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


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Author 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.

Running heads
Crizotinib and vinblastine for relapsed ALK+ALCL

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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 methodological sound proposal for data usage.
Proposals should be directed to the corresponding author.

Conflict of interest
FK, HT, AR, JF, JLP and WW declare that they have no conflict of interest relevant to this
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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 before allogeneic stem cell transplantation (SCT) for consolidation\textsuperscript{1-3}. Treatment intensity of re-induction chemotherapy results in considerable treatment-related morbidity and mortality during and after SCT\textsuperscript{3}. Based on the efficacy of crizotinib\textsuperscript{4-6} and weekly vinblastine\textsuperscript{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\textsuperscript{8}. We report on 13 patients treated with crizotinib and vinblastine for relapsed ALK-positive ALCL, either enrolled in 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 1B open-label international clinical trial (CRISP, ITCC-053, EudraCT: 2015-005437-53) to assess the recommended phase 2 dose (RP2D) for vinblastine in combination with crizotinib. With the trial not yet open in Germany, the combination was used on an individual basis for patients with a high-risk relapse in the Non-Hodgkin Lymphoma (NHL) - Berlin-Frankfurt-Münster (BFM) study group since 2016. Because the individual treatment and the trial treatment were comparable, we jointly analyzed the data.

In stratum I of the CRISP trial, patients with relapsed ALK-positive ALCL received a fixed dose of crizotinib 2x150\textsuperscript{mg/m}^2/d orally per 28-day cycle, based on the responses observed at 2x165\textsuperscript{mg/m}^2/d in pediatric ALCL patients\textsuperscript{4}. Intravenous vinblastine was escalated with three dose levels from 3–6 mg/m\textsuperscript{2} per week, using the overdose control method\textsuperscript{9}. At the time of trial design, unpublished data from the COG-study ANHL12P1 (NCT01979536) studying the combination of multi-agent chemotherapy with crizotinib, did not show an elevated risk for toxicities. However, based on considerations for pharmacokinetic interactions\textsuperscript{10} and overlapping toxicities, the vinblastine starting dose was set at 4.5 mg/m\textsuperscript{2}, 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 <0.5/nl, thrombocytopenia <25/nl lasting >7 days, or thrombocytopenia <50/nl with significant bleeding. Non-hematologic DLTs 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). CTCAE v4.03 was used for grading.
We retrospectively identified patients with relapsed or refractory ALK-positive ALCL from the NHL-BFM registry 2012, treated off-label with the combination therapy. All patients had high-risk relapses and were intended to be consolidated by allogeneic SCT. The recommended dose for crizotinib was 2 x 165 mg/m²/d orally. Vinblastine was administered at the discretion of the treating physicians. For prevention of CNS progression, dexamethasone (10 mg/m²/d, 5 days every 4 weeks) and intrathecal triple therapy (methotrexate, cytarabine, prednisolone) were also recommended. We collected patient 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 Declaration of Helsinki and were approved by the responsible Ethical Committees. All patients or their legal guardians provided written informed consent.

Two CRISP trial patients (TPs) and eleven NHL-BFM registry patients (RPs) received the combination therapy as second line treatment. The 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 nine relapsed within one year of diagnosis (mean, 7.6 months). Patient characteristics and treatment are summarized in Table 1, Figure 1, and Supplementary Table 1.

TP1 was not evaluable for hematological DLTs due to bone marrow involvement. Vinblastine (4.5 mg/m²) was administered despite not fulfilling protocol criteria (neutropenia grade 4) on day eight. On day 11, she developed grade 3 nausea, unresponsive to anti-emetics (DLT) and grade 3 febrile neutropenia. Because of the DLT, treatment was discontinued. The patient died from refractory shock and liver failure 7 days later, with an autopsy revealing a systemic fungal infection (Lichtheimia species) and suspected secondary hemophagocytic lymphohistiocytosis. The autopsy showed no signs of active ALCL.

Due to the severe toxicity observed in TP1, TP2 was assigned to a vinblastine dose of 3.0 mg/m². On day 15, vinblastine was administered, despite not fulfilling protocol criteria (neutropenia grade 4). The ongoing neutropenia was considered a DLT on day 22, and treatment was discontinued. Neutropenia resolved within 5 days. Per protocol, trial treatment was not resumed. TP2 remained in CR with crizotinib monotherapy (2x100 mg/m²/d orally) off-study, ongoing after 23 months. As DLTs occurred in the first two included TPs, stratum I was permanently closed in July 2020.

In the RPs, the median initial doses of crizotinib and vinblastine were 330 mg/m²/d (total daily dose, range 250–560 mg/m²) and 5.6 mg/m²/week (range, 3–6 mg/m²), respectively. In 9/11 RPs, 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 combination therapy.

For all 13 patients, OS and EFS at two years were 85% (95%-confidence interval [CI], 67–99%) and 77% (CI, 57–99%), respectively (Supplementary Figure 1 and 2). RP1 received one course of ALCL99 before the combination therapy. She 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 survived event-free with 46 months of follow-up. All other RPs received the intended allogeneic SCT at a mean time after relapse of 96 days (range, 60–125) and survived event-free. The median follow-up of 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 hematological toxicity, with neutropenia \(\geq 3^\circ\) in 92% of patients, but less severe gastrointestinal toxicity was observed in a recent pediatric phase 1b trial combining crizotinib with cytotoxic agents\(^13\). With a comparable dose of crizotinib, 4 of 20 patients in that study experienced dose-limiting toxicities. Until now, one case has been reported on 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 discussed. These include the short time between front-line and relapse treatment. Additionally, 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 3.7-fold\(^10\), possibly explaining the severe toxicity, despite the lower dose of vinblastine administered. Both TPs discontinued study treatment before pharmacokinetic sampling, which was scheduled in predicted steady state for the 2\(^{nd}\) cycle,
precluding a conclusion on 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 of 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 allow the conclusion that the combination of crizotinib and vinblastine appears to be effective for refractory or early relapsed ALK-positive ALCL, however, is associated with severe toxicities. Further (pre-)clinical pharmacokinetic and pharmacodynamic investigations may help explain the unexpected toxicity. Our observations underline the necessity 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, allow, and support practical clinical trials of combination therapies to increase safety for patients even in orphan diseases like relapsed pediatric ALCL.
References


### Table 1 – Clinical characteristics, treatment, and outcome

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Type and time of relapse</th>
<th>Total daily Dose of Crizotinib</th>
<th>Dose of Vinblastine per Week, number of doses</th>
<th>Concomitant drugs</th>
<th>Severe adverse effects, time to neutropenia, Reason for modifications</th>
<th>Allo SCT</th>
<th>Outcome</th>
<th>Last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP1</td>
<td>f 14.3</td>
<td>relapse (5 mo.)</td>
<td>300 mg/m², discontinued</td>
<td>4.5 mg/m², discontinued (n = 2)</td>
<td>none</td>
<td>Nausea 3°, Neutropenia 4° (8 d), fungal infection 4°, Anemia 4°, liver failure 5°, suspected HLH</td>
<td>no</td>
<td>Died of infection</td>
<td>(1 mo.)</td>
</tr>
<tr>
<td>TP2</td>
<td>f 2.5</td>
<td>relapse (6,5 mo.)</td>
<td>300 mg/m², discontinued</td>
<td>3 mg/m², discontinued (n = 3)</td>
<td>none</td>
<td>Neutropenia 4° (15 d)</td>
<td>no</td>
<td>FOP</td>
<td>(18 mo.)</td>
</tr>
<tr>
<td>RP1</td>
<td>m 17.7</td>
<td>progression (2,5 mo.)</td>
<td>330 mg/m²/m², paused</td>
<td>6 mg/m²/m² paused (n = 5)</td>
<td>none §</td>
<td>Neutropenia 4° (21 d), Ascites (possibly due progression of lymphoma)</td>
<td>no</td>
<td>Died of lymphoma</td>
<td>(2.9 mo.)</td>
</tr>
<tr>
<td>RP2</td>
<td>m 17.3</td>
<td>progression (1 mo.)</td>
<td>260 mg/m², reduced 100 mg/m²</td>
<td>5.2 mg/m²/m² (n = 10)</td>
<td>DEX, ITT</td>
<td>Neutropenia 4° (26 d), Febrile Neutropenia 4°, Thrombocytopenia 4° with GI hemorrhage, Hepatotoxicity 3°, Nausea 3°</td>
<td>yes</td>
<td>FOP</td>
<td>(67.7 mo.)</td>
</tr>
<tr>
<td>RP3</td>
<td>m 7.7</td>
<td>relapse (5,5 mo.)</td>
<td>420 mg/m²</td>
<td>6 mg/m² (n = 9)</td>
<td>DEX</td>
<td>Neutropenia 4° (present at initiation of combination treatment)</td>
<td>yes</td>
<td>FOP after Relapse #</td>
<td>(46.2 mo.)</td>
</tr>
<tr>
<td>RP4</td>
<td>m 14.3</td>
<td>relapse (7,6 mo.)</td>
<td>280 mg/m², reduced last dose</td>
<td>5.6 mg/m²/m² (for 13 days)</td>
<td>DEX</td>
<td>none reported</td>
<td>yes</td>
<td>FOP</td>
<td>(44,1 mo.)</td>
</tr>
<tr>
<td>RP5</td>
<td>m 11.4</td>
<td>progression (5,6 mo.)</td>
<td>230 mg/m², paused (4 days)</td>
<td>5 mg/m²/m², discontinued (n = 2)</td>
<td>ITT</td>
<td>Neutropenia 4° (7 d), Polyneuropathy 4°</td>
<td>yes</td>
<td>FOP</td>
<td>(41,7 mo.)</td>
</tr>
<tr>
<td>RP6</td>
<td>f 1.5</td>
<td>relapse (11 mo.)</td>
<td>340 mg/m², paused</td>
<td>6 mg/m²/m², reduced 4 mg/m²/m², discontinued</td>
<td>DEX</td>
<td>Neutropenia 4° (16 d)</td>
<td>yes</td>
<td>FOP</td>
<td>(30,1 mo.)</td>
</tr>
<tr>
<td>RP7</td>
<td>f 10.7</td>
<td>relapse (5,8 mo.)</td>
<td>320 mg/m², discontinued</td>
<td>5 mg/m²/m², reduced 6 mg/m²/m² (n = 8)</td>
<td>DEX, ITT</td>
<td>Neutropenia 4° (35 d), Febrile Neutropenia, Colitis, Polyneuropathy</td>
<td>yes</td>
<td>FOP</td>
<td>(38,1 mo.)</td>
</tr>
<tr>
<td>RP8</td>
<td>f 4.0</td>
<td>relapse (7,1 mo.)</td>
<td>560 mg/m², discontinued</td>
<td>6 mg/m²/m², paused and reduced 5 mg/m²/m²,</td>
<td>DEX, ITT</td>
<td>Polyneuropathy, Gastroparesis</td>
<td>yes</td>
<td>FOP</td>
<td>(18,8 mo.)</td>
</tr>
<tr>
<td>RP9</td>
<td>m 11.8</td>
<td>relapse (10,1 mo.)</td>
<td>370 mg/m², discontinued</td>
<td>6 mg/m²/m², paused and reduced 4 mg/m²/m² (n = 9)</td>
<td>DEX, ITT</td>
<td>Neutropenia 4° (13 d), Febrile Neutropenia, Paralytic ileus, Peritonitis</td>
<td>yes</td>
<td>FOP</td>
<td>(30,9 mo.)</td>
</tr>
<tr>
<td>RP10</td>
<td>m 6.5</td>
<td>progression (3,1 mo.)</td>
<td>330 mg/m²</td>
<td>3 mg/m²/m² reduced to biweekly, last dose: 1.5 mg/m²/m² (n = 8)</td>
<td>DEX, ITT</td>
<td>Neutropenia 4° (20 d), Febrile Neutropenia</td>
<td>yes</td>
<td>FOP</td>
<td>(23,1 mo.)</td>
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<tr>
<td>RP11</td>
<td>m 15.9</td>
<td>relapse (6,1 mo.)</td>
<td>250 mg/m²</td>
<td>3 mg/m²/m² reduced to biweekly</td>
<td>DEX, ITT</td>
<td>Neutropenia 4° (12 d)</td>
<td>yes</td>
<td>FOP</td>
<td>(19,2 mo.)</td>
</tr>
</tbody>
</table>

§ the patient received one course of ALCL99 chemotherapy BM (5-day course with dexamethasone, methotrexate 3 g/m², cyclophosphamide 5 x 200 mg/m², doxorubicin 2 x 25 mg/m²) after diagnosis of relapse, and brentuximab vedotin after subsequent progression; # the patient received 9 courses of brentuximab vedotin after the 2nd relapse CTCAE v4.03 was used to grade the adverse effects. Allo SCT, allogeneic stem cell transplantation, TP, trial patient, RP, registry patient, ITT, intrathecal triple therapy, FOP freedom of progression, DEX, dexamethasone
Figure legends

Figure legend: 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 BM course of the ALCL99 chemotherapy regimen after diagnosis of relapse. BM (5-day course with dexamethasone, methotrexate 3 g/m², cyclophosphamide 5 x 200 mg/m², doxorubicin 2 x 25 mg/m²), SCT, allogeneic stem cell transplantation, TP, trial patient, RP, registry patient, BV, brentuximab vedotin.
Supplementary appendix
Combination therapy with crizotinib and vinblastine for relapsed or refractory pediatric ALK-positive anaplastic large cell lymphoma

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**Supplementary Table 1: Additional patient characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Diagnosis</th>
<th>Relapse Diagnosis</th>
<th>MRD*</th>
<th>Response</th>
<th>Outcome, last FU</th>
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<tbody>
<tr>
<td>TP1</td>
<td>pos. (BM)</td>
<td>neg. (CNS)</td>
<td>n.d.</td>
<td>pos. (BM)</td>
<td>neg. (CNS)</td>
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<td>neg. (CNS)</td>
<td>pos. (MDD)</td>
<td>neg. (BM)</td>
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<td>neg. (CNS)</td>
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<td>pos. (BM)</td>
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<td>neg. (CNS)</td>
<td>neg. (MDD)</td>
<td>neg. (BM)</td>
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<td>neg. (MDD)</td>
<td>neg.</td>
<td>pos. (BM)</td>
</tr>
</tbody>
</table>

BM, bone marrow involvement, CNS, central nervous system involvement, MDD, minimal disseminated disease, MRD, minimal residual disease, allo-SCT, allogeneic stem-cell transplantation, PR, partial response, CR, complete response, as defined by the International Pediatric Non-Hodgkin Lymphoma Response Criteria, n. d., not done, n. a., not available

* before allogeneic SCT or last MRD measurement after initiation of second line therapy
**Supplementary Figure 1: Event-free survival** of 13 patients treated with the combination of vinblastine and crizotinib. Event-free time is defined as time from first relapse to any event (Relapse, Progression, Secondary Malignancy, Death from any cause).

**Supplementary Figure 2: Overall survival** of 13 patients treated with the combination of vinblastine and crizotinib. Overall survival time is defined as time from first relapse to death of any cause.