case reports

Minimal Residual Disease–Guided Intermittent Dosing in Patients With Cancer: Successful Treatment of Chemoresistant Anaplastic Large Cell Lymphoma Using Intermittent Lorlatinib Dosing

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JCO Precis Oncol 6:e2100525.

Introduction

There are about 100 new children presenting with anaplastic large cell lymphoma (ALCL) in the United States and Europe each year. Among these patients, approximately 90% harbor *ALK* gene rearrangements, with *NPM1-ALK* being the most prevalent.[1] Despite the use of several different intensive chemotherapy approaches, about one third of patients will experience a relapse of the disease.[2] In relapsed patients, multiple therapeutic strategies can be considered. The frequency of *ALK* gene rearrangements in ALCL and the success of ALK inhibitors in other cancer types[3] led to early use of tyrosine kinase inhibitors (TKIs) in patients with *ALK* gene rearrangement–positive ALCL (ALK-positive ALCL). Crizotinib, which showed to be not only well-tolerated in the pediatric population but also to have high response rates,[4] is already approved for relapsed ALCL in children and young adults.

The inhibition of *ALK* gene rearrangements represents a promising therapeutic option for ALK-positive ALCL, as long as several issues are addressed. First, there are concerns about frequent disease recurrence with the completion of monotherapy.[5] Second, there is a likelihood of observing similar toxicities as those associated with long-term use of other TKIs like imatinib.[6] These concerns, along with the risk of acquired ALK inhibitor resistance seen in other ALK-positive cancers,[7] suggest a need for innovative treatment strategies.

Intermittent dosing of TKI as means to prevent drug resistance has been previously explored in the past; however, different mechanisms of resistance to different TKIs in various malignancies need to be considered here. For ALK-positive ALCL, upregulated ALK signaling leads to a resistance to continuous TKI administration. After TKI withdrawal, increased ALK signaling may result in cell death, which allows prolonged disease control compared with continuous dosing.[8] In the presented case with the best treatment not being defined, we commenced intermittent lorlatinib treatment with frequent minimal residual disease (MRD) monitoring to assess the efficacy of this approach.

Case Presentation

We present a case of a 2-year-old male admitted to University Hospital Brno in November 2020 with disseminated *NPM1-ALK*–positive, CD30+ ALCL (see Fig 1). At presentation, the child had skin, bone marrow, and generalized lymph node involvement, with a WBC count of 47×10^9/L with more than 30% of ALCL blasts in peripheral blood.

The patient was treated as per Children's Oncology Group ALCL protocol ANHL12P1 on the brentuximab vedotin arm.[9] Despite achieving clinical and radiologic remission after three cycles of this therapy, MRD levels decreased by only one log. Moreover, after the fourth cycle, he had overt clinical disease progression manifested by generalized lymphadenopathy, skin involvement, fever, and malaise. The Lansky score was only 20. The diagnosis of disease progression was documented by skin, bone marrow, and lymph node biopsies with partial CD30 loss by immunohistochemistry in ALCL cells. Flow cytometry revealed 35% of ALCL blasts in peripheral blood.

Discussion with the family concerning the patient's further treatment covered possible options like weekly vinblastine, second-line intensive chemotherapy followed by allogeneic bone marrow transplantation, or

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 26, 2022 and published at ascopubs.org/journal/po on June 14, 2022: DOI https://doi.org/10.1200/PO.21.00525

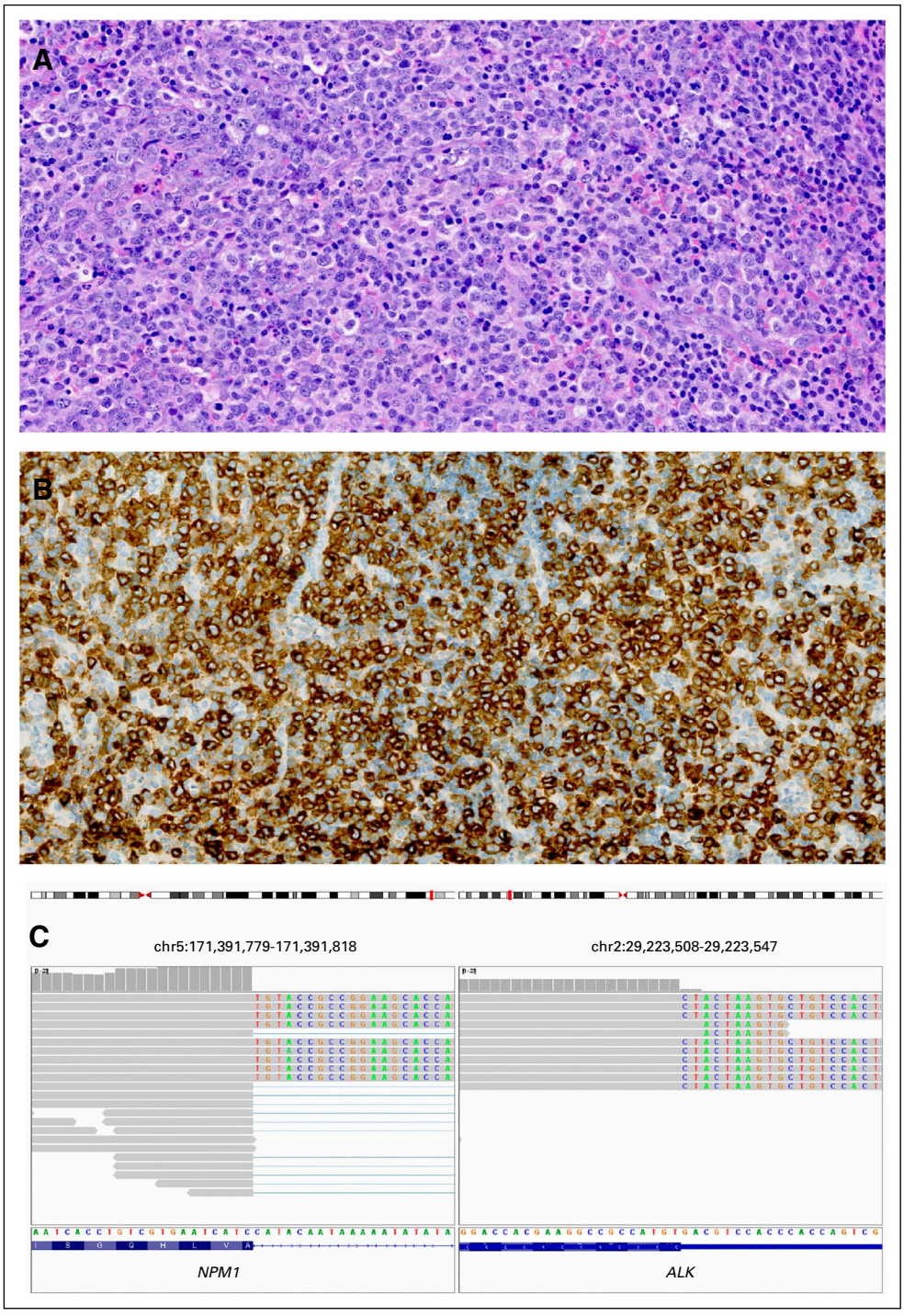

FIG 1. Histopathology and molecular diagnostic results. (A) Microscopic examination. Hematoxylin-eosin staining showing tumor cell infiltration in tonsil, magnification 200×. (B) Immunohistochemical examination. Positive IHC staining for CD30, magnification 200×. (C) Fusion gene visualization from IGV software. Sequence reads from targeted RNA sequencing are represented by gray bars. The left panel shows reads mapped to the *NPM1* gene, and the right panel reads mapped to the *ALK* gene. Bases marked by different colors indicate the presence of gene fusion with sequence matching to the corresponding partner. IHC, immunohistochemistry.

crizotinib monotherapy. On the basis of previous reports on disease progression after TKI cessations[5] and efficacy of vinblastine in the relapsed setting,[10] the parents consented to treatment with a combination of an ALK inhibitor and low-dose weekly vinblastine. As crizotinib was suspended in the ANHL12P1 trial because of reported occurrence of blood clots, third-generation ALK inhibitor lorlatinib was selected on the basis of positive reports in children with neuroblastoma.[11]

The patient started treatment with continuous weekly vinblastine (once a week, maximum dose 6 mg/m^2) and daily lorlatinib (45 mg/m^2, once a day) on an initial intermittent schedule of 2 weeks on and 2 weeks off. On the basis of MRD dynamics, we were ready to adjust the proposed scheduling and similarly to adjust vinblastine doses on the basis of absolute neutrophil counts. The child's overall condition improved markedly within the first 2 weeks of treatment. After almost 3 months

of well-tolerated lorlatinib dose, the dose was increased to 90 mg/m^2, once a day. For maximal disease control, after seven courses of lorlatinib administration, anti–programmed cell death protein 1 treatment was added on the basis of strong programmed death ligand 1 positivity of the tumor cells confirmed by immunohistochemistry staining.

The child's MRD levels were assessed since presentation using quantitative real time polymerase chain reaction for the *NPM1-ALK* fusion transcript (Appendix Table A1) and expressed as the normalized copy number (NCN) of the fusion transcript.[12] Lorlatinib administration resulted in a gradual increase of *NPM1-ALK* NCN after several days of lorlatinib administration followed by a significant decrease after TKI discontinuation. With each cycle, higher suppression of the *NPM1-ALK* NCN was achieved (Fig 2). After anti–programmed cell death protein 1 addition, the pattern of MRD response to intermittent lorlatinib administration did not change.

As the patient continues to benefit from the initially determined two weeks on/two weeks off scheme and we do not see any signs of disease progression, the administration schedule remains unchanged at the time of publication of this article. Notably, the child has been on this regimen for

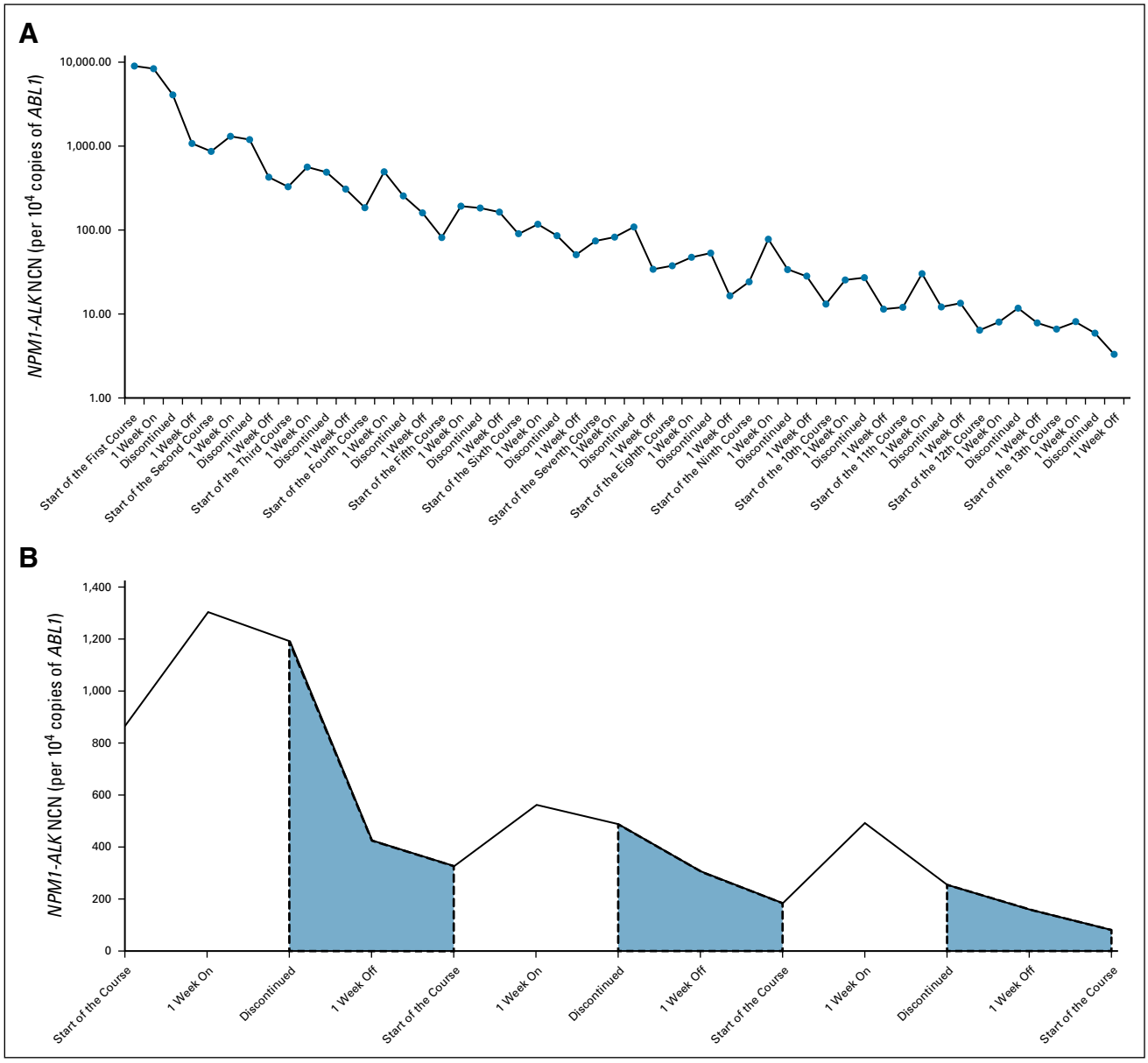

FIG 2. Levels of *NPM1 ALK* NCN throughout the treatment. (A) The overall MRD dynamics throughout 13 administration cycles. (B) MRD dynamics pattern is shown on three consecutive cycles of intermittent lorlatinib administration. *NPM1 ALK* NCN showed a characteristic dynamics pattern with a gradual increase after several days of lorlatinib administration followed by a significant decrease after TKI discontinuation (marked by blue color in the graph). Progressively higher suppression of *NPM1 ALK* NCN was observed. *ABL1*, Abelson Murine Leukemia 1 tyrosin kinase; MRD, minimal residual disease; NCN, normalized copy number; TKI, tyrosine kinase inhibitor.

12 months, which represents a 9-month extension on the three-month event-free survival (EFS) achieved with the intensive chemoimmunotherapy.

In addition to the *NPM1-ALK* NCN transcript, we also monitored the phosphorylation of STAT1 (Tyr 701) and STAT3 (Tyr 705), the key molecules in ALK-positive T-cell lymphoma,[13] in weekly intervals. Because ALCL does not have a specific immunophenotypic feature, we used the population of atypical cells within the CD45-positive lymphocyte gate that was negative for T-lineage (CD3/4/8), B-lineage (CD19), and NK-lineage (CD16/56/7) markers.[14] The pSTAT1 and pSTAT3 levels in this abnormal population were compared with levels in a healthy control sample (the child's mother), and its monitoring continued for as long as the abnormal cell population was detectable. STAT1 and STAT3 play opposite roles in tumorigenesis, with STAT3 presenting itself as an oncogene, whereas STAT1 exhibits rather tumor-suppressive functions. Consequently, at the initiation of treatment, pSTAT3 is high and pSTAT1 is low. After the first week of lorlatinib, pSTAT1 begins to rise and remains relatively high until the start of the second course. Both pSTAT1 and pSTAT3 subsequently show similar inhibition during treatment and restoration of the phosphorylation levels after lorlatinib discontinuation (Fig 3), suggesting that evaluating phosphorylation in a disappearing population is unhelpful.

Ethics Statement

Ethical approval was granted by The Ethics Committee for Multicenter Clinical Trials of the University Hospital Brno (ref. No. 10-101121/EK). Written informed consent was provided by the parents before conducting and publishing the presented analyses.

Discussion and Conclusion

Currently, there is no consensus on the best treatment for relapsed/refractory ALK-positive ALCL. Since the US Food and Drug Administration approval of crizotinib, the drug has been shown to produce a marked improvement in survival in lung cancer,[15] neuroblastoma,[16,17] and ALCL[18] and ALK inhibitors in ALK-positive ALCL are emerging as potential frontline therapies.

However, sustained maintenance treatment with TKIs has not been shown to be effective in indolent disease, and people with sustained deep molecular response can successfully discontinue TKI therapy and maintain a treatment-free remission.[19] In children, where TKIs may cause growth disturbance,[20] the treatment length and intensity become even more important. Intermittent dosing represents a promising strategy, which may prevent upregulation of the ligand or the receptor and reduce the likelihood of long-term sequelae or off-target toxicity. Its comparison with continuous dosing in terms of effectiveness and toxicity is, however, yet to be evaluated. A recent phase II randomized trial focused on intermittent versus continuous dosing of BRAF/MEK inhibitors in *BRAF*-mutated melanoma is often quoted as resulting in a shortened progression-free survival in the intermittent dosing group vs continuous dosing (5.5 *v* 9 months) although the toxicities and overall survival were similar.[21] However, this trial had chosen the on-/off-treatment interval on the basis of a pharmacokinetic modeling rather than on the basis of response biomarker.

As shown in our case, intermittent two weeks on, two weeks off lorlatinib dosing combined with low-dose metronomic vinblastine led to significantly improved treatment response and prolongation of the child's EFS. Observed MRD dynamics supported the selected administration schedule and, at least to date, circumvented acquired drug resistance.

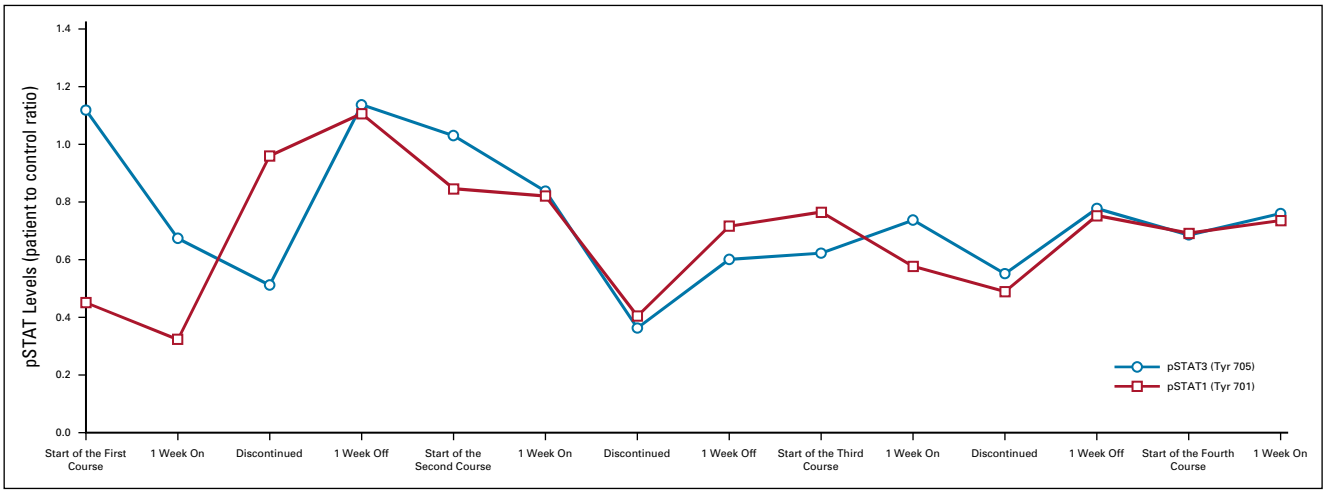

FIG 3. Weekly monitoring of the STAT phosphorylation. Phosphorylation of STAT1 (Tyr 701) and STAT3 (Tyr 705) was monitored in the population of atypical lymphocytes positive for CD45, but negative for T-lineage (CD3/4/8), B-lineage (CD19), and NK-lineage (CD16/56/7) markers. The pSTAT1 and pSTAT3 levels in this abnormal population were compared with levels in a healthy control sample (the child's mother), and its monitoring continued for as long as the abnormal cell population was detectable. As shown, after the second course, levels of pSTAT1 and pSTAT3 show similar inhibition during treatment and restoration of the phosphorylation levels after TKI discontinuation. TKI, tyrosin kinase inhibitor.

Although there is some preclinical evidence that intermittent dosing may lead to the development of drug-resistant clones,[22] this has only been shown in a monotherapy setting. Tumors harbor mixed populations of drug-sensitive and drug-resistant clones, and both clones must be eliminated for a deep molecular response. Combinations with metronomic chemotherapy may be more beneficial than standard therapies.[23-25]

Currently, we have another very similar ALK-positive ALCL patient, relapsing after the same chemoimmunotherapy as the index case. She has successfully reached second complete remission with the same treatment as the index case, and her second EFS is already three times longer than the first. The patient is not presented in the article as the ALK fusion at the time of relapse was detectable only as positive and nonquantifiable, and therefore, her MRD levels could not give a similar picture as the presented case.

In conclusion, intermittent dosing of lorlatinib appears to have sustained efficacy with manageable toxicities in ALK-positive ALCL. Our observation supports consideration of intermittent dosing in situations where target upregulation under the treatment is documented. To our knowledge, this is the first published case using this strategy in ALCL. The important, yet to be explored, questions like treatment duration and combinations with other agents such as chemotherapy, immune therapies, or others need to be evaluated. Successful development of effective treatment for relapsed or chemotherapy-refractory ALCL may avoid or defer the need for an allogeneic bone marrow transplant and its associated toxicities. Provided that the use of intermittent dosing is confirmed to be beneficial in a larger number of relapsed patients, it may become attractive for the first-line therapy setting.

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SUPPORT

Supported by NV19-03-00562, as provided by the Ministry of Health, Czech Republic; Conceptual Development of Research Organisation (FNBr, 65269705), as provided by Ministry of Health, Czech Republic; European Regional Development Fund—Project ENOCH (No. CZ.02.1.01/0.0/0.0/16_019/0000868); and MUNI/A/1427/2021 Specific University Research Grant, as provided by the Ministry of Education, Youth and Sports of the Czech Republic and supported by the Ministry of Health of the Czech Republic, grant No. NV19-03-00562. All rights reserved.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Travel, Accommodations, Expenses: BMS

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We acknowledge the Core Facility Genomics supported by the NCMG research infrastructure (LM2018132 funded by MEYS CR) and the Core Facility Bioinformatics of CEITEC Masaryk University for their support in obtaining scientific data presented in this paper.

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APPENDIX

TABLE A1. Detected Levels of *NPM1-ALK NCN* During the Treatment

Time Point	Material	*NPM1-ALK NCN*
Initial biopsy	Bone marrow	16,854.5
Before the prephase start	Peripheral blood	76,688.3
Before the first course of intensive CHT	Peripheral blood	32,123.5
Before the second course of intensive CHT	Peripheral blood	12,576.6
Before the third course of intensive CHT	Peripheral blood	12,963.1
Before the fourth course of intensive CHT	Peripheral blood	9,287.3
Clinical progression	Peripheral blood	2,982.6
Start of the first course of lorlatinib	Peripheral blood	8,974.8
1 week on	Peripheral blood	8,352.3
Lorlatinib discontinued	Peripheral blood	4,067.4
1 week off	Peripheral blood	1,072.3
9 days off	Peripheral blood	309.2
Start of the second course of lorlatinib	Peripheral blood	862.9
2 days on	Peripheral blood	1,402.8
1 week on	Peripheral blood	1,303.9
Lorlatinib discontinued	Peripheral blood	1,192.0
1 week off	Peripheral blood	425.5
9 days off	Peripheral blood	404.5
12 days off	Peripheral blood	414.0
Start of the third course of lorlatinib	Peripheral blood	326.8
1 week on	Peripheral blood	561.7
9 days on	Peripheral blood	626.4
12 days on	Peripheral blood	578.5
Lorlatinib discontinued	Peripheral blood	487.3
1 week off	Peripheral blood	306.7
Start of the fourth course of lorlatinib	Peripheral blood	184.0
1 week on	Peripheral blood	492.8
Lorlatinib discontinued	Peripheral blood	254.6
1 week off	Peripheral blood	159.6
Start of the fifth course of lorlatinib—dose increased	Peripheral blood	81.1
1 week on	Peripheral blood	192.1
Lorlatinib discontinued	Peripheral blood	182.6
1 week off	Peripheral blood	163.0
Start of the sixth course of lorlatinib	Peripheral blood	90.2
1 week on	Peripheral blood	117.2
Lorlatinib discontinued	Peripheral blood	85.4
1 week off	Peripheral blood	50.7
Start of the seventh course of lorlatinib	Peripheral blood	74.0
1 week on	Peripheral blood	82.2
Lorlatinib discontinued[a]	Peripheral blood	108.6
1 week off	Peripheral blood	34.0
Start of the eighth course of lorlatinib	Peripheral blood	37.5
1 week on	Peripheral blood	47.3
Lorlatinib discontinued	Peripheral blood	53.1
1 week off	Peripheral blood	16.4
Start of the ninth course of lorlatinib	Peripheral blood	24.1
1 week on	Peripheral blood	77.5
Lorlatinib discontinued	Peripheral blood	33.7
1 week off	Peripheral blood	28.2
Start of the 10th course of lorlatinib	Peripheral blood	13.1
1 week on	Peripheral blood	25.4
Lorlatinib discontinued	Peripheral blood	27.0
1 week off	Peripheral blood	11.4
Start of the 11th course of lorlatinib	Peripheral blood	12.0
1 week on	Peripheral blood	30.1
Lorlatinib discontinued	Peripheral blood	12.1
1 week off	Peripheral blood	13.4
Start of the 12th course of lorlatinib	Peripheral blood	6.4
1 week on	Peripheral blood	8.0
Lorlatinib discontinued	Peripheral blood	11.7
1 week off	Peripheral blood	7.8
Start of the 13th course of lorlatinib	Peripheral blood	6.6
1 week on	Peripheral blood	8.1
Lorlatinib discontinued	Peripheral blood	5.9
1 week off	Peripheral blood	3.3

Abbreviations: CHT, chemotherapy; PD-1, programmed cell death protein 1.

[a]Anti–PD-1 treatment introduced.