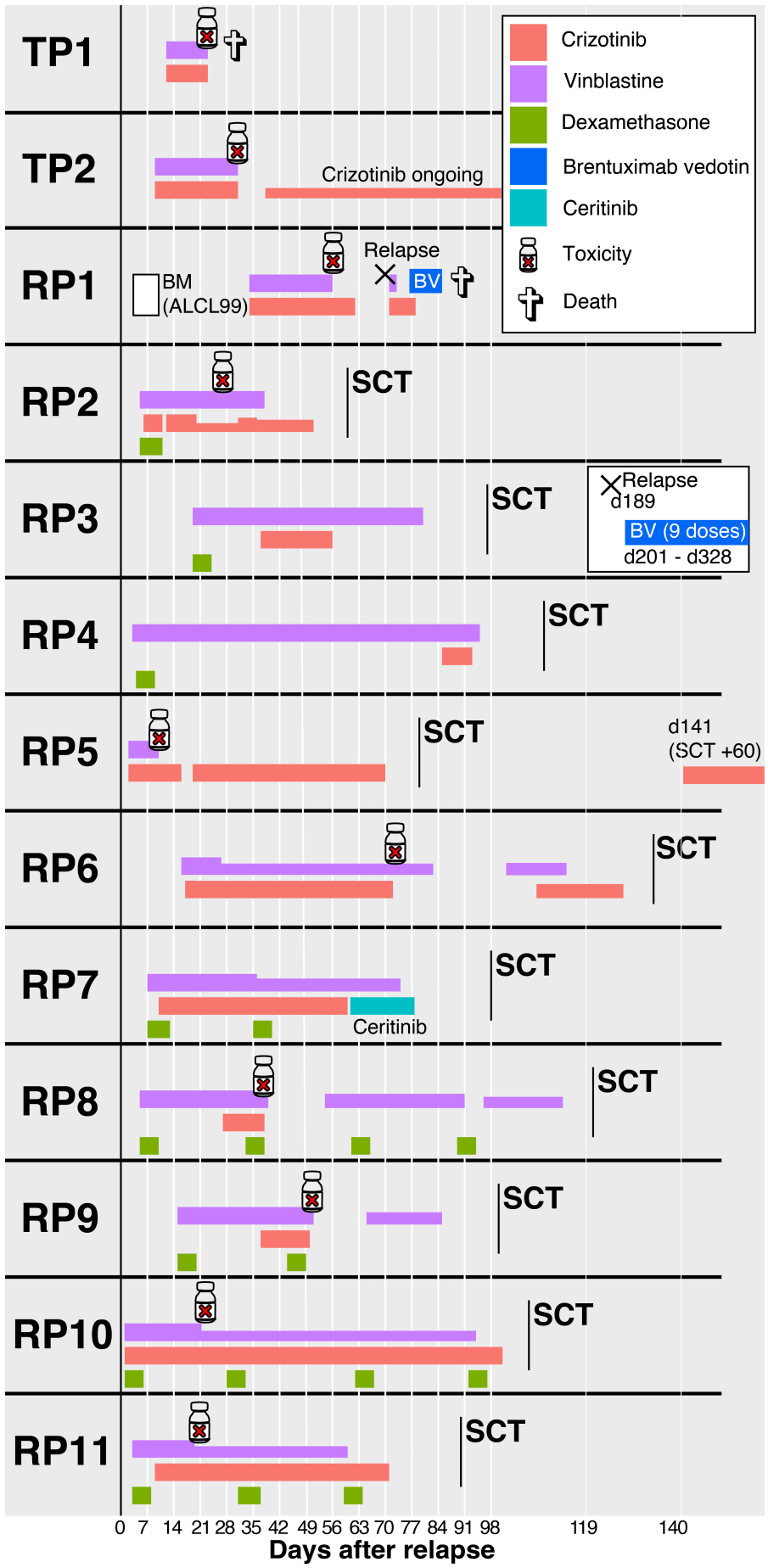

Figure 1. Treatment overview. Swimmer plot showing individual patient courses with bars representing treatment durations, height of bars reflecting dose. Occurrence of toxicity requiring dose modifications is noted. Patient RP1 received one course of the BM ALCL99 chemotherapy regimen after diagnosis of relapse: 5-day course with dexamethasone, methotrexate 3 g/m^2, cyclophosphamide 5x200 mg/m^2, doxorubicin 2x25 mg/m^2. d: day; SCT: allogeneic stem cell transplantation; TP: trial patient; RP: registry patient; BV: brentuximab vedotin.

Among the RP, the median initial doses of crizotinib and vinblastine were 330 mg/m^2/d (total daily dose, range 250-560 mg/m^2) and 5.6 mg/m^2/week (range, 3-6 mg/m^2), respectively. In 9/11 RP, crizotinib and/or vinblastine were reduced, paused, or discontinued due to toxicity. In one patient without dose reductions, crizotinib was only administered for 8 days before conditioning for SCT. Adverse effects included grade 4 neutropenia (reported in 9/11 patients), grade 3-4 febrile neutropenia (4/11), polyneuropathy (3/11), severe gastrointestinal adverse effects including paralytic ileus and hepatotoxicity (4/11). RP9 developed paralytic ileus and bacterial peritonitis after 2 weeks of combination therapy and was managed successfully with treatment discontinuation, antibiotics, and supportive care. Hospitalization was required for adverse effects in 5/11 patients. Because of these unexpected toxicities, the NHL-BFM group discouraged the use of the combination therapy.

For all 13 patients, overall survival (OS) and event-free survival (EFS) at two years were 85% (95%CI: 67-99%) and 77% (95%CI: 5-99%), respectively (*Online Supplementary Figures S1 and S2*). RP1 received one course of ALCL99 before the combination therapy. This patient had a subsequent relapse three weeks later and died of progressive disease despite treatment with brentuximab vedotin. RP3 had a subsequent relapse after SCT, reached remission with brentuximab vedotin, and has survived event-free with 46 months of follow-up at the time of writing. All other RP received the intended allogeneic SCT at a mean time after relapse of 96 days (range, 60-125) and remained event-free. Median follow-up of the 11 surviving patients was 30.9 months.

Shorter time to relapse is the main risk factor for subsequent relapse,[1,2] so the observed OS and EFS in our high-risk cohort of 13 pediatric patients with refractory or early relapsed ALCL compared favorably to previous reports.[2] Given the favorable safety profile of crizotinib and vinblastine in monotherapies,[5,7,12] the severity of toxicity was unexpected, leading to termination of stratum I of the CRISP trial and advice against the combination in the NHL-BFM group. In most patients, the doses had to be reduced due to grade 3-4 toxicities, and one patient died of an infection. In addition, the severe gastrointestinal toxicity we

observed is unusual during monotherapy with either of the drugs. Similar hematologic toxicity, with ≥ grade 3 neutropenia in 92% of patients, but less severe gastrointestinal toxicity were observed in a recent pediatric Phase Ib trial combining crizotinib with cytotoxic agents.[13] With a comparable dose of crizotinib, 4/20 patients in that study experienced dose-limiting toxicities. So far, one case has been reported with the combination of vinblastine and crizotinib in a patient with relapsed ALCL, who also suffered from severe toxicity, including prolonged neutropenia.[14]

Several reasons for the unexpected toxicities might be considered. These include the short time between frontline and relapse treatment. In addition, crizotinib and vinblastine are substrates of CYP3A,[15] and crizotinib has been identified as a moderate CYP3A inhibitor, increasing the exposure to the CYP3A4 model substrate midazolam by 3.7-fold,[10] possibly explaining the severe toxicity despite the lower dose of vinblastine administered. Both TP discontinued study treatment before pharmacokinetic sampling had been conducted; this had been scheduled in a predicted steady state for the second cycle. Because of this, no conclusions can be reached about the possible pharmacokinetic interactions. In TP1, neutropenia could have also been influenced by bone marrow involvement and hemophagocytosis.

The main limitation of our study is the implementation of the combination strategy on an individual patient basis in most patients, resulting in treatment heterogeneity. The retrospective collection of toxicity data in those patients does not allow for detailing exact frequencies and grading adverse effects with the combination treatment. With the premature closure of the trial, no safe dose for the combination treatment could be established.

Our real-world observations bring us to the conclusion that the combination of crizotinib and vinblastine appears to be effective for refractory or early relapsed ALK-positive ALCL; however, it is associated with severe toxicities. Further (pre-)clinical pharmacokinetic and pharmacodynamic investigations may help explain the unexpected toxicity. Our observations underline the need to perform clinical trials, even for treatment strategies considered low-risk, such as the combination of well-known drugs. Clinicians, regulators, and funding bodies should be encouraged to initiate, approve, and support practical clinical trials of combination therapies to improve patient safety even in orphan diseases such as relapsed pediatric ALCL.

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Contributions

FK and KS collected and analyzed the data, and wrote the first draft of the manuscript; HT and JLP provided patient data; AR, JF and NE collected patient data; AB, CMZ, AH, JvdL and WW were involved in the conceptualization and study design of Stratum I of the CRISP trial; JvdL, RS and WW supervised the analyses; all authors reviewed and revised the manuscript, and approved the final version for submission.

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Data-sharing statement

Individual patient data that underlie the results reported in this article will be made available in deidentified form to researchers who provide a methodologically sound proposal for data usage. Proposals should be directed to the corresponding author.

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