

NCCN Guidelines® Insights

Non-Hodgkin's Lymphomas, Version 3.2012

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights summarize several key updates to the 2012 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Hodgkin's Lymphomas (NHL) and describe the clinical evidence supporting the updates. The featured updates include changes to the recommendations for treatment options in patients with chronic lymphocytic leukemia (including in elderly or frail patients and patients with poor-risk cytogenetics), guidance surrounding surveillance imaging for follow-up of patients with NHL, and the addition of first-line consolidation options for patients with mantle cell lymphoma. (*JNCCN* 2012;10:1487–1498)

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Disclosures for the NCCN Non-Hodgkin's Lymphomas Panel

Individual disclosures of potential conflicts of interest for the NCCN Non-Hodgkin's Lymphomas Panel can be found online at NCCN.org.

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Non-Hodgkin's Lymphomas, Version 3.2012

SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant co-morbidity
(not able to tolerate purine analogs)

- Chlorambucil ± rituximab
- Rituximab (single)
- Pulse corticosteroids

See Monoclonal Antibody
Directed at CD20 and Viral
Reactivation (NHODG-D)See Suggested Regimens for
CLL with del (17p) (2 of 5)See Suggested Regimens for
CLL with del (11q) (3 of 5)^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.^bAntibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.^cMonitor for myelosuppression.^dLess effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.^fIn patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.^gSee Discussion for further information on oral fludarabine.^hLong and short response cannot be rigorously defined based on available data. A major factor is that the definition would be influenced by the prior treatment. Clinicians will need to use clinical judgement. For instance, after a regimen such as FCR, 3 years may be a reasonable cutoff based on the data from MDACC. However, after chlorambucil, 18-24 months may be a reasonable cutoff.**First-line therapy^b**

- Age ≥ 70 y or younger patients with co-morbidities
 - ▶ Chlorambucil ± rituximab
 - ▶ BR (bendamustine, rituximab)^c
 - ▶ Cyclophosphamide, prednisone ± rituximab
 - ▶ Alemtuzumab^d
 - ▶ Rituximab
 - ▶ Fludarabine^{e,f,g} ± rituximab
 - ▶ Cladribine
- Age < 70 y or older patients without significant co-morbidities
 - ▶ Chemoimmunotherapy^{c,g}
 - ◊ FCR (fludarabine, ^ecyclophosphamide, rituximab)
 - ◊ FR (fludarabine, ^erituximab)
 - ◊ PCR (pentostatin, cyclophosphamide, rituximab)
 - ◊ BR

Relapsed/Refractory therapy

- Long response^h
 - ▶ Retreat as in first line therapy until short response
- Short response^h for age ≥ 70 y
 - ▶ Chemoimmunotherapy^{c,g}
 - ◊ Reduced-dose FCR^e
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine ± rituximab
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - ▶ Chlorambucil ± rituximab (if not used first-line)
 - ▶ Ofatumumab
 - ▶ Alemtuzumab^d ± rituximab
 - ▶ Dose-dense rituximab (category 2B)
- Short response^h for age < 70 y or older patients without significant co-morbidities
 - ▶ Chemoimmunotherapy^{c,g}
 - ◊ FCR^e
 - ◊ PCR
 - ◊ BR
 - ◊ Fludarabine^e + alemtuzumab
 - ◊ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
 - ◊ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
 - ◊ Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
 - ◊ OFAR (oxaliplatin, fludarabine, ^ecytarabine, rituximab)
 - ▶ Ofatumumab
 - ▶ Alemtuzumab^d ± rituximab
 - ▶ HDMP + rituximab

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1 of 5**NCCN Categories of Evidence and Consensus****Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.**All recommendations are category 2A unless otherwise noted.****Clinical trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**Overview**

Non-Hodgkin's lymphomas (NHLs) represent a highly heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes, or natural killer (NK) cells. B-cell lymphomas constitute approximately 80% of NHL cases, with 15% to 20% being of T-cell origin; NK cell lymphomas are rare.¹ In the United States alone, 70,130 new cases of NHL and 18,940 deaths from the disease are estimated in 2012; cases of chronic lymphocytic leukemia are estimated separately, as discussed later.² NHL is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths.² The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NHLs are developed and updated as a result of annual meetings convened by a multidisciplinary panel of NHL experts, with the goal of providing recommendations on the standard practices for diagnostic workup, treatment, and sur-

Non-Hodgkin's Lymphomas, Version 3.2012

SUGGESTED TREATMENT REGIMENS^a

CLL with del (17p)

First-line therapy^b (in order of preference)

- FCR (fludarabine, ^{e,g} cyclophosphamide, rituximab)^c
- FR (fludarabine, ^{e,g} rituximab)^c
- High-dose methylprednisolone (HDMP) + rituximab
- Alemtuzumab^d ± rituximabⁱ
- Bendamustine^{e,g} ± rituximabⁱ

Relapsed/Refractory therapy (in alphabetical order)

- Alemtuzumab^d ± rituximabⁱ
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab^{c,i}
- CFAR (cyclophosphamide, fludarabine, ^{e,g} alemtuzumab, rituximab)^c
- HDMP ± rituximabⁱ
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab^c
- Ofatumumab^j
- OFAR (oxaliplatin, fludarabine, ^{e,g} cytarabine, rituximab)^c
- Bendamustine^{e,g} ± rituximabⁱ

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)

See Suggested Regimens for CLL with del (11q) (3 of 5)

^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.

^bAntibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

^cMonitor for myelosuppression.

^dLess effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^gSee Discussion for further information on oral fludarabine.

ⁱRituximab should be added unless patient is known to be refractory to rituximab.

^jThis is not effective in patients with lymph nodes > 5 cm.

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CSLL-D
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veillance strategies based on the current evidence. These NCCN Guidelines Insights summarize several key updates to the 2012 NCCN Guidelines for NHL and describe the clinical data supporting the recommendations made by the NCCN NHL Panel. The updates discussed in this article include recommendations on treatment regimens for chronic lymphocytic leukemia (CLL), surveillance imaging for the follow-up of patients with NHL, and first-line consolidation options for mantle cell lymphoma.

CLL

CLL remains the most commonly diagnosed leukemia among adults in the United States, with approximately 16,000 new cases estimated for 2012.² The median age at diagnosis is 72 years, with approximately 70% of patients diagnosed at older than 65 years (and 40% diagnosed at age ≥75 years).³ Thus, CLL mainly affects “elderly” adults, which poses im-

portant challenges regarding the treatment approach in this population. Although chemoimmunotherapy with fludarabine, rituximab, and cyclophosphamide (FCR) represents the standard of care in younger or “fit” patients with CLL,^{4,5} older patients frequently present with comorbid conditions, which may decrease their ability to tolerate myelosuppressive regimens.⁶ In a phase III randomized trial conducted by the German CLL Study Group (GCLLSG), elderly patients (age >65 years; median age 70 years) were randomized to first-line treatment with fludarabine or chlorambucil (N=193).⁷ Fludarabine, compared with chlorambucil, resulted in significantly improved overall response rates (ORR; 72% vs. 51%), complete response (CR; 7% vs. 0%), and median time to treatment failure (18 vs. 11 months). However, no advantage with fludarabine was observed for median progression-free survival (PFS; 19 vs. 18 months) or overall survival (OS; 46 vs. 64 months).⁷ This study suggested that in older patients (or in patients with

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SUGGESTED TREATMENT REGIMENS^a(in order of preference)
CLL with del (11q)**First-line therapy^b**

- Age \geq 70 y or younger patients with co-morbidities
 - ▶ Chlorambucil \pm rituximab
 - ▶ BR (bendamustine, rituximab)^c
 - ▶ Cyclophosphamide, prednisone \pm rituximab
 - ▶ Reduced-dose FCR (fludarabine, ^{e,g}cyclophosphamide, rituximab)^c
 - ▶ Alemtuzumab^d
 - ▶ Rituximab
- Age < 70 y or older patients without significant co-morbidities
 - ▶ Chemoimmunotherapy^c
 - ◊ FCR^g
 - ◊ BR
 - ◊ PCR (pentostatin, cyclophosphamide, rituximab)

See Monoclonal Antibody Directed at CD20 and
Viral Reactivation (NHODG-D)See Suggested Regimens for CLL without del (11q) or
del (17p) (1 of 5)

See Suggested Regimens for CLL with del (17p) (2 of 5)

^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.^bAntibiotic prophylactic therapy for shingles and pneumocystis is recommended in
purine analog-based and/or alemtuzumab combination therapy^cMonitor for myelosuppression.^dLess effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination
therapy containing fludarabine and patients should be observed carefully.^gSee Discussion for further information on oral fludarabine.^hLong and short response cannot be rigorously defined based on available data. A
major factor is that the definition would be influenced by the prior treatment. Clinicians
will need to use clinical judgement. For instance, after a regimen such as FCR, 3
years may be a reasonable cutoff based on the data from MDACC. However, after
chlorambucil, 18-24 months may be a reasonable cutoff.**Relapsed/Refractory therapy**

- Long response^h
 - ▶ Retreat as in first line therapy until short response
- Short response^h for age \geq 70 y
 - ▶ Chemoimmunotherapy^{c,g}
 - ◊ Reduced-dose FCR^e
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine \pm rituximab
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - ◊ Chlorambucil \pm rituximab (if used first line)
 - ▶ Ofatumumab
 - ▶ Alemtuzumab^d \pm rituximab
 - ▶ Dose-dense rituximab (category 2B)
- Short response^h for age < 70 y or older patients without
significant co-morbidities
 - ▶ Chemoimmunotherapy^{c,g}
 - ◊ FCR^e
 - ◊ PCR
 - ◊ BR
 - ◊ Fludarabine^e + alemtuzumab
 - ◊ CHOP (cyclophosphamide, doxorubicin, vincristine,
prednisone) + rituximab
 - ◊ HyperCVAD (cyclophosphamide, vincristine, doxorubicin,
and dexamethasone alternating with high-dose methotrexate
and cytarabine) + rituximab
 - ◊ Dose-adjusted EPOCH (etoposide, prednisone, vincristine,
cyclophosphamide, doxorubicin) + rituximab
 - ◊ OFAR (oxaliplatin, fludarabine, ^{e,g}cytarabine, rituximab)
 - ▶ Ofatumumab
 - ▶ Alemtuzumab^d \pm rituximab
 - ▶ HDMP + rituximab

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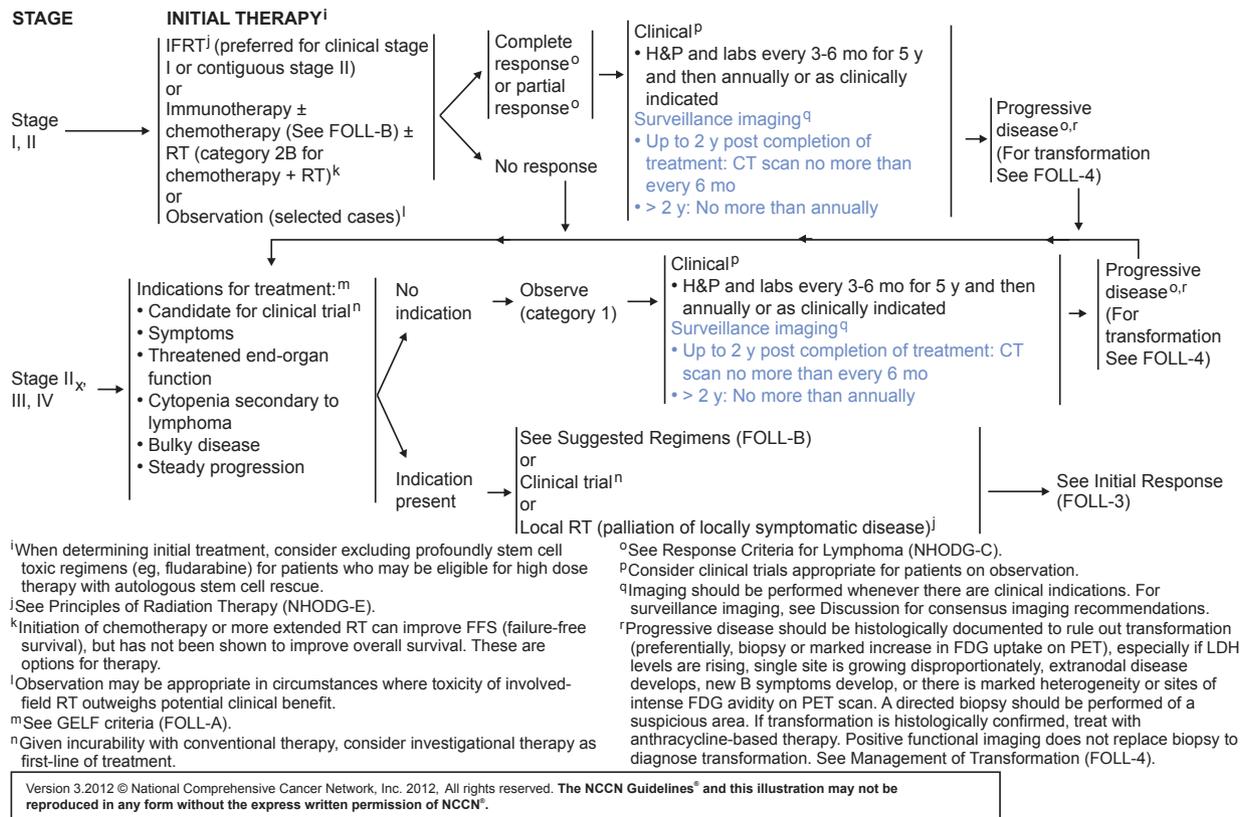
comorbidities) with CLL for whom more intensive regimens are not appropriate, chlorambucil remains a valid treatment option.

Two recent phase II studies reported outcomes with the combination of rituximab and chlorambucil as first-line treatment in patients with CLL, including in elderly patients.⁸⁻¹⁰ In the multicenter Italian study, elderly patients (age >60 years; median age 70 years; N=85 evaluable) received induction therapy with chlorambucil combined with rituximab (up to 8 cycles).⁸ Although responders were subsequently randomized to receive rituximab maintenance (every 2 months for 2 years) or observation, only data regarding induction therapy are currently available.⁸ After induction, the ORR was 81%, with CR (confirmed by CT scan) in 16.5% of patients; response rates were similar across Binet stages and age subgroups.^{8,9} The regimen was well tolerated, with treatment-related serious adverse events reported in 7

patients (8%).⁸ The multicenter phase II study from the United Kingdom (N=100) reported similar response outcomes and a favorable safety profile with chlorambucil combined with rituximab in previously untreated patients (median age 70 years; range, 43-86 years); the ORR and CR rates were 80% and 12%, respectively.¹⁰ Median PFS in this study was approximately 24 months. An ongoing randomized phase III study is evaluating first-line therapy with chlorambucil combined with rituximab versus chlorambucil alone (CLL11 study).

Bendamustine is an alkylating agent with a benzimidazole ring component, and exhibits low or incomplete cross-resistance with other alkylating agents.^{11,12} The activity of bendamustine compared with chlorambucil in patients with previously untreated CLL was established in a pivotal phase III randomized study (N=319).¹³⁻¹⁵ After a median observation time of 54 months, the median PFS was

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FOLL-2

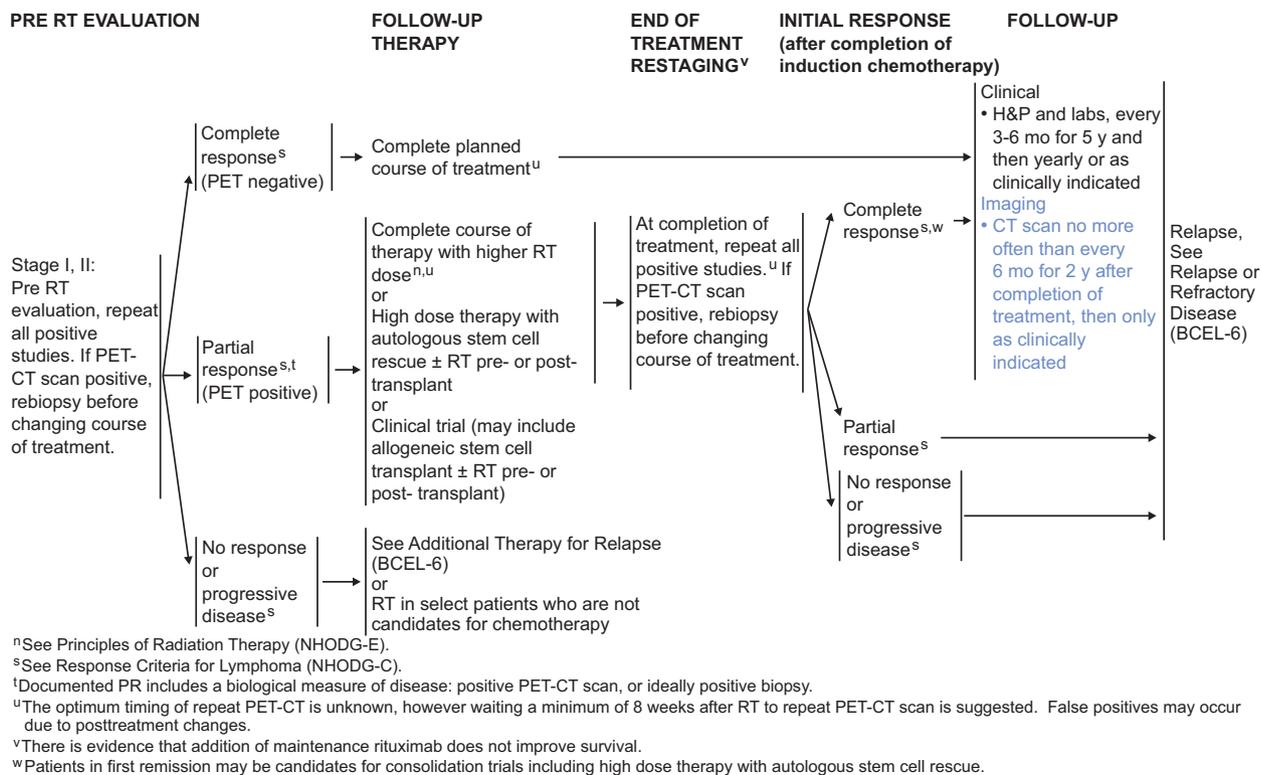
significantly longer with bendamustine (21 vs. 9 months; $P < .0001$).^{14,15} The higher response rates and PFS benefit with bendamustine were retained in the subgroup of older patients (age >65 years) on this trial.¹⁶ No differences in OS outcomes were observed between the treatment groups.¹⁵ Bendamustine is also being evaluated as part of a chemoimmunotherapy regimen in National patients with CLL. In a multicenter phase II study from the GCLLSG, bendamustine in combination with rituximab (BR) showed high response rates (ORR 88%; CR 23%) in previously untreated patients, with similar response and survival outcomes among the subgroup of elderly patients (age >70 years).¹⁷ After a median observation time of 27 months, the median PFS for all patients was 34 months. However, the BR regimen seemed to have limited activity in patients with del(17p). In the small subgroup of patients with del(17p) (n=8), the ORR (all partial remissions) was 37.5% and me-

dian PFS was only 8 months.¹⁷ An ongoing phase III randomized trial is comparing outcomes between chemoimmunotherapy with FCR and BR in “fit” patients with previously untreated CLL (CLL10 study). The BR regimen was also active (ORR, 59%; CR, 9%) in patients with relapsed/refractory disease (N=78) in a separate phase II study from the GCLLSG.¹⁸ The median PFS and OS in this study were 15 and 34 months, respectively. Similar outcomes were observed in the subgroup of elderly patients (age >70 years). Patients with del(17p) (n=14) had poorer outcomes with treatment; the ORR in this subgroup was 7% (1 CR) and the median PFS and OS were 7 and 16 months, respectively.¹⁸

NCCN Recommendations

The NCCN NHL Panel recommended changing chlorambucil with or without prednisone to chlorambucil with or without rituximab as one of the preferred treatment options listed for the following

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BCEL-4

patient subgroups with CLL: first-line regimen for patients who are frail or have significant comorbidities; and first-line or relapsed/refractory treatment for patients without del(17p) or those with del(11q) [but without del(17p)], who are aged 70 years or older or who are younger with comorbidities (see CSLL-D 1 of 5 and CSLL-D 3 of 5, pages 1488 and 1490, respectively). This recommendation was based on available data (discussed earlier) from multicenter phase II studies with chlorambucil combined with rituximab in first-line CLL (including in elderly patients), and the phase III randomized study in elderly patients that showed no advantage with first-line fludarabine over chlorambucil monotherapy. For the subgroup of poor-risk patients with del(17p), the panel recommended removing bendamustine with or without rituximab from the first-line and relapsed/refractory treatment options (see CSLL-D 2 of 5, page 1489) in light of data from multicenter phase II

studies that showed limited activity of the BR regimen in subgroups with del(17p).

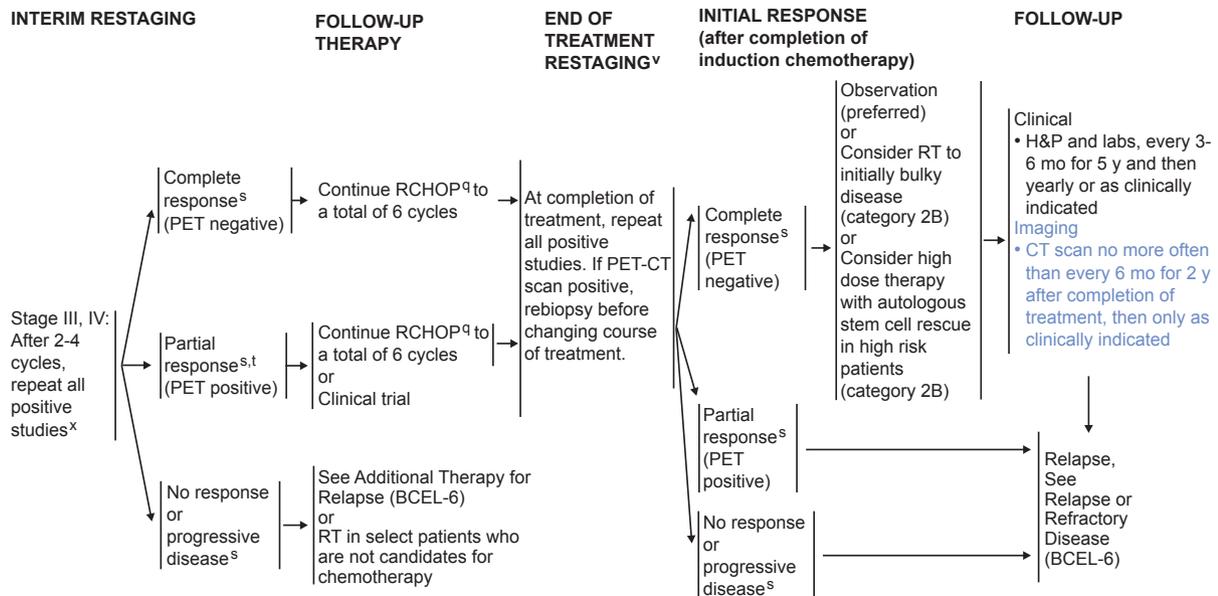
Surveillance Imaging in NHL

Imaging studies using modalities such as CT or PET/CT scans are important components of diagnostic workup, interim restaging, and posttreatment assessments in patients with lymphomas. Although functional imaging studies are now considered a standard part of posttreatment response evaluation in patients with aggressive NHL and Hodgkin lymphoma, their role in indolent lymphomas or for routine surveillance during longer-term follow-up of patients with NHL remains to be clarified by additional data.

Follicular Lymphoma

Only a few studies have evaluated the role of follow-up surveillance imaging for detecting relapse in patients with indolent NHL. In an early retrospective

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^aFor other regimens, see BCEL-C.

^sSee Response Criteria for Lymphoma (NHODG-C).

^tDocumented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.

^vThere is evidence that the addition of maintenance rituximab does not improve survival.

^xPET-CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.

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BCEL-5

study, patients with stage I–III follicular lymphoma (FL) with a CR after induction were evaluated with clinical, laboratory, and imaging studies during routine follow-up (N=257).¹⁹ Patients underwent CT scans of the abdomen and/or pelvis during follow-up visits. Follow-up was typically performed every 3 to 6 months for the first 5 years of treatment, and then annually thereafter. The median follow-up time was 80 months (range, 13–209 months). Among the patients included in this analysis, relapse was detected in 78; most relapses (77%) occurred within the first 5 years of treatment.¹⁹ Eleven of the relapses were detected with abdominal and/or pelvic CT scans alone. In this analysis, 4% of patients with an initial CR had recurrence determined by routine surveillance with CT scans.¹⁹

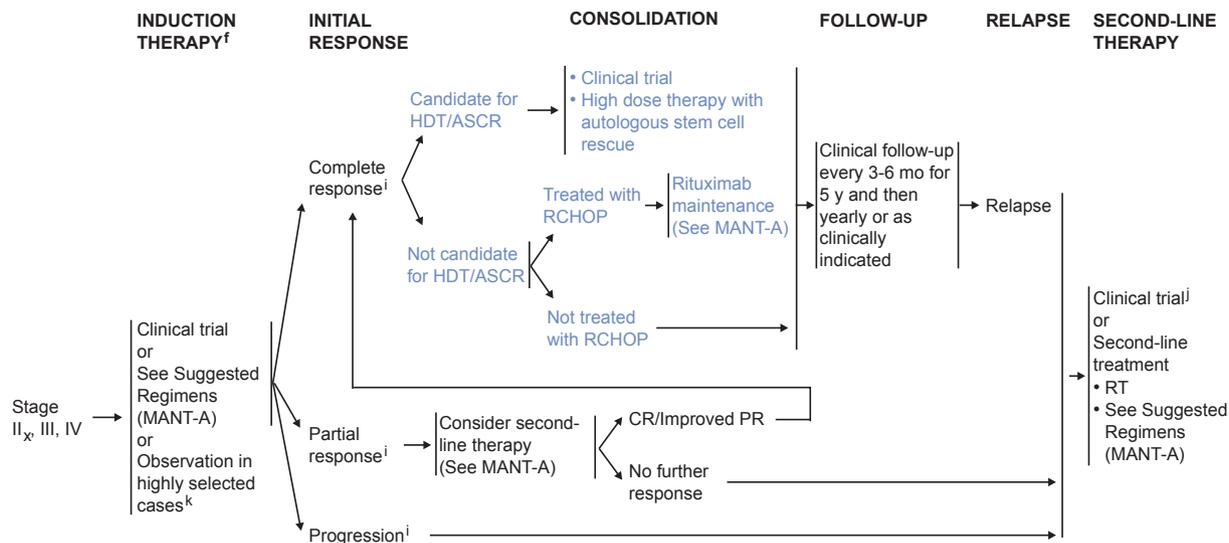
A recent prospective study evaluated the role of surveillance PET scans in patients with lymphomas (Hodgkin lymphoma and NHL) with a CR af-

ter induction.²⁰ PET scans were performed every 6 months for the first 2 years after completion of induction, then annually thereafter. In the cohort of patients with indolent NHL (n=78), follow-up PET scans detected true relapses in 10% of patients at 6 months (8 of 78), 12% at 12 months (8 of 68), 9% at 18 months (5 of 56), 9% at 24 months (4 of 47), 8% at 36 months (3 of 40), and 6% at 48 months (2 of 34).²⁰ Among 13 patients who had PET-positive findings without a corresponding abnormality on CT scan, relapse was documented in 8 of these cases by biopsy. Notably, of the 47 PET-positive relapses, 38 were detected on CT scan and 30 were detected clinically at the same time as PET. Whether this earlier detection of relapse in a proportion of patients translates to improved outcomes is unclear.

Diffuse Large B-Cell Lymphoma

Considerable debate remains in the routine use of follow-up imaging for surveillance in patients with

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^fEarly referral for high dose therapy with stem cell rescue is advisable for planning purposes.

ⁱSee Response Criteria for Lymphoma (NHODG-C).

^jOption for clinical trials of adjuvant therapy or for relapsed disease involving high dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.

^kMartin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol* 2009;27:1209-1213.

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MANT-3

diffuse large B-cell lymphoma (DLBCL) who achieve a CR after induction therapy. Although positive imaging scans can help identify patients with early asymptomatic relapse, false-positivity remains common. This is problematic when it leads to unnecessary radiation exposure for patients and increased health care costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of therapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 experienced relapse, and only 6% of these relapses were detected on follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.²¹ The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR after induction. In a retrospective study that evaluated the use of surveillance imaging

in patients with relapsed aggressive lymphoma who experienced a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.²² In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. The cases of relapse detected on imaging were more likely to represent a population of patients with low-risk disease based on age-adjusted International Prognostic Index at relapse.²² Thus, routine imaging during remission seemed to help identify patients with more limited disease at relapse, which had a nonsignificant trend showing improved outcome. In the prospective study mentioned earlier,²⁰ the role of PET scans was also evaluated in patients with aggressive NHL who experienced a CR after induction (n=183). In this cohort of patients with aggressive lymphomas, follow-up PET scans detected true relapses in 10% of patients at 6 months (19 of 183), 5% at 12 months (8 of 163), 11% at 18

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SUGGESTED TREATMENT REGIMENS^a

(in alphabetical order)

Induction Therapy

- Aggressive therapy
 - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
 - NORDIC regimen^b (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)
 - CALGB regimen^b (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])
 - Sequential RCHOP/RICE^b (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab, ifosfamide, carboplatin, etoposide)
 - Alternating RCHOP/RDHAP^b (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)
- Less aggressive therapy
 - Bendamustine + rituximab
 - CHOP + rituximab^c
 - Cladribine + rituximab
 - CVP (cyclophosphamide, vincristine, prednisone) + rituximab
 - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
 - Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y

^aSee references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.

^bThese regimens include first-line consolidation with high dose therapy and autologous stem cell rescue (HDT/ASCR).

^cThere is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

^dTypically patients will receive an aggressive induction regimen prior to

First-line Consolidation^d

- Clinical trial
- High dose therapy with autologous stem cell rescue^e

[For patients without intention for high dose therapy with stem cell rescue consolidation](#)

- If treated with RCHOP, consider rituximab maintenance 375 mg/m² every 8 wks until progression

Second-line Therapy

- Bendamustine ± rituximab
- Bortezomib ± rituximab
- Cladribine + rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
- FMR (fludarabine, mitoxantrone, rituximab)
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)^f

Second-line Consolidation

- Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

consolidation; however, less aggressive regimens followed by consolidation with high dose therapy may also result in a good long-term outcome.

^eRandomized data with anthracycline-containing regimens suggest an improvement in progression free survival with the addition of first-line high dose therapy with autologous stem cell consolidation.

^fThese agents can be administered without restriction for transplantability.

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MANT-A
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months (16 of 152), 2% at 24 months (3 of 134), 1% at 36 months (1 of 130), and 1% at 48 months (1 of 129).²⁰ Of the 56 PET-positive relapses, 45 were detected on CT scan and 40 were detected clinically at the same time as the PET scan. Again, the value of early detection of relapse was not demonstrated by improved outcomes.²⁰ In another recent study, the use of follow-up PET/CT scan was retrospectively evaluated in patients with DLBCL who experienced a CR after induction (N=75).²³ Follow-up PET/CT scans detected 27 cases of relapse, of which 23 were confirmed as relapses based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse in this study was 0.85. Among 35 asymptomatic patients with surveillance PET scans, 4 had positive scans and recurrence was confirmed in 3.²³ Thus, the clinical utility of surveillance PET scans in asymptomatic patients was limited in this study.

NCCN Recommendations

In the absence of evidence showing improved survival outcomes with early PET detection of relapse, PET scans are not recommended for routine surveillance of FL or DLBCL in patients who have achieved a CR after treatment. However, results of several studies suggest that surveillance imaging with CT may identify early asymptomatic relapse. However, it has not been clearly established that this early detection is associated with a superior long-term outcome. To minimize the potential risks associated with ongoing surveillance imaging (ie, unnecessary biopsies or radiation exposure), the NCCN NHL Panel recommended follow-up surveillance imaging with CT scans no more than once every 6 months for up to 2 years after completion of therapy for patients with FL in remission, and no more than once yearly thereafter unless clinically indicated (see FOLL-2, page 1491). For patients with DLBCL in remission, the

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panel recommended follow-up surveillance imaging with CT scans no more than once every 6 months for up to 2 years (after completion of therapy), with no ongoing routine surveillance imaging after that time unless prompted by clinical signs or symptoms (see BCEL-4 and BCEL-5, pages 1492 and 1493). For patients with symptoms or clinical findings, imaging is appropriate to evaluate for potential disease recurrence and evaluate extent of disease.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a less common subtype of NHL, constituting approximately 6% of cases.¹ MCL generally follows an aggressive disease course and remains incurable with current therapies. The standard of care for initial treatment of MCL is not well defined. Several regimens have shown significant activity in patients with newly diagnosed MCL, but none of these regimens are curative in patients with advanced disease. In general, rituximab used in combination with aggressive chemotherapy regimens has resulted in favorable PFS and OS outcomes.²⁴⁻²⁷ For patients who are physically fit, consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR) after remission-induction therapy (usually with an intensive rituximab-containing regimen) may offer the best chance for longer-term remission.^{25,26,28,29} In the Nordic MCL trial, induction therapy with rituximab and dose-intensified CHOP (maxi-CHOP) alternating with high-dose cytarabine resulted in an ORR and CR rate of 96% and 54%, respectively, in previously untreated patients (age ≤ 65 years) with MCL (N=160).²⁵ Responding patients were eligible to proceed with HDT/ASCR. The 6-year PFS and OS rates were 66% and 70%, respectively, with no relapses occurring after 5 years.²⁵ A recently published analysis from the NCCN Oncology Outcomes Database reported superior PFS outcomes with R-hyper-CVAD alone or with rituximab-containing regimens followed by HDT/ASCR, compared with R-CHOP alone, in the first-line setting for younger patients (age < 65 years) with MCL.³⁰

Not all patients with MCL are physically fit or eligible to undergo aggressive first-line treatment regimens and HDT/ASCR. For patients who are older or otherwise not candidates for HDT/ASCR, postremission maintenance with rituximab may

prolong remission duration.³¹⁻³⁴ An early study with rituximab maintenance after a modified (less intensive) R-hyper-CVAD regimen seemed to show PFS benefit.³² More recently, the European MCL Network conducted a phase III randomized trial in older patients (age > 60 years not eligible for HDT/ASCR) with previously untreated MCL (N=560; n=485 evaluable for response) to evaluate induction with R-FC (rituximab, fludarabine, cyclophosphamide) versus R-CHOP, with a second randomization to maintenance with rituximab versus interferon alfa (given until progression occurred in both arms).³⁴ Response after induction therapy with R-CHOP and R-FC was similar (CR/unconfirmed CR rate, 49% vs. 53%; ORR, 86% vs. 78%, respectively), but more patients experienced progression during R-FC than with R-CHOP (14% vs. 5%). The median duration of response was similar between R-CHOP and R-FC (36 vs. 37 months). After a median follow-up of 36 months, OS (from time of first randomization) was significantly longer with R-CHOP compared with R-FC (median, 67 vs. 40 months; 4-year OS rate, 62% vs. 47%; $P=.005$) in the intent-to-treat analysis.³⁴ Grade 3/4 hematologic toxicities occurred more frequently with R-FC induction. Among the patients who responded to induction and underwent second randomization (n=316), remission duration (from time of second randomization) was significantly improved with rituximab maintenance compared with interferon alfa (median, 75 vs. 27 months; 4-year rate, 57% vs. 34%; $P<.001$). Survival outcomes (from time of first randomization) were not significantly different between maintenance with rituximab and interferon alfa (4-year OS rate, 79% vs. 67%) after a median follow-up of 42 months. However, in the subgroup of patients treated with R-CHOP induction (n=174), OS was significantly longer with rituximab maintenance compared with interferon alfa (median not reached vs. 64 months; 4-year OS rate, 87% vs. 63%; $P=.005$).³⁴ Results from this study suggests that for patients who are not eligible for HDT/ASCR as part of first-line therapy, R-CHOP induction followed by rituximab maintenance may offer the best chance to prolong remission duration. Given the positive outcomes reported in this study (with median duration of response exceeding 6 years with rituximab maintenance and a 4-year OS rate of 87% in patients treated with R-CHOP and rituximab maintenance), whether first-line consolidation

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with HDT/ASCR provides an advantage over rituximab maintenance is unknown. Currently, no data from randomized studies are available that would allow direct comparison of outcomes between these different consolidation approaches.

NCCN Recommendations

Based on evidence from the phase III randomized study in elderly patients with MCL, the NCCN NHL Panel recommended the inclusion of rituximab maintenance as postinduction consolidation for patients in remission after first-line R-CHOP who are not eligible to undergo consolidation with HDT/ASCR (see MANT-3, page 1494). The recommended dose schedule for rituximab maintenance (derived from the phase III study) is rituximab 375 mg/m² every 8 weeks until disease progression (see MANT-A 1 of 3, page 1495).

Conclusions

These NCCN Guidelines Insights for NHL highlight several key updates and changes to the management of patients with CLL and the most common B-cell lymphomas, FL and DLBCL. Clinicians are encouraged to consult the full version of the 2012 Guidelines for NHL (to view the most recent version of these guidelines, visit NCCN.org). Although these updates are derived from evaluation of the most current available evidence at the time of the annual panel meetings (or at the time of an interim panel meeting held in response to publication or presentation of potentially practice-changing clinical data), the NCCN NHL Panel recognizes that guidelines updates are an iterative process given the rapidly evolving field of cancer research. Moreover, every patient with NHL presents with a unique set of patient- and disease-related factors that influence the course of treatment. Thus, to provide optimal and individualized disease management strategies for each patient, clinicians must use their clinical judgment when interpreting the recommendations put forth in the guidelines. The NCCN NHL Panel also emphasizes the importance of participation in prospective clinical trials when possible and appropriate for the patient.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997;89:3909–3918.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10–29.
3. National Cancer Institute. SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia. Bethesda, MD: 2012. Available at: <http://seer.cancer.gov/statfacts/html/clyl.html>. Accessed August 2012.
4. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010;376:1164–1174.
5. Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol* 2010;28:1756–1765.
6. Eichhorst B, Goede V, Hallek M. Treatment of elderly patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2009;50:171–178.
7. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood* 2009;114:3382–3391.
8. Foa R, Alietti A, Guarini A, et al. A phase II study of chlorambucil rituximab (CLB-R) followed by R maintenance vs observation in elderly patients with previously untreated chronic lymphocytic leukemia (CLL): induction phase results [abstract]. *Haematologica* 2011;96(Suppl 2):Abstract 532.
9. Foa R, Ciulli S, Di Raimondo F, et al. Rituximab plus chlorambucil as initial treatment for elderly patients with chronic lymphocytic leukemia (CLL): effect of pre-treatment biological characteristics and gene expression patterns on response to treatment [abstract]. *Blood* 2011;118:Abstract 294.
10. Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlorambucil (R-Chlorambucil) as first-line treatment for chronic lymphocytic leukaemia (CLL): final analysis of an open-label phase II study [abstract] *Ann Oncol* 2011;22(Suppl 4):Abstract 120.
11. Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. *Clin Cancer Res* 2008;14:309–317.
12. Strumberg D, Harstrick A, Doll K, et al. Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines. *Anticancer Drugs* 1996;7:415–421.
13. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol* 2009;27:4378–4384.
14. Knauf WU, Lissichkov T, Aldaoud A, et al. Bendamustine induces higher remission rates, prolongs progression free survival as well as time to next treatment, and improves overall survival for patients in complete remission without compromising quality of life when compared to chlorambucil in first line treatment of chronic lymphocytic leukemia [abstract]. *Blood* 2010;116:Abstract 2449.
15. Knauf WU, Lissichkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. *Br J Haematol* 2012;159:67–77.
16. Knauf WU, Lissichkov T, Aldaoud A, et al. Bendamustine in the treatment of chronic lymphocytic leukemia-consistent superiority over chlorambucil in elderly patients and across clinically defined risk groups [abstract]. *Blood* 2009;114:Abstract 2367.

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17. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2012;30:3209–3216.
18. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2011;3559–3566.
19. Oh YK, Ha CS, Samuels BI, et al. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. *Radiology* 1999;210:483–486.
20. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J Clin Oncol* 2009;27:1781–1787.
21. Guppy AE, Tebbutt NC, Norman A, Cunningham D. The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma* 2003;44:123–125.
22. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Ann Oncol* 2006;17:909–913.
23. Petrusch U, Samaras P, Haile SR, et al. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. *Ann Oncol* 2010;21:1694–1698.
24. Romaguera JE, Fayad L, Rodriguez MA, et al. 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* 2005;23:7013–7023.
25. 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* 2008;112:2687–2693.
26. 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* 2009;27:6101–6108.
27. Schaffel R, Hedvat CV, Teruya-Feldstein J, et al. Prognostic impact of proliferative index determined by quantitative image analysis and the International Prognostic Index in patients with mantle cell lymphoma. *Ann Oncol* 2010;21:133–139.
28. 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* 2007;86:101–105.
29. 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 [abstract]. *Blood* 2010;116:Abstract 965.
30. Lacasce AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database. *Blood* 2012;119:2093–2099.
31. Chang JE, Peterson C, Choi S, et al. VcR-CVAD induction chemotherapy followed by maintenance rituximab in mantle cell lymphoma: a Wisconsin Oncology Network study. *Br J Haematol* 2011;155:190–197.
32. 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* 2006;17:1418–1423.
33. Kluin-Nelemans JC, Hoster E, Walewski J, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: outcome of the first randomized trial for elderly patients with mantle cell lymphoma [abstract]. *Blood* 2011;118:Abstract 439.
34. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med* 2012;367:52–531.