



MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 08/25/10
LAST REVIEW DATE: 03/19/19
LAST CRITERIA REVISION DATE: 10/24/17
ARCHIVE DATE:

IMMUNOTHERAPY, ADOPTIVE

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Adoptive immunotherapy (AIT) is a term describing treatment to boost an individual's immune system using the individual's own lymphocytic cells which are treated to become more aggressive at fighting cancer and other diseases. With AIT, the individual's lymphocytes are removed from the body, specially treated and reinfused into the body. AIT has been investigated in the treatment of various cancers and viruses. Adoptive immunotherapy may also be referred to as cellular adoptive immunotherapy and adoptive cell transfer.

MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 08/25/10
LAST REVIEW DATE: 03/19/19
LAST CRITERIA REVISION DATE: 10/24/17
ARCHIVE DATE:

IMMUNOTHERAPY, ADOPTIVE (cont.)

Description: (cont.)

The transfer (removal, treatment and replacement) of the lymphocytic cells takes place using either adoptive cellular therapy (ACT) or through antigen-loaded dendritic cell infusions. The common steps in ACT are:

- Lymphocyte harvesting from tumor biopsy or peripheral blood
- Reproduction of tumor specific lymphocytes in vitro using various immune modulators
- Selection of lymphocytes with reactivity to common tumor antigens with ELISA
- Lymphodepletion with immunosuppressive agents
- Transfusion (adoptive transfer) of lymphocytes back into the individual

Originally, lymphokine-activated killer cells (LAK) were taken peripherally and activated in vitro with interleukin-2 (IL-2) and other cytokines. Newer techniques that yield populations of cytotoxic T-lymphocytes include the use of autologous dendritic cells (ADC) or tumor-infiltrating lymphocytes (TIL) or cytokine-induced killer (CIK) cells. If the lymphocytes are harvested from peripheral blood, ADC pulsed with tumor antigens are used to propagate the antigen-loaded autologous dendritic cells. If the lymphocytes are collected from the tumor biopsy, these TIL are propagated with IL-2 and OKT3. Genetically engineered T-cell immunotherapy uses gene transfer of tumor antigen-specific T-cell receptors (TCR) or synthetic chimeric antigen receptors (CAR).

Criteria:

For chimeric antigen receptor T (CAR T) cell immunotherapy with Kymriah™ (tisagenlecleucel) criteria, refer to BCBSAZ Medical Coverage Guideline #O1037, “Kymriah™ (tisagenlecleucel)”.

For gene therapy criteria, refer to BCBSAZ Medical Coverage Guideline #O680, “Gene Therapy”.

- Adoptive immunotherapy is considered ***experimental or investigational*** based upon:
1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
 2. Insufficient evidence to support improvement of the net health outcome, and
 3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
 4. Insufficient evidence to support improvement outside the investigational setting.



MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 08/25/10
LAST REVIEW DATE: 03/19/19
LAST CRITERIA REVISION DATE: 10/24/17
ARCHIVE DATE:

IMMUNOTHERAPY, ADOPTIVE (cont.)

Resources:

Literature reviewed 08/21/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

1. 8.01.01 BCBS Association Medical Policy Reference Manual. Adoptive Immunotherapy. Re-issue date 07/12/2018, issue date 12/01/1996.
2. American Society of Clinical Oncology. Adoptive immunotherapy for melanoma and renal cell carcinoma using haploidentical natural killer (NK) infusions. 2003.
3. Bleumer I, Tiemessen DM, Oosterwijk-Wakka JC, et al. Preliminary analysis of patients with progressive renal cell carcinoma vaccinated with CA9-peptide-pulsed mature dendritic cells. *J Immunother* (1997). 2007 Jan 2007;30(1):116-122.
4. Fazle Akbar SM, Abe M, Yoshida O, Murakami H, Onji M. Dendritic cell-based therapy as a multidisciplinary approach to cancer treatment: present limitations and future scopes. *Curr Med Chem*. 2006 2006;13(26):3113-3119.
5. Fred Hutchinson Cancer Research Center. Adoptive Immunotherapy. 04/30/2001 2001.
6. Fujimoto K, Tomonaga M, Goto S. A case of recurrent ovarian cancer successfully treated with adoptive immunotherapy and lentinan. *Anticancer Res*. 2006 Nov-Dec 2006;26(6A):4015-4018.
7. Gallagher RC, Waterfall M, Samuel K, Turner ML. Blood donor derived dendritic cells and cytotoxic T cells for specific fusion-gene adoptive immunotherapy. *Vox Sang*. 2007 May 2007;92(4):351-360.
8. Gandhi MK, Wilkie GM, Dua U, et al. Immunity, homing and efficacy of allogeneic adoptive immunotherapy for posttransplant lymphoproliferative disorders. *Am J Transplant*. 2007 May 2007;7(5):1293-1299.
9. Gottlieb DJ, Micklethwaite K, Bradstock KF, Li YC. Rapid expansion of tumor-reactive cells from HLA-matched siblings for adoptive immunotherapy of melanoma. *Cytotherapy*. 2007 2007;9(2):133-143.
10. Harrison SJ, Cook G, Nibbs RJ, Prince HM. Immunotherapy of multiple myeloma: the start of a long and tortuous journey. *Expert Rev Anticancer Ther*. 2006 Dec 2006;6(12):1769-1785.

IMMUNOTHERAPY, ADOPTIVE (cont.)

Resources: (cont.)

11. Hildenbrand B, Sauer B, Kalis O, et al. Immunotherapy of patients with hormone-refractory prostate carcinoma pre-treated with interferon-gamma and vaccinated with autologous PSA-peptide loaded dendritic cells--a pilot study. *Prostate*. 2007 Apr 1 2007;67(5):500-508.
12. Koido S, Tanaka Y, Tajiri H, Gong J. Generation and functional assessment of antigen-specific T cells stimulated by fusions of dendritic cells and allogeneic breast cancer cells. *Vaccine*. 2007 Mar 30 2007;25(14):2610-2619.
13. Kroon HM, Li Q, Teitz-Tennenbaum S, Whitfield JR, Noone AM, Chang AE. 4-1BB costimulation of effector T cells for adoptive immunotherapy of cancer: involvement of Bcl gene family members. *J Immunother*. 2007 May-Jun 2007;30(4):406-416.
14. Lesimple T, Neidhard EM, Vignard V, et al. Immunologic and clinical effects of injecting mature peptide-loaded dendritic cells by intralymphatic and intranodal routes in metastatic melanoma patients. *Clin Cancer Res*. 2006 Dec 15 2006;12(24):7380-7388.
15. Liu S, Foster BA, Chen T, Zheng G, Chen A. Modifying dendritic cells via protein transfer for antitumor therapeutics. *Clin Cancer Res*. 2007 Jan 1 2007;13(1):283-291.
16. Quereux G, Pandolfino MC, Knol AC, et al. Tissue prognostic markers for adoptive immunotherapy in melanoma. *Eur J Dermatol*. 2007 Jun 1 2007;17(4):295-301.
17. Thanarajasingam U, Sanz L, Diaz R, et al. Delivery of CCL21 to metastatic disease improves the efficacy of adoptive T-cell therapy. *Cancer Res*. 2007 Jan 1 2007;67(1):300-308.
18. Tuettenberg A, Schmitt E, Knop J, Jonuleit H. Dendritic cell-based immunotherapy of malignant melanoma: success and limitations. *J Dtsch Dermatol Ges*. 2007 Mar 2007;5(3):190-196.
19. Wysocki PJ, Zolnierek J, Szczylik C, Mackiewicz A. Recent developments in renal cell cancer immunotherapy. *Expert Opin Biol Ther*. 2007 May 2007;7(5):727-737.



MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 08/25/10
LAST REVIEW DATE: 03/19/19
LAST CRITERIA REVISION DATE: 10/24/17
ARCHIVE DATE:

IMMUNOTHERAPY, ADOPTIVE (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nilinígíí Blue Cross Blue Shield of Arizona haada yit'éego bina'idííkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yina'idííkidgo beehaz'áanii hólg díí t'áa hazaadk'ehjí háká a'doowołgo bee haz'ą doo baqah ilínígóó. Ata' halne'ígíí kojí' bich'í' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

