TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Rituximab

INDICATION: Mantle cell lymphoma, untreated, induction therapy, in combination with anthracycline-based regimens

COMPENDIA TRANSPARENCY REQUIREMENTS	
1	Provide criteria used to evaluate/prioritize the request (therapy)
2	Disclose evidentiary materials reviewed or considered
3	Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest
4	Provide meeting minutes and records of votes for disposition of the request (therapy)

EVALUATION/PRIORITIZATION CRITERIA: **A, C, E, S**
*to meet requirement 1

CODE	EVALUATION/PRIORITIZATION CRITERIA
A	Treatment represents an established standard of care or significant **advance** over current therapies
C	**Cancer** or cancer-related condition
E	Quantity and robustness of **evidence** for use support consideration
L	**Limited** alternative therapies exist for condition of interest
P	**Pediatric** condition
R	**Rare** disease
S	**Serious**, life-threatening condition

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Lenz G, Dreyling M., Hoster E, et al: Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). J Clin Oncol Mar 20, 2005; 23(9):1984-1992.	Study methodology comments: This was a randomized, open-label, multicenter, phase III trial that compared patients receiving CHOP with those receiving rituximab plus CHOP. Additional strengths of the study included: 1) defined primary and secondary outcomes and clinical response; 2) responses were confirmed at 4 weeks; 3) had both inclusion and exclusion criteria; 4) compared baseline characteristics of treatment groups; 5) controlled the effect of potential confounding factors on treatment outcome; 6) had a control group; 7) conducted a power analysis; 8) confirmed diagnosis; and 9) made statistical adjustments to preserve the type I error rate. Weaknesses included 1) partial explanation of method of randomization; 2) partial explanation of power calculation; 3) open-label design without the use of independent assessors; and 4) possible selection bias since patients were not recruited in a random or consecutive manner.	S
Geisler CH, Kolstad A, Laurell A, et al: Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood Oct 01, 2008; 112(7):2687-2693.	Study methodology comments: This was an open-label, single-arm, phase II trial. The Nordic Lymphoma Group conducted two consecutive studies (MCL1 and MCL2). The second Nordic MCL protocol (NLG MCL2) was initiated in 2000, with both high-dose cytarabine and rituximab added to the dose-intensified CHOP induction treatment. The patients from the MCL1 study served as historical controls. This evaluation will focus on the MCL2 study. Additional strengths of the study included: 1) defined response; 2) had both inclusion and exclusion criteria; 3) confirmed diagnosis; 4) controlled the effect of potential confounding factors on treatment outcome; and 5) reduced selection bias by recruiting consecutively presenting patients. Weaknesses included 1) absence of power analysis; 2) did not present 95% confidence intervals; and 3) open-label design without the use of independent assessors	S
Damon LE, Johnson JL, Niedzwiecki D, et al. Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol Dec. 2009; 27(36):6101-6108		3

Howard OM, Gribben JG, Neuberg DS, et al: Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol Mar 01, 2002; 20(5):1288-1294.		3
Hess G, Flohr T, Huber C, et al: Safety and feasibility of CHOP/rituximab induction treatment followed by high-dose chemo/radiotherapy and autologous PBSC-transplantation in patients with previously untreated mantle cell or indolent B-cell-non-Hodgkin's lymphoma. Bone Marrow Transplant May 2003; 31(9):775-782.		3
Romaguera JE High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with Rituximab plus hyper-CVAD alternating with Rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol, Oct 01, 2005; 23(28):7013-7023	Study methodology comments: This was an open-label, single-arm, phase II trial. A major weakness of the study was the absence of a control group which would have controlled for many potential confounds. Additional weaknesses included 1) absence of a power analysis; and 2) open-label design without the use of independent assessors. Strengths were 1) defined response as well as primary and secondary endpoints; 2) had both inclusion and exclusion criteria; 3) confirmed diagnosis; 4) controlled the effect of potential confounding factors on treatment outcome; 5) presented 95% confidence intervals; 6) reduced possible selection bias by enrolling consecutively presenting patients; and 7) the use of a within-subject design to control for confounding effects of patient characteristics.	S
Romaguera JE, Fayad LE, Feng L, et al: Ten-year follow-up after intense chemoimmunotherapy with rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol July 2010; 150(2):200-208.		S

Gressin R, Caulet-Maugendre S, Deconinck E, et al: Evaluation of the (R)VAD plus C regimen for the treatment of newly diagnosed mantle cell lymphoma. Combined results of two prospective phase II trials from the French GOELAMS group. Haematologica; Jan 2010; 95(8): 1350-1357		3
Kahl BS, Longo WL, Eickhoff JC, et al: Maintenance Rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol Sep 2006; 17(9):1418-1423.		3
Ritchie DS, Seymour JF, Grigg AP, et al: The hyper-CVAD-Rituximab chemotherapy programme followed by high-dose busulfan, melphalan and autologous stem cell transplantation produces excellent event-free survival in patients with previously untreated mantle cell lymphoma. Ann Hematol Feb 2007; 86(2):101-105.		3
Fayad L, Thomas D, Romaguera J. Update of the M. D. Anderson Cancer Center experience with hyper-CVAD and Rituximab for the treatment of mantle cell and Burkitt-type lymphomas. Clin Lymphoma Myeloma Dec 2007; 8(2):S57-S62.		3

Inwards DJ, Fishkin PA, Hillman DW, et al: Long-term results of the treatment of patients with mantle cell lymphoma with cladribine (2-CDA) alone (95-80-53) or 2-CDA and rituximab (N0189) in the North Central Cancer Treatment Group. Cancer Jul 01, 2008; 113(1):108-116.		3
Dreger P, Rieger M, Seyfarth B, et al: Rituximab-augmented myeloablation for first-line autologous stem cell transplantation for mantle cell lymphoma: effects on molecular response and clinical outcome. Haematologica Jan 2007; 92(1): 42-49.		1
Ghielmini M, Rufibach K, Salles G, et al: Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol Oct 2005; 16(10):1675-1682.		1
Ruan J, Martin P, Furman RR, et al: Bortezomib plus CHOP-Rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. J Clin Oncol Feb 2011; 29(6):690-697.		1
Thieblemont C, Antal D, Lacotte-Thierry L, et al: Chemotherapy with rituximab followed by high-dose therapy and autologous stem cell transplantation in patients with mantle cell lymphoma. Cancer Oct 01, 2005; 104(7):1434-1441.		1

Lossos IS, Hosein PJ, Morgensztern D, et al: High rate and prolonged duration of complete remissions induced by rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosfamide, etoposide, cytarabine, and thalidomide (R-MACLO-IVAM-T), a modification of the National Cancer Institute 89-C-41 regimen, in patients with newly diagnosed mantle cell lymphoma. Leuk Lymphoma Mar 2010; 51(3):406-414.		1
Sachanas S, Pangalis GA, Vassilakopoulos TP, et al. Combination of rituximab with chlorambucil as first line treatment in patients with mantle cell lymphoma: a highly effective regimen. Leuk Lymphoma Mar 2011; 52(3):387-93		1
Economopoulos T, Psyrri A, Dimopoulos MA, et al: CEOP-21 versus CEOP-14 chemotherapy with or without rituximab for the first-line treatment of patients with aggressive lymphomas: results of the HE22A99 trial of the Hellenic Cooperative Oncology Group. Cancer J Sep 2007; 13(5):327-334.		3
Wilson WH, Gutierrez M, O'Connor P, et al. The role of rituximab and chemotherapy in aggressive B-cell lymphoma: a preliminary report of dose-adjusted EPOCH-R. Semin Oncol. 2002 Feb; 29(1 Suppl 2):41-47.		3

Martin P, Chadburn A, Christos P, et al: Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies. Ann Oncol Jul 2008; 19(7):1327-1330.		3
Thieblemont C, et al: Rituximab/chemotherapy induction treatment followed by high-dose therapy and autologous transplantation in patients with mantle cell lymphoma. Blood Nov 16, 2004; 104(11 pt.1):390A	Study methodology comments: Meeting abstract	3
Romaguera J, Fayad L, Rodriguez A, et al: Rituximab (R) plus Hypercvad alternating with R-methotrexate/cytarabine after 9 years: Continued high rate of failure-free survival in untreated mantle cell lymphoma (MCL). Blood Nov 16, 2008; 112(11):833.	Study methodology comments: Meeting abstract	3
Romaguera J, et al: Mantle cell lymphoma (MCL): High rates of complete remission (CR) and prolonged failure-free survival (FFS) with Rituxan-HyperCVAD (R-HCVAD) without stem cell transplant (SCT). Blood Nov. 16, 2001; 98(11 Pt 1): 726a.	Study methodology comments: Meeting abstract	3
Romaguera J, Fayad LE, Wang M, et al. High (95%) response rates in relapsed/refractory mantle cell lymphoma after R-HCVAD alternating with R-methotrexate/cytarabine (R-M-A). Blood Nov. 2005; 106: 2446.	Study methodology comments: Meeting abstract	3

Dunleavy, KM, et al. Rituximab is associated with late onset neutropaenia (LON) when administered with doxorubicin-based chemotherapy for the initial treatment of aggressive B-cell lymphomas. Blood, Nov. 2003, 201(11).	Study methodology comments: Meeting abstract	3
Spurgeon S, Pindyck T, Loriaux MM, et al. Cladribine plus rituximab is an effective therapy for newly diagnosed mantle cell lymphoma. Blood, Nov 2010; 116: 4910.	Study methodology comments: Meeting abstract	3
Thieblemont C, Antal D, Lacotte-Thierry V, et al. Rituximab/chemotherapy induction treatment followed by high-dose therapy and autologous transplantation in patients with mantle cell lymphoma. Blood, Nov 2004; 104: 1389.	Study methodology comments: Meeting abstract	3
Le Gouill S, Thieblemont C, Gyan E, et al. High response rate after 4 courses of R-DHAP in untreated mantle cell lymphoma (MCL) patients in the ongoing phase III randomized GOELAMS and GELA LyMa Trial. Blood, Nov 2010; 116: 1758.	Study methodology comments: Meeting abstract	3

Hermine O, Hoster E, Walewski J, et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). Blood, Nov 2010; 116: 110.	Study methodology comments: Meeting abstract	3
Pott C, Hoster E, Beldjord K, et al. R-CHOP/R-DHAP compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: Results of the MCL Younger Intergroup Trial of the European MCL Network. Blood, Nov 2010; 116: 965.	Study methodology comments: Meeting abstract	3
Levine AM, Tulpule A, Smith L, et al. Results of a pilot trial of fludarabine, mitoxantrone and rituxan in mantle cell lymphoma. Blood, Nov 2005; 106: 945.	Study methodology comments: Meeting abstract	3

Dreyling MH, The addition of a Fludarabine combination (R-FCM) significantly improves remission rates and overall survival in recurrent follicular as well as mantel cell lymphoma – follow-up of a prospective randomized trial of the German low grade lymphoma study group (GLSG). Abstract. 9th International conference on Malignant Lymphoma June 8-11 2005, Lugano Switzerland.	Study methodology comments: Meeting abstract	3
Dreyling MH, Combined immuno-chemotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantel cell lymphoma – follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). American Society of Clinical Oncology 41st Annual Meeting 2005.	Study methodology comments: Meeting abstract	3
Rule S, et al. A randomized phase II study of Fludarabine/cyclophosphamide +/- rituximab in patients with untreated mantle cell lymphoma. 9th International Conference on Malignant Lymphoma June 8-11 2005, Lugano Switzerland	Study methodology comments: Meeting abstract	3
Wilson WH, Dose-adjusted EPOCH-Rituximab in untreated diffuse large B-cell Lymphoma: benefit of rituximab appears restricted to tumors harboring anti-apoptotic mechanisms. American Society of Hematology Meeting 2003. Abstract.	Study methodology comments: Meeting abstract	3

Wilson WH, et al. Idiotype vaccine following EPOCH-rituximab treatment in untreated mantle cell lymphoma. ASH Meeting 2002.	Study methodology comments: Meeting abstract	3
Williams ME, et al: Management of mantle cell lymphoma: key challenges and next steps. Clin Lymphoma Myeloma Leuk Oct 2010; 10(5):336-346		4
Rodriguez J, Gutierrez A, Obrador-Hevia A, et al. Therapeutic concepts in mantle cell lymphoma. Eur J Haematol Nov. 2010; 85(5):371-386.		4
Alexander E, Weiss L, Melchardt T, et al. Final analysis of induction treatment with fludarabine, cyclophosphamide plus rituximab (FCR) followed by fludarabine plus rituximab (FR) and remission maintenance therapy with rituximab In previously untreated B-chronic lymphocytic leukemia (B-CLL): The Chairos AGMT CLL4/Roche ML18434 Study. Blood Nov. 2010; 116: 1380	Study methodology comments: Meeting abstract	3

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

TRUVEN HEALTH ANALYTICS

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Margi Schiefelbein, PA	None	Keith A. Thompson, MD	None
Stacy LaClaire, PharmD	None	Gerald J. Robbins, MD	None
Felicia Gelsey, MS	None	Jeffrey F. Patton, MD	None
		James E. Liebmann, MD	None
		Edward P. Balaban, DO	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---	Indication specificity discussion	B
Keith A. Thompson, MD	Evidence Favors Efficacy	Class IIa: Recommended, In Most Cases	None	N/A
Gerald J. Robbins, MD	Effective	Class I: Recommended	Unless contra-indicated Rituximab significantly increased several parameters of efficacy in several trials, and should be part of regimen.	N/A
Jeffrey F. Patton, MD	Effective	Class IIa: Recommended, In Most Cases	None	N/A

James E. Liebmann, MD	Evidence Favors Efficacy	Class I: Recommended	Mantle cell lymphoma (MCL) at present is not curable with current therapy. Reasonable goals of treatment are prolongation of life and improvement of quality of life. Improved disease free survival may be a surrogate for improved quality of life. Rituximab improves response rates & time to treatment failure in MCL. Improved TTF likely represents an improvement in quality of life. Improved response rates may result in improved survival after post-induction treatments (e.g. HSCT). Rituximab adds little to the toxicity of standard chemotherapy. It should be routinely used in MCL (Class I – Recommended).	N/A
Edward P. Balaban, DO	Evidence Favors Efficacy	Class I: Recommended	Enough evidence to make this recommended Class I.	N/A