Anaplastic Lymphoma Kinase Inhibitors for Therapy of Neuroblastoma in Adults

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ABSTRACT

PURPOSE Adult-onset neuroblastoma (AON) differs significantly in biology and clinical behavior from childhood-onset disease. AON poses therapeutic challenges since tolerance of intensive multimodality therapies that are standard of care for pediatric neuroblastoma (NB) is poor. AON is enriched for somatic mutations including anaplastic lymphoma kinase (*ALK*), deemed to be an oncogenic driver in NB. ALK inhibitors (ALKis), therefore, have the potential to be of therapeutic benefit. The purpose of this study is to report on their use in AON.

METHODS A single-center retrospective review of adults with NB receiving ALKi (2012-2022) was performed. Response was evaluated using International Neuroblastoma Response Criteria.

RESULTS Fifteen patients with *ALK*-mutated AON were treated with US Food and Drug Administration–approved ALKi starting at a median age of 34 (16-71) years. Initial ALKi was lorlatinib, crizotinib, and alectinib in seven, five, and three patients respectively; seven received multiple ALKis due to progressive disease/intolerability of one agent. All patients experienced ≥grade 2 adverse events (AEs): crizotinib and alectinib were associated primarily with gastrointestinal AEs, lorlatinib with neurologic AEs, weight gain, and hyperlipidemia resulting in dose reduction or discontinuation of ALKi in several patients. No responses were observed with crizotinib (n = 5 patients), ceritinib, alectinib, or brigatinib (n = 1 each). Of the 13 patients receiving lorlatinib, four, five, and four patients had a complete or partial response (major response rate 69%), and stable disease, respectively. Responses were noted in all disease compartments; complete metabolic response was seen in two L2 patients. Ten of 13 patients remain progression-free at a median of 19 (6-50) months on lorlatinib. Three (two receiving dose-reduced therapy) had progressive disease. Median survival from start of first ALKi was 43 ± 26 months.

CONCLUSION ALKis, particularly lorlatinib, are effective treatment options for AON. However, AEs necessitating dose reduction are common.

INTRODUCTION

Neuroblastoma (NB), a rare embryonal tumor of the sympathetic nervous system, is most commonly diagnosed in infants and young children, and <10% of cases are diagnosed beyond age 5 years.[1] NB is extremely rare in adults and differs significantly in biology and clinical behavior from childhood-onset disease. *MYCN* amplification, seen commonly in children, is almost never seen in adult-onset neuroblastoma (AON), while *ATRX* aberrations are more common in the latter.[2] Although adults have more indolent disease, it is usually metastatic at diagnosis, more chemotherapy-resistant than childhood-onset NB, and almost invariably lethal. Furthermore, standard therapies used for the treatment of NB, including high-dose chemotherapy and anti-GD2 monoclonal antibodies, are poorly tolerated by adults.[3]

The tyrosine kinase anaplastic lymphoma kinase (*ALK*) is mutated in a variety of tumor types, and ALK inhibitors (ALKis) have been approved for the therapy of translocation-associated malignancies such as lung cancer. *ALK* is deemed to be an oncogenic driver in NB, and somatic mutations occur in 8%-10% of patients.[4] Unlike other malignancies, *ALK* mutations in NB are single-nucleotide variants rather than associated with chromosomal translocations.[5] *ALK* mutations are enriched in AON.[6] Tumor responses to ALKi are far less frequent and robust in children with NB

CONTEXT

Key Objective

Adult-onset neuroblastoma (AON) is biologically different from neuroblastoma (NB) diagnosed in young children. Treatment is challenging because of significant toxicity from standard NB therapy. Higher prevalence of anaplastic lymphoma kinase *(ALK)* mutations in AON may provide a viable target for therapy with various ALK inhibitors (ALKis). We conducted a single-center retrospective review to clarify the effects of ALKi in adults with NB.

Knowledge Generated

Fifteen patients were treated with a variety of ALKi. Of the 13 patients treated with lorlatinib, nine had complete or partial response (69%), including among those previously treated with other ALKi. Lorlatinib was associated with significant adverse events, several requiring dose reduction; however, ongoing responses were seen even at doses below the recommended adult dose.

Relevance

While not without toxicity, ALKi is overall well tolerated in patients with AON and its toxicity profile allows consideration of combination with chemotherapy.

than in translocation-associated *ALK*-mutated malignancies.[7] However, the use of ALKi in AON has not been specifically reported.

METHODS

After approval from the Institutional Review Board of Memorial Sloan Kettering Cancer Center (MSK), we retrospectively reviewed medical records of patients with NB treated with ALKi when they are older than 18 years. *ALK* mutations were evaluated on tumor samples using Clinical Laboratory Improvement Amendments (CLIA)–certified assays[8,9] or focused sequencing of *ALK*.[10] Circulating tumor DNA (ctDNA) was also assessed by CLIA-certified assay.[11] Response was evaluated using International Neuroblastoma Response Criteria (INRC).[12] Objective responses in tumor compartments were also noted. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier methods.

RESULTS

Sixty-five adult patients with NB were seen at MSK between 1979 and 2022. Upon introduction of *ALK* mutation testing, 17/27 tested (63%) had somatic *ALK* mutations identified using CLIA-certified assays.[10] Fifteen patients (eight female and seven male) were treated with US Food and Drug Administration–approved ALKi starting at a median age of 34 (range, 16-71) years, 14/15 without concomitant anti-NB therapy. Thirteen had AON (diagnosed when they are older than 18 years); one patient was diagnosed with NB at 12 years but initiated ALKi after a relapse 15 years later. Another diagnosed at 16 years continues ALKi into adulthood. All patients had received chemotherapy, immunotherapy, and/or radiotherapy before ALKi. Indications for ALKi included refractory unresectable locoregional (stage L2; n = 3) or metastatic disease (stage M; n = 6), and relapsed or progressive metastatic disease (n = 7). Loci of mutations were F1174L (n = 8), R1275Q (n = 4), and other (n = 3). As expected in this adult population, *ATRX* aberrations were observed in 9/14 tested (64%) tumors (Table 1).

Initial ALKi was lorlatinib, crizotinib, and alectinib in seven, five, and three patients, respectively; seven went on to receive multiple ALKis due to progressive disease (PD)/intolerability of one agent. Most patients experienced ≥grade 2 adverse events (AEs): crizotinib and alectinib were associated primarily with gastrointestinal AEs, and lorlatinib with neurologic AEs, weight gain, and hyperlipidemia (Table 2). Dose reduction (either transient or permanent) or discontinuation of ALKi was needed in 2/5, 1/1, 1/3, and 5/13 patients receiving crizotinib, ceritinib, alectinib, and lorlatinib, respectively. AEs resolved or diminished when ALKi were withheld or discontinued.

All patients were evaluable for response. No responses were observed with crizotinib (n = 5), ceritinib, alectinib, or brigatinib (n = 1 each). Among these patients, 4/8 harbored the ALKF1174 mutation. Of the 13 patients treated with lorlatinib (including five previously treated with other ALKis), best response was complete response (n = 4) or partial response (n = 5) and stable disease (n = 4; Table 2). Responses were noted in all disease compartments: soft tissue, bone, and bone marrow (Fig 1). In addition, one patient had an almost complete metabolic response to lorlatinib, with near loss of fluorodeoxyglucose uptake suggesting disease maturation (Fig 2). Responses to lorlatinib were durable: 9/13 patients continue lorlatinib at a median age of 19 (6-36) months. Three patients relapsed while receiving lorlatinib after a median age of 21 (12-27) months, and two while receiving <100 mg once daily. All three had persistence of the original *ALK* mutation on ctDNA testing at

TABLE 1. Clinical Information Before Starting ALKi

Patient ID	Sex	Age at Dx, Years	Stage at Dx	Treatment at Diagnosis	Type of Mutation	How Tested	Other Mutated Genes	Stage at ALKi	Indication for ALKi	No. of Previous Relapses	Age at First ALKi, Years
1	F	12	L2	HD chemo, antibody, XRT	*ALKR1275Q*	Foundation	*ATRX*	M	Relapsed stage M	4	27
2	F	16	L2	HD chemo, XRT	*ALKF1174L*	MSK-IMPACT	*ATRX*	M	Refractory stage L2	1	16
3	F	20	L2	IM dose chemo	*ALKF1174L*	MSK-IMPACT	*ATRX, RICTOR, STK40, RAD54L, BLM, PIK3R2, MSH2, IRS1, NSD1*	L2	Refractory stage L2	0	20
4	F	20	M	HD chemo, XRT, chemoimmunotherapy	*ALKF1174L*	MSK-IMPACT	*ATRX, FBXW7*	M	Relapsed stage M	2	25
5	M	23	M	Lu-dotatate, surgery	*ALKR1275Q*	Foundation	*ATRX, EIF4E3-FOXP1* fusion	M	Refractory stage M	0	23
6	F	24	M	HD chemo, antibody, XRT	*ALKF1174L*	MSK-IMPACT	*ATRX*	M	Relapsed stage M	2	36
7	M	27	L2	Surgery; chemo and XRT for relapse	*ALKF1174C*	MSK-IMPACT	*ATM, BRAFV600E, FGFR1, MTOR, NRAS*	M	Relapsed stage M	5	34
8	F	28	L2	HD chemo, XRT, cis-retinoic acid	*ALKD1276_R1279*	Foundation	*BRCA2, PRKCI*	M	Relapsed stage M	4	46
9	F	30	M	HD chemo, antibody, XRT, allo Tx	*ALKR1275Q*	MSK-IMPACT	*BRCA1 Q910E, DUSP4*	M	Relapsed stage M	1	30
10	M	30	M	HD chemo	*ALKF1174V*	MSK-IMPACT	*ATRX, JAK3*	M	Refractory stage M	0	31
11	F	33	M	HD chemo, antibody, XRT	*ALKF1174L*	MSK-IMPACT	*BRCA2, KMT2B, MYCL, IKZF1*	M	Refractory stage M	0	34
12	M	33	M	HD chemo, chemoimmunotherapy	*ALKF1174L*	Focused	Not tested	M	Refractory stage M	0	34
13	M	35	L2	Focal XRT	*ALKF1245V*	MSK-IMPACT	*NSD1 R1535C, MPL G431D*	L2	Refractory stage L2	1	36
14	M	44	M	XRT, HD chemo	*ALKF1245V*	MSK-IMPACT	*ATRX*	M	Refractory stage M	0	44
15	M	70	M	Focal XRT	*ALKR1275Q*	Foundation	*ATRX, FOXP1* fusion	M	Relapsed stage M	1	71

Abbreviations: ALK, anaplastic lymphoma kinase; ALKi, ALK inhibitor; Dx, diagnosis; F, female; HD, high-dose; ID, identification; IM, intermediate; M, male; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; Tx, transplant; XRT, radiation therapy.

TABLE 2. Lorlatinib Toxicities and Responses Use and Toxicity

Patient ID	Initial Dose	Adverse Events	Dose Reduction?	Highest Tolerable Dose	Sites of Evaluable Disease	Best INRC Response	Objective Response	Overall INRC Response	Months on Drug
1	150	Grade 2 neuropathy Grade 2 hypercholesterolemia Grade 2 weight gain/edema	N	100	Soft tissue	PR	>50% reduction of soft tissue	Continuing PR	≥44
3	100	Grade 1 nausea Grade 1 constipation	N	100	Bone and BM	CR	CR in bone and BM	PD	36
4	100	Grade 2 hypercholesterolemia Grade 2 weight gain/edema	N	125	Bone	CR	CR in bone	Continuing CR	≥6
5	100	Grade 2 edema Grade 2 hyperlipidemia Grade 2 hypertriglyceridemia	N	150	Bone	PR	PR in bone	Continuing SD	≥44
6	100	Grade 3 hallucinations	Y	50	Soft tissue	SD	<50% reduction of soft tissue	PD	41
7	100	Grade 1 nausea Grade 1 constipation	N	100	Bone and BM	SD	No response	PD	8
8	100	Grade 2 weight gain/fluid retention Grade 2 constipation	Y	75	Soft tissue	SD	<50% reduction of soft tissue; complete metabolic response on FDG PET; residual soft tissue completely resected	Continuing SD	≥44
9	100	Grade 2 memory loss Grade 2 fluid retention Grade 2 peripheral neuropathy	Y	75	Soft tissue, bone and BM	SD	<50% reduction of soft tissue; <50% reduction in MIBG score; CR in BM	Continuing SD	8
10	100	Grade 2 mood changes Grade 2 peripheral neuropathy Grade 2 weight gain	Y	125	Bone and BM	CR	CR in bone and BM	Continuing CR	≥20
11	100	Grade 2 edema	Y	75	Bone	CR	CR in bone	Continuing CR	≥51
12	100	Grade 2 mood changes Grade 2 peripheral neuropathy Grade 2 weight gain	N	100	Soft tissue, bone and BM	PR	>50% reduction of soft tissue; PR in bone; <5% in BM	Continuing PR	≥14
14	125	Grade 1 weight gain	N	150	Bone, BM	PR	PR in bone; <5% in BM	PD	≥15
15	100	Grade 1 weight gain	N	150	Soft tissue, bone and BM	PR	PR in soft tissue and bone, CR in BM	Continuing PR	≥7

NOTE. All doses were given once daily.

Abbreviations: BM, bone marrow; CR, complete remission; FDG, fluorodeoxyglucose; ID, identification; INRC, International Neuroblastoma Response Criteria; MIBG, meta-iodobenzylguanidine; N, no; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease; Y, yes.

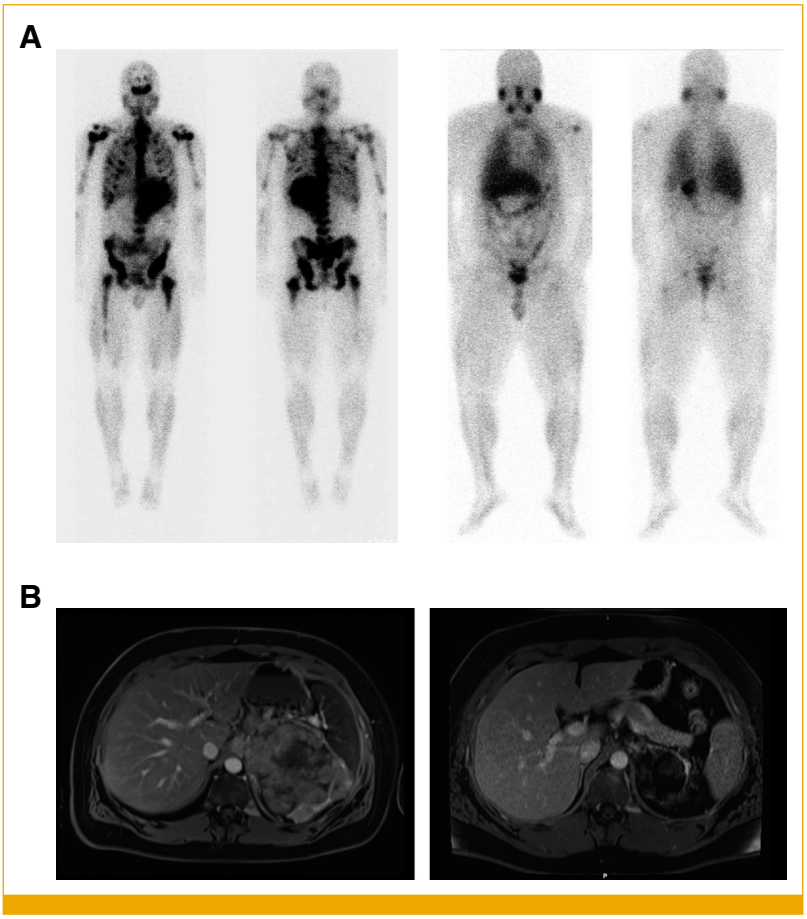

FIG 1. A 31-year-old man with PR after 5 months on lorlatinib. (A) MIBG with near-complete resolution of metabolic disease including large left adrenal mass and diffuse bony disease. (B) MR abdomen with significant decrease in size of left adrenal primary. MIBG, meta-iodobenzylguanidine; MR, magnetic resonance; PR, partial response.

relapse. Mean PFS and OS for patients receiving lorlatinib was 40.1 ± 4.7 and 47.5 ± 4 months from the start of lorlatinib, respectively; only one patient has died in the lorlatinib cohort with a median follow-up of 21 months from starting lorlatinib. Five-year OS from diagnosis for the entire cohort of 15 patients was 89% ± 10%.

Five patients received 1 additional ALKi or more after discontinuing first ALKi for PD or intolerability. Two patients received four ALKis each. Of the five patients receiving lorlatinib as the second ALKi or later, responses were noted in 4 (80%).

DISCUSSION

NB diagnosed in adolescents and adults is a dramatically different disease from NB diagnosed in young children. Treating AON is challenging, and long-term prognosis for adults is poor. Standard treatment for NB includes high-dose chemotherapy and anti-GD2 monoclonal antibodies; however, adults do not tolerate either of these therapies well because of severe chemotherapy-associated myelosuppression, and pain associated with anti-GD2 immunotherapy. Additionally, AON is often chemoresistant, with poor responses reported even to dose-intensive therapy. Like other pediatric malignancies, NB has few actionable genomic aberrations limiting the use of genomically targeted therapies, and the lack of HLA class I expression, low mutational load, immune evasion strategies, and poor tumor infiltration by cytotoxic T cells make consideration of immune checkpoint inhibitors moot. Finally, adults are generally excluded from pediatric NB trials, and conversely, NB is rarely included in adult trials, making the introduction of novel therapies difficult.[3]

We previously reported that AON is enriched for activating ALK mutations, providing a potential for the use of this ALK-targeted therapy in adults with NB.[3] Over the past decade, several generations of ALKi have been developed for the use in a variety of *ALK*-mutated tumors. We demonstrate here that ALKis, especially the third-generation ALKi lorlatinib, are promising for AON therapy. Sixty-nine percent of AON had durable major responses and nearly all patients treated

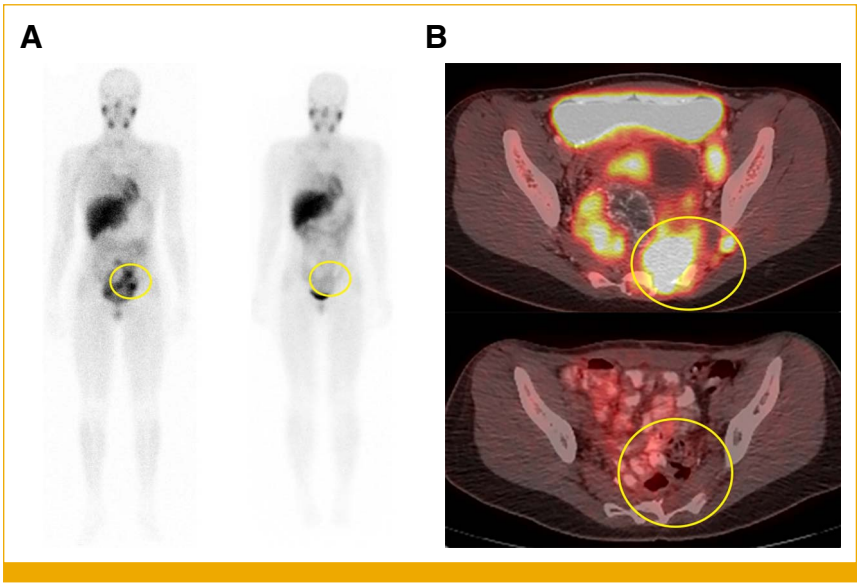

FIG 2. Complete metabolic response with use of lorlatinib. (A) MIBG scan before and after showing MIBG avid multiloculated presacral and multiple pelvic soft tissue masses and full resolution of MIBG avid disease 25 months on drug. (B) FDG PET demonstrating same disease with full resolution. FDG, fluorodeoxyglucose; MIBG, meta-iodobenzylguanidine; PET, positron emission tomography.

had objective responses to lorlatinib. Additionally, responses were noted at doses as low as 75 mg once daily, lower than the recommended adult dose of 100 mg once daily.

As a third-generation inhibitor of *ALK* and *ROS*, lorlatinib was developed with the goal of overcoming resistance to crizotinib and other earlier-generation ALKis. Preclinical and early clinical trials showed that lorlatinib was more potent than earlier ALKis and was effective against a wide range of *ALK* mutations, including F1174 known to confer resistance to earlier-generation ALKis.[13,14] It has now superseded crizotinib as first-line therapy for *ALK*-mutated non–small-cell lung cancer (NSCLC).[15] Additionally, nearly 50% of patients with NSCLC who experienced PD on early generations of ALKi responded to lorlatinib.[16] We observed similar results in our patients; responses to other ALKis were modest or absent as opposed to high response rates to lorlatinib, and 4/5 patients who had PD on or who could not tolerate other ALKis responded to lorlatinib. Unfortunately, as previously reported,[15] lorlatinib was more toxic than other ALKis even at doses as low as 75 mg once daily. This is consistent with reports from a phase II trial in which 74% of patients required dose reduction due to toxicity and ultimately study participants received a mean dose of 70 mg once daily.[17] However, anti-NB activity was noted even at a dose of 75 mg. On the basis of our observations and those of other investigators, lorlatinib should be considered as the inhibitor of choice for *ALK*-mutated NB.

Early reports on ALKi use in children have demonstrated that as opposed to inflammatory myofibroblastic tumor or anaplastic large cell lymphoma, responses in children with NB are infrequent.[18,19] It has been hypothesized that the lack of response of NB to ALK inhibition is due to the presence of point mutations in NB compared with ALK fusions and translocations in other tumor types leading to heightened ATP-binding affinity, making the tumor cells less sensitive to inhibition (particularly shown to be true with crizotinib).[20] Given the presence of the same mutations in NB across all age groups, we were surprised to see robust and durable responses with lorlatinib including in tumors harboring F1174 mutations. Recently published data from the phase I trial of lorlatinib in NB support these observations with a much higher response rate in patients older than 18 years (INRC response of 47% in patients older than 18 years *v* 13% in younger patients). Additionally, 86% of the patients younger than 18 years experienced PD while on treatment or by the end of the planned course.[21] NB with mutations at F1174, which has been particularly resistant to early-generation ALKis, has been shown to respond to lorlatinib in preclinical studies.[22] Our experience is consistent with this observation. The reason for robust responses in adults compared with children is unclear and might possibly be related to drug kinetics. Further clinical investigation is clearly warranted to understand this phenomenon.

Although in general, responses in patients with NB receiving lorlatinib were durable, we encountered relapse in four patients, two of whom were unable to tolerate the full adult dose. Interestingly, ctDNA showed the persistence/recurrence of the initial *ALK*-mutated clone suggesting

that the mechanism of resistance is related to other oncogenic pathways. A variety of newer agents have been developed and are currently being studied in early-phase trials, including multikinase inhibitors such as repotrectinib, and other newer ALKis designed to target malignancies harboring multiple *ALK* mutations.[23] Furthermore, investigating the combination of lorlatinib with chemotherapy to determine if more robust or sustained responses can be achieved is warranted.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Sait S, Modak S: Anti-GD2 immunotherapy for neuroblastoma. Expert Rev Anticancer Ther 17:889-904, 2017
2. Brady SW, Liu Y, Ma X, et al: Pan-neuroblastoma analysis reveals age- and signature-associated driver alterations. Nat Commun 11:5183, 2020
3. Suzuki M, Kushner BH, Kramer K, et al: Treatment and outcome of adult-onset neuroblastoma. Int J Cancer 143:1249-1258, 2018
4. Azarova AM, Gautam G, George RE: Emerging importance of ALK in neuroblastoma. Semin Cancer Biol 21:267-275, 2011
5. Bresler SC, Weiser DA, Huwe PJ, et al: ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma. Cancer Cell 26:682-694, 2014
6. Duan K, Dickson BC, Marrano P, et al: Adult-onset neuroblastoma: Report of seven cases with molecular genetic characterization. Genes Chromosomes Cancer 59:240-248, 2020
7. Mosse YP: Anaplastic lymphoma kinase as a cancer target in pediatric malignancies. Clin Cancer Res 22:546-552, 2016
8. Cheng DT, Mitchell TN, Zehir A, et al: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn 17:251-264, 2015
9. Milbury CA, Creeden J, Yip WK, et al: Clinical and analytical validation of FoundationOne®CDx, a comprehensive genomic profiling assay for solid tumors. PLoS One 17:e0264138, 2022
10. O'Donohue T, Gulati N, Mauguen A, et al: Differential impact of ALK mutations in neuroblastoma. JCO Precision Oncol 10.1200/PO.20.00181, 2021
11. Woodhouse R, Li M, Hughes J, et al: Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One 15:e0237802, 2020
12. Park JR, Bagatell R, Cohn SL, et al: Revisions to the international neuroblastoma response criteria: A consensus statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35:2580-2587, 2017
13. Infarinato NR, Park JH, Krytska K, et al: The ALK/ROS1 inhibitor PF-06463922 overcomes primary resistance to crizotinib in ALK-driven neuroblastoma. Cancer Discov 6:96-107, 2016
14. Zou HY, Friboulet L, Kodack DP, et al: PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. Cancer Cell 28:70-81, 2015
15. Shaw AT, Bauer TM, de Marinis F, et al: First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med 383:2018-2029, 2020
16. Solomon BJ, Besse B, Bauer TM, et al: Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. Lancet Oncol 19:1654-1667, 2018
17. Dagogo-Jack I, Oxnard GR, Evangelist M, et al: Phase II study of lorlatinib in patients with anaplastic lymphoma kinase-positive lung cancer and CNS-specific relapse. JCO Precis Oncol 10.1200/PO.21.00522, 2022
18. Mosse YP, Lim MS, Voss SD, et al: Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. Lancet Oncol 14:472-480, 2013
19. Fischer M, Moreno L, Ziegler DS, et al: Ceritinib in paediatric patients with anaplastic lymphoma kinase-positive malignancies: An open-label, multicentre, phase 1, dose-escalation and dose-expansion study. Lancet Oncol 22:1764-1776, 2021
20. Foster JH, Voss SD, Hall DC, et al: Activity of crizotinib in patients with ALK-aberrant relapsed/refractory neuroblastoma: A Children's Oncology Group Study (ADVL0912). Clin Cancer Res 27:3543-3548, 2021
21. Goldsmith KC, Park JR, Kayser K, et al: Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: Phase 1 trial results. Nat Med 29:1092-1102, 2023
22. Liu T, Merguerian MD, Rowe SP, et al: Exceptional response to the ALK and ROS1 inhibitor lorlatinib and subsequent mechanism of resistance in relapsed ALK F1174L-mutated neuroblastoma. Cold Spring Harb Mol Case Stud 7:a006064, 2021
23. O'Donohue TJ, Ibáñez G, Coutinho DF, et al: Translational strategies for repotrectinib in neuroblastoma. Mol Cancer Ther 20:2189-2197, 2021