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NCCN Guidelines Panel: **T-Cell Lymphomas**

Dear NCCN Guidelines Panel for T-Cell Lymphomas:

On behalf of Genentech, Inc., please find the below request for your review regarding the use of Alecensa® (alectinib) in patients with anaplastic lymphoma kinase-positive (ALK+) anaplastic large cell lymphoma (ALCL).

Request:[1]
Please consider the inclusion of Alecensa as a single-agent treatment for relapsed or refractory ALCL (ALK+ only) in the **NCCN Guidelines® for T-Cell Lymphomas Version 1.2021, Page TCEL-B 4 of 5**.

- Second-line therapy (with intention to process to transplant) and subsequent therapy
- Second-line or initial palliative intent therapy (no intention to transplant) and subsequent therapy

Rationale:
ALCL is a rare peripheral T-cell lymphoma that accounts for 10%-15% of pediatric non-Hodgkin lymphoma (NHL) cases and 1-2% of adult NHL cases.[1] Approximately 90% of pediatric and almost 50% of adult ALCL cases are ALK+. Published literature on Alecensa, a second generation ALK inhibitor, for the treatment of ALK+ ALCL currently include a Phase II study, case series, and case reports.[2-8]

Phase II Study
A single-arm, open-label phase II trial was conducted in Japan to evaluate the efficacy and safety of Alecensa in 10 patients (6 years of age or older) with relapsed or refractory ALK+ ALCL.[2] Alectinib was administered orally twice daily with weight-based dosing for 16 cycles (21 days each). The primary endpoint was objective response assessed by an independent central review board. The median age was 19.5 years (range, 6-70 years). The objective response rate was 80% (90% CI, 56.2-95.9) with 6 complete responses. Two patients received allogeneic HSCT in remission following treatment with Alecensa. The 1-year progression-free survival, event-free survival, and overall survival rates were 58%, 70%, and 70%, respectively. The median duration of therapy was 340 days and median duration of follow-up was 508 days. The most common Grade 3-5 adverse event (AE) was decreased neutrophil count (n=2). The most common AEs which occurred in 40% of patients were diarrhea, upper respiratory tract infection, maculopapular rash, and increased blood alkaline phosphatase. No unexpected AEs were observed and no patient required discontinuation or dose reduction of Alecensa due to AEs.

Case Series and Reports
Shen et al. presented a series of 3 relapsed/refractory pediatric ALCL patients, including 1 patient with central nervous system (CNS) involvement.[3] All 3 patients were treated with either crizotinib or alectinib and achieved complete responses.

Additional case reports have been reported on the use of Alecensa in patients with relapsed or refractory ALK+ ALCL.[4-8]

- Reed et al. presented a 27-year-old male with ALK+ ALCL and CNS involvement who achieved complete response with Alecensa after relapse from first-line systemic and intrathecal chemotherapy.[4] The patient then underwent an allogeneic stem cell transplant and relapsed early in his transplant course. He responded at re-initiation of Alecensa.

- Nakai et al. presented the successful use of Alecensa as a bridge to allogeneic stem cell transplantation in a 22-year-old female patient with ALK+ ALCL refractory to both conventional chemotherapies and brentuximab vedotin.[5]
- Tomlinson et al. presented the case of a 36-year-old male with ALK+ ALCL that relapsed to the CNS who achieved a durable second remission (>12 months ongoing at the time of report) with high-dose methotrexate followed by continuous Alecensa monotherapy.[6]
- Yang et al. presented the case of a 8-year-old female with ALK+ ALCL who experienced CNS relapse after complete remission with chemotherapy. The patient achieved a durable second remission with high-dose chemotherapy and continuous treatment with Alecensa and vinblastine.[7]
- Saito et al. presented an 18-year old female with chemotherapy- and brentuximab vedotin-resistant ALK+ ALCL that was successfully treated with Alecensa after relapse from allogeneic bone marrow transplantation and intolerance to crizotinib. At the time of report, the patient remained in complete response under maintenance treatment with Alecensa for >16 months.[8]

FDA Clearance:

- Alecensa is not FDA-approved for use in patients with relapsed or refractory ALK+ ALCL.
- Please refer to the Alecensa prescribing information for the full FDA-approved indications and safety information, available at: http://www.gene.com/download/pdf/alecensa_prescribing.pdf

Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Aileen Le, PharmD

References

1. Turner SD, Lamant L, Kenner L, et al. Anaplastic large cell lymphoma in paediatric and young adult patients. Br J Haematol 2016;173(4):560-572.
2. Fukano R, Mori T, Sekimizu M, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: an open-label phase II trial. Cancer Sci 2020;111:4540-4547. https://pubmed.ncbi.nlm.nih.gov/33010107/.
3. Shen D, Song H, Zhang J, et al. Treatment of relapsed and refractory ALK-positive anaplastic large cell lymphoma with ALK-specific tyrosine kinase inhibitor in children: a case series. J Pediatr Hematol Oncol 2021;Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/33661174/.
4. Reed DR, Hall RD, Gentzler RD, et al. Treatment of refractory ALK rearranged anaplastic large cell lymphoma with alectinib. Clin Lymphoma Myeloma Leuk 2019;19(6):e247-250. https://pubmed.ncbi.nlm.nih.gov/30992232/.
5. Nakai R, Fukuhara S, Maeshima AM, et al. Alectinib, an anaplastic lymphoma kinase (ALK) inhibitor, as a bridge to allogeneic stem cell transplantation in a patient with ALK-positive anaplastic large-cell lymphoma refractory to chemotherapy and brentuximab vedotin. Clin Case Rep 2019;7(12):2500-2504. https://pubmed.ncbi.nlm.nih.gov/31893088/.
6. Tomlinson SB, Sandwell, S, Chuang ST, et al. Central nervous system relapse of systemic ALK-arranged anaplastic large cell lymphoma treated with alectinib. Leuk Res 2019;83:106164. https://pubmed.ncbi.nlm.nih.gov/31226541/.
7. Yang J, Li J, Gu WY, et al. Central nervous system relapse in a pediatric anaplastic large cell lymphoma patients with CLTC/ALK translocation treated with alectinib: a case report. World J Clin Cases 2020;8(9):1685-1692. https://pubmed.ncbi.nlm.nih.gov/32420302/.
8. Saito S, Tashiro H, Sumiyoshi R, et al. Second allogeneic transplantation using umbilical cord blood for a patient with relapsed ALK+ anaplastic large cell lymphoma after allogeneic bone marrow transplantation in the era of ALK inhibitors: a case report. Medicine 2021;100(15):e25576. https://pubmed.ncbi.nlm.nih.gov/33847688/.