Clinical Criteria

Subject:	Adcetris (brentuximab vedotin)		
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Overview

This document addresses the use of Adcetris (brentuximab vedotin). Adcetris is a monoclonal antibody-drug conjugate (ADC) that consists of a chimeric IgG1 directed antibody against CD30 and a small molecule, monomethyl auristatin E (MMAE), a microtubule-disrupting agent. The anticancer activity is due to the binding of the ADC to CD30-expressing cells causing disruption of the microtubule network leading to cell death. Adcetris is FDA approved for certain patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Adcetris.

Hodgkin Lymphoma (HL)

Adcetris was FDA approved in 03/2018 for previously untreated stage III or IV classical HL, in combination with chemotherapy. This FDA indication was updated in 11/2018 to read "in combination with doxorubicin, vinblastine, and dacarbazine". NCCN give additional combination options for older adults with HL, including sequential therapy or in combination with dacarbazine. Adcetris is also approved as a single agent for relapsed HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens when individuals were ineligible for transplant. In this space, NCCN recommends Adcetris alone or in combination with bendamustine or nivolumab, and regardless of individual's eligibility for transplant. It is also approved as post-auto-HSCT consolidation therapy for those at high risk of relapse or progression. The clinical trial supporting this indication defined high risk as: primary refractory HL (failure to achieve complete remission, as determined by investigator), relapsed HL with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy. NCCN recommends as maintenance therapy for 1 year if brentuximab naïve and Deauville score less than 5.

Non-Hodgkin Lymphoma (NHL)

NHLs are a broad and diverse group of malignancies affecting both B- and T-lymphocytes. Adcetris is mostly used for T-Cell Lymphomas. These can broadly be classified as cutaneous or non-cutaneous. Cutaneous T-cell lymphomas include mycosis fungoides (MF) and sezary syndrome (SS), lymphomatoid papulosis (LyP), and the cutaneous form of anaplastic large cell lymphoma (ALCL), known as primary cutaneous ALCL. "Non-cutaneous" T-cell lymphomas are diverse and NCCN divides the treatment algorithms into certain types such as peripheral t-cell lymphoma (PTCL), Adult T-cell leukemia/lymphoma (ATLL), breast implant-associated ALCL, extranodal NK/T-Cell lymphoma, nasal type (NKTL), and hepatosplenic T-Cell Lymphoma (HSTCL). Subtypes of PTCLs include but are not limited to PTCL-NOS (not-otherwise-specified), systemic ALCL, and angioimmunoblastic t-cell lymphoma.

Adcetris is FDA approved for *relapsed* primary cutaneous ALCL and CD30 expressing MF. NCCN recommends it also as first-line treatment of primary cutaneous ALCL and MF/SS when there is advanced disease presentation (which would disease that is stage IIB or higher, large cell transformation, extensive skin involvement, higher skin disease burden, primarily plaque disease, blood involvement, or inadequate response to skin-directed therapy). NCCN also recommends Adcetris for relapsed/refractory LyP with extensive lesions. Adcetris is also FDA approved to treat relapsed systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. In the area of relapsed disease, NCCN also recommends Adcetris for PTCL, angioimmunoblastic t-cell lymphoma, NKTL, HTL, and breast implant-associated ALCL. NCCN also recommends Adcetris as adjuvant therapy for breast implant-associated ALCL.

Adcetris also was recently FDA approved in combination cyclophosphamide, doxorubicin, and prednisone (CHP) for previously untreated CD30 expressing PTCL and systemic ALCL (which is a type of PTCL) based on the results of the ECHELON-2 study (Horwitz 2018). Study inclusion criteria states "newly diagnosed CD30+ mature T-cell lymphomas". NCCN additionally recommends this front-line regimen for patients with ATLL and the following types of PTCL: angioimmunoblastic t-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma. NCCN also recommends Adcetris as secondary treatment for ATLL.

Other Uses

NCCN also provides 2A recommendations for the use of Adcetris in relapsed or refractory CD30+ diffuse large B-cell lymphoma (DLBCL) for individuals who are not candidates for a transplant. Recommendation was upgraded from 2B to 2A with no rationale, and cites the same lower quality evidence of one phase 2 study (Jacobsen 2015). NCCN algorithms for various other relapsed/refractory B-cell lymphomas (High-grade, post-transplant lymphoproliferative disorders [PTLD], transformed follicular lymphoma, AIDS-related) direct to this same recommendation regarding DLBCL. Recommendation for T-Cell type PTLD cites ECHELON-2 trial that studied peripheral T-Cell Lymphomas. The recently published NCCN guidelines for Pediatric Hodgkin Lymphoma also include recommendations for Adcetris in combination with gemcitabine. Supportive studies include a single-arm phase 1/2 study (Cole 2018), but high quality data is lacking.

Adcetris (brentuximab vedotin) has a black box warning for John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML). Fatal cases of JC virus infection resulting in PML have been reported in individuals receiving Adcetris.

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Autologous stem cells: Stem cells harvested from the individual's own bone marrow or peripheral blood.

Consolidation: Repetitive cycles of treatment during the immediate post-remission period; used especially for leukemia; also known as intensification therapy.

Deauville Score: 5-point rating scale used in staging and response of HL and NHL; visual assessment of F-fluorodeoxyglucose (FDG) uptake in the involved sites. Score of 5 indicates markedly higher uptake initially involved site and/or new lesions.
High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.

Maintenance therapy: Designed to maintain a condition to prevent a relapse.

Mycosis fungoides: A sub-type of cutaneous T-cell lymphoma in which tumor cells invade the skin causing reddening (erythroderma) and/or plaques. There may also be involvement of lymph nodes, blood, and internal organs.

One line of therapy: Single line of therapy.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Sézary Syndrome: A sub-type of cutaneous T-cell lymphoma characterized by itching and redness with T cell leukemia whose cells clonally match those invading the skin. Sézary Syndrome has historically been more difficult to treat than mycosis fungoides.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Adcetris (brentuximab)

Requests for Adcetris (brentuximab vedotin) may be approved if the following criteria are met:

I. Individual has a diagnosis of Hodgkin Lymphoma (HL); **AND**
II. Individual is using for one of the following:
    A. Previously untreated stage III or IV classical HL, in combination with doxorubicin, vinblastine, and dacarbazine; **OR**
    B. Previously untreated classical HL in older adults (≥60 years), as sequential therapy with doxorubicin, vinblastine, and dacarbazine, or in combination with dacarbazine (NCCN 2A); **OR**
    C. Relapsed or refractory disease in a single line of therapy as a single agent or in combination with bendamustine (Label, NCCN 2A); **OR**

D. As consolidation therapy after an autologous stem cell transplantation for individuals at high risk of relapse or progression, defined as individuals with any of the following:
    1. Primary refractory HL; **OR**
    2. Relapsed HL with an initial remission duration of less than 12 months; **OR**
    3. Extranodal involvement at the start of pre-transplantation salvage chemotherapy;

OR

E. As maintenance therapy for 1 year following high-dose therapy and autologous stem cell rescue for relapsed or refractory disease in those who are brentuximab vedotin naïve and have a Deauville score of less than 5 (NCCN 2A);

OR

III. Individual has a diagnosis of CD30+ Non-Hodgkin Lymphoma; **AND**

IV. Individual is using for one of the following:

A. Cutaneous anaplastic large cell lymphoma; **OR**

B. Cutaneous T-cell lymphoma, including mycosis fungoides/Sézary syndrome, for the following:
    1. Relapsed or refractory disease; **OR**
    2. As first-line therapy for advanced disease presentation (for example, ~~folliculotropic, large-cell transformation or extracutaneous disease~~large cell transformation, extensive skin involvement, higher skin disease burden, primarily plaque disease, blood involvement, inadequate response to skin-directed therapy, or state IIB or higher) (NCCN 2A);

OR

C. Relapsed or refractory lymphomatoid papulosis with extensive cutaneous lesions (NCCN 2A);

OR

~~C.~~D. In combination with cyclophosphamide, doxorubicin, and prednisone, for previously untreated:
    1. Peripheral T-cell lymphoma (including systemic anaplastic large cell lymphoma, angioimmunoblastic t-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma) (Label, NCCN 2A); ~~**OR**~~
    ~~2. Adult T-cell leukemia/lymphoma (NCCN 2A); **OR**~~
    ~~3. Hepatosplenic Gamma-Delta T-Cell Lymphoma (NCCN 2A);~~

OR

~~D.~~E. ~~As a single agent for a~~Adult T-cell leukemia/lymphoma ~~that has not responded to first-line therapy~~ (NCCN 2A);

OR

~~E. Relapsed or refractory disease after at least one prior multi-agent chemotherapy regimen for treatment of any of the following:~~
    ~~1. Systemic anaplastic large cell lymphoma; **OR**~~
    ~~2. T-cell lymphoma (excluding cutaneous T-cell lymphoma) (NCCN 2A); **OR**~~
    ~~3. Lymphomatoid papulosis that is symptomatic or characterized by extensive cutaneous lesions (NCCN 2A);~~

OR

F. One of the following T-cell lymphomas, as treatment for relapsed or refractory disease:
    1. Systemic anaplastic large cell lymphoma (Label);
    2. Extranodal NK/T-Cell lymphomas (NCCN 2A);
    3. Hepatosplenic T-Cell lymphoma (NCCN 2A);
    4. Breast implant-associated anaplastic large cell lymphoma (NCCN 2A);
    5. Peripheral T-cell lymphoma (NCCN 2A);
    6. Angioimmunoblastic T-cell lymphoma (NCCN 2A);

OR

~~F.~~G. As an adjuvant systemic therapy for breast implant-associated anaplastic large cell lymphoma for either of the following (NCCN 2A):
    1. Residual, localized disease (confined to capsule/implant/breast) following partial excision or capsulectomy; **OR**
    2. Extended disease (stage II-IV).

Requests for Adcetris (brentuximab vedotin) may not be approved when the above criteria are not met and for all other indications.

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9042	Injection, brentuximab vedotin, 1 mg [Adcetris]

ICD-10 Diagnosis	
C81.00-C81.99	Hodgkin lymphoma
C84.00-C84.19	Mycosis fungoides, Sézary disease
C84.40-C84.49	Peripheral T-cell lymphoma, not classified
C84.60-C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70-C84.79	Anaplastic large cell lymphoma, ALK-negative
C84.A0-C84.A9	Cutaneous T-cell lymphoma, unspecified
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C91.50-C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated)
Z85.71	Personal history of Hodgkin lymphoma
Z85.72	Personal history of non-Hodgkin lymphomas

Document History

Revised: 05/20/2022
Document History:

- 05/20/2022 – Annual Review: Update Non-hodgkin lymphoma section to list specific examples of T-cell lymphoma, include additional examples per NCCN 2A recommendations; simplify criteria for Adult T-cell lymphoma; update mycosis fungoides/Sézary syndrome criteria for definition of advanced disease per NCCN; remove untreated Hepatosplenic T-cell lymphoma as NCCN 2B; add combination with nivolumab for relapsed or refractory Hodgkin lymphoma per NCCN. Coding Reviewed: No changes.
- 05/21/2021 – Annual Review: No changes. Coding Reviewed: No changes.
- 05/15/2020 – Annual Review: Add additional regimens for older adults with classical Hodgkin Lymphoma; update adult T-cell leukemia language to align with NCCN. Coding reviewed: No changes.
- 05/17/2019 – Annual Review: First review of Adcetris clinical criteria. Add criteria for previously untreated adult T-cell leukemia/lymphoma and hepatosplenic gamma-delta T-cell lymphoma. Add references for off label indications. Coding Reviewed: Added ICD-10 DX code range C84.Z0-C84.Z9.

References

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9. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
10. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed March 2022.
    a. B-Cell Lymphomas. V2.2022. Revised March 21, 2022.
    b. Hodgkin Lymphoma. V2.2022. Revised February 23, 2022.
    c. Pediatric Hodgkin lymphoma. V3.2021. Revised March 18, 2021.
    d. Primary Cutaneous Lymphomas. V1.2022. Revised January 26, 2022.
    e. T-Cell Lymphomas. V2.2022. Revised March 7, 2022.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.