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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF ALAMEDA

COORDINATION PROCEEDING SPECIAL TITLE (Rule 3.550) ROUNDUP PRODUCTS CASES THIS DOCUMENT RELATES TO: *Alva Pilliod v. Monsanto Company, et al.*, Case No. RG17862702	JCCP NO. 4953 Case No.: RG17862702 **DEFENDANTS' OPPOSITION TO MOTION FOR TRIAL PREFERENCE; DECLARATIONS OF DAVID GORDON, M.D. AND MARTIN CALHOUN; EXHIBITS** [Filed concurrently with Defendants' Evidentiary Objections] Judge Ioana Petrou Hearing Date: October 9, 2018 Time: 9:00 a.m. Department: 17 Reservation No. R-1997208

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INTRODUCTION

Plaintiff Alva Pilliod and his wife Alberta Pilliod's Motion for Trial Preference ("the Motion"), seeking a trial date in December 2018, should be denied. Mr. and Mrs. Pilliod seek an expedited trial date based on CCP §§ 36(a) and 36(e), but they have not carried their burden under either provision of showing exigent circumstances justifying that extraordinary relief. As discussed below, Mrs. Pilliod is not even a proper plaintiff in the case.

First, the medical records show that both Mr. and Mrs. Pilliod were in remission when the Miller Firm included their claims in this Judicial Council Coordinated Proceeding ("JCCP") without suggestion of any need for an expedited trial date – and that they both remain in remission now with no indication of any imminent cancer recurrence or relapse. Mr. and Mrs. Pilliod thus cannot establish that their health "is such that a preference is necessary to prevent prejudicing the[ir] interest in the litigation." CCP § 36(a)(2).

Second, granting the motion would impede, rather than advance, the "interests of justice." CCP § 36(e). Plaintiffs' counsel's request would subvert the purposes of this JCCP, by depriving the Court of the broad authority and discretion granted to all JCCP judges to manage many cases efficiently and equitably for the benefit of all parties, including ensuring that cases selected for bellwether trials are representative of the overall universe of cases in this JCCP. It is hard to imagine a ***less representative*** trial than a joint trial of a husband and wife who each allege that they developed NHL caused by exposure to Roundup®-branded herbicides. Moreover, plaintiffs' counsel's strategic invocation of CCP § 36 would force the Court and defendants to rush to trial after trial of plaintiffs' counsel's choosing, because this JCCP includes significant numbers of plaintiffs over 70 years of age. The responsibility bestowed upon a JCCP judge requires that the Civil Code provisions for expedited trial not be misused and that those provisions be read in the context of the essential coordination and case management powers bestowed on JCCP judges. *See In re Toyota Motor Cases*, No. 4621, 2012 WL 965830, at p.7 (Los Angeles County Super. Ct. March 5, 2012) (JCCP judge holding that his coordination "power trumps the otherwise mandatory application of Cal. Civ. Proc. section 36") (attached as Exhibit 1 to Declaration of Martin Calhoun ("Calhoun Declaration") (attached hereto)).

ARGUMENT

I. Mr. And Mrs. Pilliod Cannot Meet The Requirements Of CCP § 36(a).

Mr. Pilliod and Mrs. Pilliod fail to carry their burden of satisfying CCP § 36(a)'s requirements. As the language of that code provision makes clear, the mere fact that the Pilliods are over 70 years old does not alone entitle them to an expedited trial. Rather, each person must also persuade the Court that: (1) he or she "has a substantial interest in the action as a whole"; and (2) his or her "health . . . is such that a preference is necessary to prevent prejudicing [his or her] interest in the litigation." CCP § 36(a).

A. Mr. Pilliod has Failed to Satisfy his CCP § 36(a) Burden.

Mr. Pilliod falls well short of making the showing required for this Court to find that his health "is such that a preference is necessary to prevent prejudicing [his] interest in the litigation." CCP § 36(a)(2). Mr. Pilliod has not submitted any persuasive evidence, such as medical records or a treating physician's declaration, establishing that his interest in this lawsuit will be prejudiced if the trial does not start in December 2018 or within 120 days of the October 9, 2018 hearing date for the Motion.

Mr. Pilliod's medical history shows that he cannot meet his burden. Mr. Pilliod was diagnosed with diffuse large B-cell lymphoma ("DLBCL") in 2011 and was treated with standard immunochemotherapy (six cycles of R-CHOP) from June to October 2011. Declaration of David Gordon, M.D. ¶ 7 ("Gordon Declaration") (attached hereto). The medical records, including August 2018 progress notes from Mr. Pilliod's oncologist, show that the R-CHOP chemotherapy treatment was successful and has worked very well for Mr. Pilliod; that he has been in complete remission since he completed that course of chemotherapy in October 2011; and that he continues to be in complete remission. *Id.* ¶ 7. In fact, Mr. Pilliod's retained expert Dr. Chadhi Nabhan admits that Mr. Pilliod "was treated successfully with chemotherapy" and that he "has been in remission for several years." 8/30/18 Declaration of Chadhi Nabhan, M.D. ¶ 8 ("Nabhan Declaration").[1]

[1] A March 2018 PET/CT scan showed a new 0.7 centimeter mildly hypermetabolic subcentimeter right supraclavicular lymph node, which has been addressed during follow-up visits with Mr.

As Dr. Gordon has explained (with supporting citations to published medical literature), Mr. Pilliod's long period of remission shows that it is very unlikely that Mr. Pilliod will relapse. Although some DLBCL patients can relapse after going into remission from R-CHOP treatment, most relapses occur within the first couple of years. Gordon Decl. ¶ 8 (citing studies published in 2014 and 2010 in the Journal of Clinical Oncology ("JCO")). In a study of a large group of DLBCL patients treated with immunochemotherapy, for patients who achieved complete remission and had no recurrence of disease by 24 months after their DLBCL diagnosis – *i.e.*, event-free survival at 24 months, known as "EFS24" – the risk of DLBCL relapse occurring in the following five years was only 8%, which was the same as the risk of death from unrelated causes. Gordon Decl. ¶ 8 (citing 2014 JCO study). This means that "patients who have achieved EFS24 have subsequent survival comparable to that of the age- and sex-matched general population (ie, a normal life expectancy)." *Id.* (quoting 2014 JCO study).

Mr. Pilliod continues to be in complete remission and has experienced event-free survival for much longer than 24 months, so ***he has the normal, substantial life expectancy of a 76-year-old male***. *Id.* ¶ 10. If Mr. Pilliod does not develop any other life-threatening illness or medical problem, Dr. Gordon expects his life expectancy to be in excess of five years. *Id.*

Furthermore, the studies cited by Dr. Gordon that address rare late relapses in DLBCL patients are consistent with his clinical experience treating DLBCL patients with R-CHOP immunochemotherapy. *Id.* ¶ 11. Drawing on his 40-plus years experience as a practicing oncologist, Dr. Gordon has concluded that relapses typically occur in DLBCL patients within the first couple of years and that it is highly unlikely for relapse to occur more than five years after diagnosis in a patient who has gone into complete remission after R-CHOP immunochemotherapy.

Pilliod's oncologist and has been shown not to be of concern. Gordon Decl. ¶ 9. For example, in an April 25, 2018 progress note, the oncologist stated that the "PET/CT scan shows no evidence of disease." *Id.* More recent notes from the oncologist with respect to August 2018 office visits say that there is clinically no evidence of disease from a lymphoma standpoint. *Id.* As Dr. Gordon explains in his declaration, a lymph node that is less than one centimeter and shows only mildly hypermetabolic activity on a PET/CT scan is usually not malignant and therefore not cause for concern because these radiographic characteristics could be due to an inflammatory response or other benign conditions. *Id.*

Id. When a patient has been in complete remission for more than five years, like Mr. Pilliod, the likelihood of DLBCL relapse for that patient is rare. *Id.* (citing and quoting 2010 JCO study).

In attempting to satisfy his CCP § 36(a)(2) burden, Mr. Pilliod relies exclusively on the Nabhan Declaration, but that declaration is inadmissible because Dr. Nabhan's assertions are cursory, conclusory, and unsubstantiated. "An opinion is only as good as the facts and reasons on which it is based." *Bozzi v. Nordstrom, Inc.*, 186 Cal. App. 4th 755, 763 (2010) (affirming exclusion of declarant's conclusory opinions). Dr. Nabhan's opinions, which are not based on any concrete evidence and simply assert a bottom-line conclusion, are the kind of *ipse dixit* that the Supreme Court held to be inadmissible under *Daubert*. *See, e.g., Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Dr. Nabhan's failure to state his opinions to a reasonable degree of medical certainty or medical probability further supports the conclusion that the opinions are unduly speculative. *See Ochoa v. Pac. Gas & Elec. Co.*, 61 Cal. App. 4th 1480, 1487 (1998) (holding that physician's declaration was flawed because, *inter alia*, it presented speculation and "did not express [the physician's] opinion with any reasonable degree of medical certainty"); *see also Sargon Enters., Inc. v. Univ. of S. Cal.*, 55 Cal. 4th 747, 771-72 (2012) (requiring courts to act as gatekeepers to exclude speculative expert opinion testimony); *Bozzi*, 186 Cal. App. 4th at 762-63 (affirming exclusion of declarant's opinions because, *inter alia*, they were impermissibly speculative); *Morgenroth v. Pac. Med. Ctr., Inc.*, 54 Cal. App. 3d 521, 533 (1976) (holding that physician's testimony was "speculative" and fell "short of meeting the 'probability' standard of proximate cause").

Even if the Court holds that the Nabhan Declaration is admissible as to Mr. Pilliod, Dr. Nabhan's shaky, unpersuasive opinions fail to satisfy Mr. Pilliod's burden of establishing that his health "is such that a preference is necessary to prevent prejudicing [his] interest in the litigation," CCP § 36(a)(2). Dr. Nabhan's vague, speculative assertion that he "would urge [the Pilliods'] cases to go to trial as soon as possible before [the Pilliods] are unable to meaningfully participate in trial," Nabhan Decl. ¶ 9, does not establish that a trial is necessary for Mr. Pilliod ***by December 2018*** (as requested in the Motion) to avoid prejudicing his interest in the litigation. Dr. Nabhan tries to get around the "problem" of Mr. Pilliod's years-long period of remission (from the

completion of chemotherapy in 2011 to the present) by speculating about the possibility that Mr. Pilliod could have a late relapse, vaguely asserting that "late relapses of large cell lymphomas have been reported in the literature." Nabhan Decl. ¶ 8. But Dr. Nabhan does not cite any of those reports, probably because they show – as discussed above and in the Gordon Declaration – that a late relapse is very unlikely for Mr. Pilliod.

In sum, Mr. Pilliod is well beyond the period when relapse would be expected to occur, and the Nabhan Declaration provides only unsupported, unscientific speculation to the contrary. Gordon Decl. ¶ 12. Accordingly, a trial within 120 days from October 9, 2018 is not necessary to allow Mr. Pilliod to participate at a trial without impairing his interest in the litigation. *Id.* ¶ 13.

B. Mrs. Pilliod has Failed to Satisfy her CCP § 36(a) Burden.

Mrs. Pilliod has failed to satisfy ***both*** prongs of her CCP § 36(a) burden. First, she does not have a "substantial interest" in the action within the meaning of CCP § 36(a)(1). Although the operative Complaint in the *Pilliod* case includes Mrs. Pilliod's name in the caption, the body of the pleading does not assert any claims by her – and does not even mention her. Accordingly, Mrs. Pilliod is not a proper plaintiff. *See Davaloo v. State Farm Ins. Co.*, 135 Cal. App. 4th 409, 418 (2005) ("[T]he allegations in the body of the complaint, not the caption, constitute the cause of action against the defendant."). The Pilliods' much-belated attempt to cure this problem through their recent motion for leave to add her claims to this lawsuit by amendment should be denied for the reasons set forth in Defendants' Opposition to Motion for Leave to File a First Amended Complaint (filed this same date), which defendants incorporate herein by reference.

Second, even if the Court were to grant Mrs. Pilliod leave to amend, she also fails to make the showing required for this Court to conclude that her health "is such that a preference is necessary to prevent prejudicing [her] interest in the litigation," CCP § 36(a)(2). Like Mr. Pilliod, Mrs. Pilliod has not submitted sufficient evidence, such as medical records or a treating physician's declaration, to prove that her interest in this lawsuit will be prejudiced if she does not go to trial in December 2018 or within 120 days of the October 9, 2018 hearing date.

Mrs. Pilliod's medical records show that she went into complete remission following successful chemotherapy treatments provided after a relapse of her primary central nervous system

lymphoma ("PCNSL") in July 2016. *See* Gordon Decl. ¶¶ 15-22. An April 5, 2017 progress note by her oncologist stated that Mrs. Pilliod was "in remission" and that she was "doing well" with a score of 90 on the Karnofsky Performance Scale ("KPS"). *Id.* ¶ 17. The KPS is a standard scoring system that oncologists use to evaluate and track the overall performance status of patients. *Id.* The highest possible KPS score is 100, and a KPS score of 90 is very good, meaning that the patient is able to carry on normal activity, with only minor signs or symptoms of disease. *Id.* The oncologist's May 24, 2017 progress note provides further evidence of the improvement in Mrs. Pilliod's medical condition: she was "[o]verall doing great"; had "[n]o specific complaints"; and was in complete remission, with a "KPS 100" score and "no neurologic deficits." *Id.* ¶ 18. A brain MRI done in October 23, 2017 also shows that Mrs. Pilliod was in complete remission; the report stated that there was "[n]o significant interval change" compared to a brain MRI report from February 25, 2017 "with no evidence of new or progressive disease." *Id.* ¶ 19.

Mrs. Pilliod has remained in complete remission during 2018. *Id.* ¶ 20. Her oncologist's March 28, 2018 progress note stated that Mrs. Pilliod was "[d]oing well after EA [chemotherapy treatment] without complaints" and he assigned her a KPS score of "90-100." *Id.* The most recent MRI brain imaging (done August 8, 2018) showed "[n]o evidence of disease progression compared with brain MRI on 10/23/17." *Id.* ¶ 21. The oncologist's August 8, 2018 progress note stated that she was "[o]verall doing well"; that there was "[n]o change" from the prior visit (on March 28, 2018, when he had given her a KPS score of 90-100); and that she was in complete remission. *Id.*

Mrs. Pilliod received substantial benefits from the particular chemotherapy regimen administered by her oncologist at USCF Medical Center – known as MT-R (methotrexate, temozolomide/temodar, and rituximab) plus EA consolidation (etoposide and cytarabine, also called, ara-C (cytosine arabinoside)). *See* Gordon Decl. ¶¶ 15-17. The successful treatment of PCNSL patients in a multi-center study was reported by Mrs. Pilliod's oncologist in 2013 in a highly respected oncology journal. *Id.* ¶ 16 & n.3 (citing 2013 JCO study by Dr. Rubenstein, *et al.*). The favorable results for long-term survival reported in that study support Dr. Gordon's opinion that Mrs. Pilliod will continue to do well in the future. *Id.* ¶ 23.

Moreover, certain factors relating to Mrs. Pilliod's presentation and treatment have contributed to a more favorable outcome and prognosis for her. *Id.* ¶ 25. For example, the medical records show that her tumor is BCL6 negative. *Id.* According to the 2013 study by Dr. Rubenstein, patients who were BCL6 positive (*i.e.*, patients whose PCNSL tumors expressed BCL6 (a gene re-arrangement)) had shorter survival than BCL6-negative patients. *Id.* In addition, Mrs. Pilliod began her MT-R treatment on April 15, 2015, just six days after she was diagnosed with PCNSL (on April 9, 2015). *Id.* ¶¶ 14, 26. The 2013 study by Dr. Rubenstein identified treatment delay – specifically, a delay of over thirty days between diagnosis of PCNSL and the start of MT-R therapy – as leading to shorter progression-free survival for those patients as compared to patients whose MT-R therapy started within 30 days of their PCNSL diagnosis. *Id.* ¶ 26. This lack of treatment delay provides further support for Dr. Gordon's opinion regarding her prognosis. *Id.*

Mrs. Pilliod relies exclusively on the Nabhan Declaration in trying to satisfy CCP § 36(a)(2) but, for the same reasons discussed above (page 4), Dr. Nabhan's opinions regarding Mrs. Pilliod are inadmissible and should be excluded. The opinions are cursory, conclusory, unsubstantiated *ipse dixit*. Moreover, Dr. Nabhan fails to address the applicable CCP § 36(a)(2) legal standard – and instead vaguely and speculatively asserts that he "would urge" the case "to go to trial as soon as possible" before the Pilliods "are unable to meaningfully participate in trial," Nabhan Decl. ¶ 9. Dr. Nabhan also fails to state his opinions to a reasonable degree of medical certainty or medical probability, which further supports the conclusion that his opinions are unduly speculative and therefore inadmissible.

However, even if the Court declines to exclude Dr. Nabhan's opinions regarding Mrs. Pilliod, they do not come close to satisfying her CCP § 36(a)(2) burden. In light of the records that show how well Mrs. Pilliod has been doing (which Dr. Nabhan essentially concedes, Nabhan Decl. ¶ 6), Dr. Nabhan resorts to unsupported speculation about dire events that could happen in the future, *see id.* ¶¶ 6-7. For example, without citing any medical literature, Dr. Nabhan asserts that median survival for Mrs. Pilliod's sub-type of lymphoma is less than five years, *id.* ¶ 7, and Mrs. Pilliod in turn relies on that assertion to claim that she "is quickly approaching this five-year

period," Trial Preference Motion Memorandum at 7. But, even assuming that this five-year median survival figure is reliable and applies to Mrs. Pilliod, that would suggest an expected survival until ***April 2020***.[2] Even under those hypothetical circumstances, there would be no need to rush to trial in ***December 2018***.

Other aspects of the Nabhan Declaration also are unpersuasive. For instance, the assertion that Mrs. Pilliod is at high risk for disease recurrence, progression, and relapse is unreliable speculation. Gordon Decl. ¶ 24. Dr. Nabhan relies on her condition when she was first diagnosed with PCNSL in 2015. However, Mrs. Pilliod's continued complete remission status throughout 2018, following completion of MT-R and EA consolidation, is a more reliable predictor of her future well-being than her initial presentation when she was diagnosed with PCNSL in 2015. Gordon Decl. ¶ 24.

Dr. Nabhan also relies on improper and unfounded speculation about relapse and asserts (without citing any medical literature) that there are no effective therapies for PCNSL upon second relapse. *See* Nabhan Decl. ¶ 6. But as Dr. Gordon explains – with proper citation to the medical literature – Mrs. Pilliod's favorable response to prior courses of high dose methotrexate indicate that, even if she were to relapse, she probably would benefit from another course of high dose methotrexate therapy. Gordon Decl. ¶ 28. Patients who have responded well to prior courses of high dose methotrexate tend to respond well to another course of high dose methotrexate after relapse, even after a second relapse. *Id.* (citing oncology journal papers from 2014 and 2004). Likewise, Dr. Nabhan provides no basis for his suggestion that Mrs. Pilliod's advanced age at the time of her PCNSL diagnosis puts her at high risk for recurrence, progression, and relapse. To the contrary, in the 2013 study by Dr. Rubenstein, older patients (patients over 60 years old) had outcomes similar to younger patients' outcomes. *Id.* ¶ 27.

In sum, Dr. Nabhan's prognosis for Mrs. Pilliod is based on speculation and is contrary to the most recent medical records, which show that she has been doing well in complete remission in 2017 and 2018 after receiving the MT-R and EA consolidation chemotherapy treatments

[2] Mrs. Pilliod was initially diagnosed with PCNSL in April 2015. Gordon Decl. ¶ 14.

discussed above. *Id.* ¶ 29. There is no basis to conclude that a trial within 120 days from October 9, 2018 is needed to allow Mrs. Pilliod to participate at a trial without impairing her interest in the litigation. *Id.*

II. The Motion Also Fails To Satisfy CCP § 36(e).

The Pilliods cannot avoid their failure of proof under CCP § 36(a) through their separate invocation of CCP § 36(e). Section 36(e) requires "a showing that satisfies the [C]ourt that the interests of justice will be served," by granting the trial preference motion. But "[g]enerally, judges are *reluctant* to grant preferential trial setting [based on CCP § 36(e)]. With the age and terminal illness situations already provided for . . . [in other parts of CCP § 36], there are relatively few situations that justify preempting other cases waiting in line for a trial date." Weil & Brown, *Cal. Practice Guide: Civil Procedure Before Trial* (The Rutter Group 2017 Update), 12:256.3 (emphasis in original). The requested trial preference here would undermine – not serve – the interests of justice. As discussed above in Section I, rushing this case to trial is not necessary to ensure that Mr. or Mrs. Pilliod will be able to participate in a trial. As discussed below in Section III, plaintiffs' counsel are trying to subvert the purposes of this JCCP and interfere with the Court's broad authority and discretion to manage cases efficiently and equitably for the benefit of all parties – and the excessively short period for completing discovery and trial preparation work in time for a December 2018 trial in this complex lawsuit would unfairly prejudice defendants.

Thus, there is no valid reason for the Court to conclude that the "interests of justice" standard in CCP § 36(e) supports granting the Motion.

III. The Motion Seeks Relief That Is Contrary To The Purpose Of This JCCP – Managing Cases Efficiently And Equitably To Benefit All Parties – And Would Unfairly Prejudice Defendants.

Granting the Motion would permit plaintiffs' counsel to subvert the purposes of this JCCP to their own ends and materially curtail the substantial authority and broad discretion granted to this Court to coordinate and manage numerous complex cases efficiently and equitably for the benefit of all parties, including by ensuring that representative cases are selected for bellwether trials. By their very nature, the cases in this JCCP likely involve a substantial percentage of

plaintiffs who are over seventy years old. If the Court does not fully weigh the important case management responsibilities granted to all JCCP judges when the Court exercises its discretion regarding whether to schedule expedited trials, plaintiffs' counsel will take control of this JCCP by attempting to unilaterally set expedited trial after expedited trial in cases that are not representative of the litigation as a whole.

Such a one-sided approach to managing complex, coordinated cases would be antithetical to the purpose of this JCCP. Having been appointed by the Judicial Council to preside over this JCCP, the Court "must assume an active role in managing all steps of the pretrial, discovery, and trial proceedings to expedite the just determination of the coordinated actions without delay." CRC 3.541(b). It "is the intent of the Judicial Council to vest in the coordinating judge ***whatever great breadth of discretion may be necessary and appropriate*** to ease the transition through the judicial system of the logjam of cases which give rise to coordination." *McGhan Medical Corp. v. Superior Court*, 11 Cal. App. 4th 804, 812 (1992) (emphasis added); *see Ford Motor Warranty Cases*, 11 Cal. App. 5th 626, 645 (2017) (quoting *McGhan*, 11 Cal. App. 4th at 812); *Abelson v. Nat'l Union Fire Ins. Co.*, 28 Cal. App. 4th 776, 786 (1994) (same). Thus, "the procedures which may be utilized by the coordinating judge are flexible indeed." *McGhan*, 11 Cal. App. 4th at 812; *see Ford Motor*, 11 Cal. App. 5th at 644 (quoting *McGhan*, 11 Cal. App. 4th at 812).

The flexibility and broad discretion required for a JCCP judge would be lost here if the Court were to grant a series of trial preference motions for the plaintiffs whose claims their counsel believe are strongest. That would prevent the Court from fulfilling its obligation to focus on the overall coordinated litigation to benefit ***all*** parties and promote the efficient use of judicial resources. "One of the purposes . . . of a centralized coordinating authority is to vest in one administrator the power to organize the litigation in an efficient and equitable manner, ***for the benefit of all.***" *McGhan*, 11 Cal. App. 4th at 813 (emphasis added); see *Ford Motor*, 11 Cal. App. 5th at 644 n.9 (quoting *McGhan*, 11 Cal. App. 4th at 813); *Abelson*, 28 Cal. App. 4th at 786 ("The purposes of coordination include promoting the efficient use of judicial resources."). Taking a broader view and not focusing undue attention on any one case at the expense of the overall JCCP is an intrinsic part of presiding over a JCCP. As the *McGhan* court stated: "It is possible that

some delay in certain cases may be experienced. We view this potential detriment to the few to be a modest price to pay for the efficiency to be gained by the majority of cases through coordination." *McGhan*, 11 Cal. App. 4th at 813; *see Ford Motor*, 11 Cal. App. 5th at 644 n.9 (quoting *McGhan*, 11 Cal. App. 4th at 813).

Thus, the Pilliods' reliance on ***non-JCCP cases*** for the proposition that CCP § 36(a) gives them a "mandatory" or "absolute" right to a trial preference is without merit. A JCCP judge's broad authority and discretion to manage cases in a coordinated fashion efficiently and equitably to benefit all parties are not restricted by the code provisions authorizing judges to grant trial preference requests in certain circumstances in individual cases.[3] That is what a JCCP judge (Judge Anthony Mohr) concluded when addressing a trial preference request in the *Toyota Motor Cases* JCCP ruling (Calhoun Decl., Exhibit 1). Relying on the authorities cited above – the *Abelson* case, CRC 3.504(b) (and its almost identical predecessor, CRC 1504), and CCP § 404.7 – Judge Mohr held that his coordination power as a JCCP judge "trumps the otherwise mandatory application of Cal. Civ. Proc. section 36." *Toyota Motor Cases*, 2012 WL 965830, at p.7.[4] Likewise, this Court's power as a JCCP judge trumps any otherwise mandatory application of the trial preference provisions in CCP § 36.

Plaintiffs' counsel's request for a preferential trial setting at the very outset of this JCCP would significantly impair, in numerous respects, this Court's ability to manage the JCCP efficiently and equitably for the benefit of all parties:

First, plaintiffs' counsel's proposed approach would effectively usurp the Court's authority

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[3] Indeed, it is so important for JCCP judges to have flexibility and broad discretion to manage cases that JCCP judges are governed by a separate set of California Rules of Court provided by the Judicial Council – and those rules supersede conflicting provisions of law that are generally applicable to civil actions. *See* CRC 3.504(b) ("To the extent that the rules in this chapter conflict with provisions of law applicable to civil actions generally, the rules in this chapter prevail, as provided by Code of Civil Procedure section 404.7."); CCP § 404.7 ("Notwithstanding any other provision of law, the Judicial Council shall provide by rule the practice and procedure for coordination of civil actions in convenient courts, including provision for giving notice and presenting evidence.").

[4] That part of Judge Mohr's ruling analyzed CCP § 36(b) in the context of a JCCP. The provision now before this Court – CCP § 36(a) – also has been called "mandatory" by courts outside the JCCP context. Thus, Judge Mohr's ruling is persuasive authority for this Court to consider when deciding the Motion filed by the Pilliods.

to ensure that appropriate procedures are used for the selection of bellwether cases (which cases are chosen and when they will be tried), with input from all parties. *See Ford Motor*, 11 Cal. App. 5th at 644 (discussing "bellwether trials" and "which case or cases to try first"). The purpose of bellwether trials is to "produce a sufficient number of representative verdicts" to "enable the parties and the court to determine the nature and strength of the claims, whether they can be fairly developed and litigated on a group basis, and what range of values the cases may have if resolution is attempted on a group basis." Manual for Complex Litigation (Fourth) § 22.315 (2004); *see In re Hydroxycut Mktg. & Sales Practices Litig.*, No. 09-md-2087 BTM(KSC), 2012 WL 3637278, at *3 (S.D. Cal. Aug. 21, 2012) ("The bellwether cases should be representative cases that will best produce information regarding value ascertainment for settlement purposes or to answer causation or liability issues common to the universe of plaintiffs."). Therefore, only when a "representative . . . range of cases" is selected may "individual trials . . . produce reliable information about other mass tort cases." Manual for Complex Litigation (Fourth) § 22.315 (2004).

The Court has put in place a procedure through the requirement of Plaintiff's Fact Sheets whereby the parties and the Court soon will be in position to appropriately select representative bellwether cases for trial. *See* Case Management Order No. 11 ("Approval of Plaintiff's Fact Sheet"); Case Management Order No. 9, ¶¶ 14-15 (setting deadlines for plaintiffs to serve Plaintiff's Fact Sheets on defendants). If the Court were to grant the present Motion, however, that procedure would be subverted. Rather than a fair and equitable process in which the parties and the Court select representative bellwethers in an informed and considered manner, plaintiffs would be empowered to cherry-pick and preferentially bring to trial case after case among the likely scores of over 70-year old plaintiffs in the JCCP population, based solely on their counsel's litigation strategies and self-interest. Plaintiffs' counsel's selection of the *Pilliod* case as an expedited first JCCP trial (with no evidence of medical necessity and a belated attempt to assert new personal injury claims by Mrs. Pilliod) makes this problem clear. A joint trial of a husband and wife who each allege that they developed NHL caused by exposure to Roundup®-branded herbicides probably is one of the ***least representative*** trials in the entire universe of cases in this JCCP. Rather than "serv[ing]" "the interests of justice," the present Motion would serve the

strategic interest of plaintiffs and sharply prejudice defendants in their defense of the litigation.

Granting the Motion also would subvert this Court's scheduling order regarding expert testimony. The Court has exercised its case management discretion and coordination obligations by deciding to assess whether plaintiffs can satisfy their burden of proving general causation through expert testimony that is admissible under *Sargon* before the Court selects bellwether trials. Pursuant to Case Management Order No. 9, the period for the *Sargon*/general causation briefing is scheduled to extend from October 30, 2018 to January 8, 2019, with a hearing set for January 25, 2019. Those motions apply to all cases in this JCCP – including *Pilliod* – but the December 2018 trial requested in the Motion would allow plaintiffs to circumvent the Court's Order and disrupt the Court's exercise of its *Sargon* gatekeeping responsibility.

Moreover, the relief sought in the Motion would not serve the interests of justice because a December 2018 trial date would severely prejudice defendants' ability to conduct appropriate discovery and prepare for trial in this complex product liability lawsuit.[5] Preparing for a single-plaintiff Roundup® trial is already a massive undertaking. Calhoun Decl. ¶4. Trial preparation becomes even more complicated and time-consuming if the trial involves two plaintiffs with different medical histories who each allege different NHL sub-types caused by different individual exposures to Roundup®-branded herbicides. *Id.* Because the *Pilliod* case is not currently set for trial, defendants have not yet pursued any discovery in this case (except for recently beginning the process of requesting medical records from various treating health care providers, promptly after the Pilliods served Plaintiff's Fact Sheets and medical records releases on defendants). *Id.* ¶ 5. Extensive fact discovery remains to be conducted before defendants will be ready for trial, including issuing written discovery requests; obtaining voluminous medical records from various treating health care providers; and taking depositions of Mr. and Mrs. Pilliod, their treating physicians, and other fact witnesses. *Id.* ¶ 6.

Defendants also will need substantial time for expert disclosures and discovery, including

[5] Courts should consider prejudice to a defendant when ruling on a motion for trial preference. *See Dick v. Superior Court*, 185 Cal. App. 3d 1159, 1166 (1986); *Toyota Motor Cases*, 2012 WL 965830, at p.5 (quoting *Dick*, 185 Cal. App. 3d at 1166).

identifying the right general and plaintiff-specific expert witnesses for this lawsuit; deposing any plaintiff's expert witnesses; and defending the depositions of defendants' expert witnesses. *Id.* ¶ 7. In addition to the JCCP-wide *Sargon* briefing regarding general causation discussed above, defendants also expect that substantial time will be required for *Sargon* briefing in this case regarding experts who address issues other than general causation, dispositive motions briefing, and motion *in limine* briefing. *Id.* Moreover, defendants will need a significant amount of time to prepare for trial. *Id.* It is completely unrealistic to expect that the work required to adequately defend against the two separate plaintiffs' claims at trial can be done within approximately two months (from the October 9 hearing on the Motion to the December trial date requested in the Motion) – or even within the 120 days contemplated by CCP § 36(f). *Id.* ¶ 8.

CONCLUSION

For the reasons set forth above and in the accompanying declarations, the Court should deny the Motion for Trial Preference.[6]

Dated: September 25, 2018

Respectfully submitted,

/s/ Eric G. Lasker
Joe G. Hollingsworth (appearance *pro hac vice*)
Eric G. Lasker (appearance *pro hac vice*)
Martin C. Calhoun (appearance *pro hac vice*)
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Richard A. Clark (State Bar No. 39558)
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Attorneys for Defendants MONSANTO COMPANY, WILBUR-ELLIS COMPANY LLC, and WILBUR-ELLIS FEED, LLC

[6] Making that ruling does not mean that *Pilliod* cannot be picked later as one of the first bellwether trials for this JCCP if the Court deems that selection appropriate (though defendants do not so concede). At the appropriate time, after defendants have received and evaluated Plaintiff's Fact Sheets for the other JCCP cases, the issue of whether *Pilliod* should be chosen as a bellwether trial can be revisited by the Court. That will allow the attorneys who represent various plaintiffs in this JCCP and defense counsel to present their views regarding the process for picking bellwether trials and whether other cases are more representative of the universe of cases in this JCCP – and therefore more appropriate for selection as bellwether trials – than *Pilliod*. At that point, the Court will be able to make informed decisions to achieve the overall purpose of this JCCP by managing the cases in a coordinated fashion, efficiently and equitably to benefit all parties.

DECLARATION

DECLARATION OF DAVID GORDON, M.D.

I, David Gordon, M.D., declare as follows:

1. I am a board-certified oncologist and hematologist, licensed to practice in Texas.

2. I am over 18 years old. If I were called to testify, I could and would competently testify to the statements and opinions set forth below in this declaration.

3. This declaration is based on my personal knowledge; my education, training, and experience; my knowledge and review of medical literature; my review of medical records for Mr. Alva Pilliod and Mrs. Alberta Pilliod; and my review of the August 30, 2018 Declaration of Chadi Nabhan, M.D. I submit this declaration in support of Defendants' Opposition to Motion for Trial Preference.

4. My opinions set forth below are to a reasonable degree of medical or scientific certainty. I reserve the right to supplement or revise any opinions based on additional medical records or other information that may be presented to me in the future.

5. I am board-certified in internal medicine, oncology, and hematology and have been a practicing oncologist for more than forty years (since 1977). After graduating from Case Western Reserve University School of Medicine, I did my fellowship training in hematology and medical oncology at University of Rochester Medical Center. Over the course of my medical career, I have treated approximately 1,000 patients with various kinds of non-Hodgkin's lymphoma, including many patients with diffuse large B-cell lymphoma and some patients with a rarer sub-type of non-Hodgkin's lymphoma known as primary central nervous system lymphoma. A true and correct copy of my curriculum vitae is attached as Exhibit 1.

6. I have been asked to: (a) evaluate the medical records for Mr. Pilliod and Mrs. Pilliod; set forth my opinions regarding each person's medical condition and prognosis, including specifically whether the health of each person is such that an expedited trial within 120 days from October 9, 2018 is needed to allow each person to participate at a trial without impairing each person's interest in the litigation; and (b) respond to the Nabhan Declaration. Each person is addressed separately below.

Mr. Pilliod

7. According to the medical records for Mr. Pilliod [Valley Medical Oncology Consultants Records (numbered AP-01-000001 to AP-01-000034; AP-02-000001 to AP-02-000032; VMOC-000001 to VMOC-000032) and records from other health care providers (AP-03-000001 to AP-03-001450)], Mr. Pilliod was diagnosed with diffuse large B-cell lymphoma ("DLBCL") in 2011 and was treated with standard immunochemotherapy (six cycles of R-CHOP) from June to October 2011. Those medical records, including August 2018 progress notes from Mr. Pilliod's oncologist, show that the R-CHOP immunochemotherapy treatment was successful and has worked very well for Mr. Pilliod; that he has been in complete remission since he completed that course of treatment in October 2011; and that he continues to be in complete remission.

8. Although some DLBCL patients can relapse after going into remission from R-CHOP treatment, most relapses occur within the first couple of years [Maurer (2014)[1]; Larouche (2010)[2]]. In a study of a large group of DLBCL patients treated with immunochemotherapy, for patients who achieved complete remission and had no recurrence of disease by 24 months after their DLBCL diagnosis – *i.e.*, event-free survival at 24 months, known as "EFS24" – the risk of DLBCL relapse occurring in the following five years was only 8%, which was the same as the risk of death from unrelated causes [Maurer (2014), at 1067]. This means that "patients who have achieved EFS24 have subsequent survival comparable to that of the age- and sex-matched general population (ie, a normal life expectancy) [Maurer (2014), at 1071]."

9. Although a March 2018 PET/CT scan showed a new 0.7 centimeter mildly hypermetabolic subcentimeter right supraclavicular lymph node, it has been addressed during follow-up visits with Mr. Pilliod's oncologist and has been shown not to be of concern. For

[1] M. Maurer, *et al.*, Event-Free Survival At 24 Months Is A Robust End Point For Disease-Related Outcome In Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy, 32 J. Clin. Oncol. 1066, 1066 (2014) (stating that "[m]ost relapses occur within the first 12 to 18 months") (true and correct copy attached as Exhibit 2).

[2] J. Larouche, *et al.*, Lymphoma Recurrence 5 Years Or Later Following Diffuse Large B-Cell Lymphoma: Clinical Characteristics And Outcome, 28 J. Clin. Oncol. 2094, 2094 (2010) ("Unfortunately, some patients eventually relapse, mainly in the first 2 to 3 years following treatment.") (true and correct copy attached as Exhibit 3).

example, in an April 25, 2018 progress note, the oncologist stated that the "PET/CT scan shows no evidence of disease." More recent notes from the oncologist with respect to August 2018 office visits say that there is clinically no evidence of disease from a lymphoma standpoint. In my experience, a lymph node that is less than one centimeter and shows only mildly hypermetabolic activity on a PET/CT scan is usually not malignant and therefore not cause for concern because these radiographic characteristics could be due to an inflammatory response or other benign conditions.

10. Mr. Pilliod continues to be in complete remission and has experienced event-free survival for much longer than 24 months, so he has the normal, substantial life expectancy of a 76-year-old male. If Mr. Pilliod does not develop any other life-threatening illness or medical problem, I expect his life expectancy to be in excess of five years.

11. The studies discussed above are consistent with my clinical experience treating DLBCL patients with R-CHOP immunochemotherapy. In my experience, relapses typically occur in DLBCL patients within the first couple of years, and it is highly unlikely for relapse to occur more than five years after diagnosis in a patient who has gone into complete remission after R-CHOP immunochemotherapy. When a patient has been in complete remission for more than five years, like Mr. Pilliod, the likelihood of DLBCL relapse for that patient is rare [Larouche (2010), at 2094 (stating that late relapses occurring after five years "are considered rare events")].

12. Mr. Pilliod is well beyond the period when relapse would be expected to occur, and the Nabhan Declaration provides only unsupported, unscientific speculation to the contrary.

13. In conclusion, a trial within 120 days from October 9, 2018 is not necessary to allow Mr. Pilliod to participate at a trial without impairing his interest in the litigation.

Mrs. Pilliod

14. According to the medical records for Mrs. Pilliod (records from various medical providers, including very recent records from Dr. Rubenstein/UCSF Medical Center), Mrs. Pilliod was diagnosed with primary central nervous system lymphoma ("PCNSL") of the large B-cell type on April 9, 2015 [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000004)]. Starting on April 15, 2015, she was treated with a chemotherapy regimen called MT-R (methotrexate,

temozolomide/ temodar, and rituximab), first at Stanford University Hospital and then at Eden Medical Center [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000004); Stanford Health Care Records (AP-03-004547)]. That chemotherapy treatment resulted in significant resolution of many of Mrs. Pilliod's symptoms [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000004)], and brain MRI imaging after completion of her chemotherapy showed no evidence of residual or recurrent disease [Stanford Health Care Records (AP-03-006291 to AP-03-006292, AP-03-006281 to AP-03-006283)].

15. A brain MRI done on July 31, 2016 showed new disease [Stanford Health Care Records (AP-03-006304 to AP-03-006306); Dr. Rubenstein/UCSF Medical Center Records (AP-07-000004)]. In response to this relapse, Mrs. Pilliod received another course of MT-R chemotherapy treatment (methotrexate, temozolomide/temodar, and rituximab) [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000004 to AP-07-000025)]. Then, in 2017, she received a course of what is known as "EA consolidation" treatment with two other drugs, etoposide and cytarabine (also called, ara-C (cytosine arabinoside)) [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000015 to AP-07-000029)].

16. Dr. James Rubenstein has been one of Mrs. Pilliod's treating oncologists from September 2016 to the present. Dr. Rubenstein published a CALGB-sponsored, multi-center study in 2013 in a highly respected oncology journal that discussed successful treatment of PCNSL patients with an MT-R regimen followed by EA consolidation [Rubenstein (2013)[3]].

17. The medical records show that Mrs. Pilliod went into complete remission after, and received significant benefits from, the MT-R followed by EA consolidation treatments described above. For example, in an April 5, 2017 progress note, Dr. Rubenstein stated that Mrs. Pilliod was "in remission" and that she was "doing well" with a score of 90 on the Karnofsky Performance Scale ("KPS") [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000029)]. The KPS is a standard scoring system that oncologists use to evaluate and track the overall performance status of patients. The highest possible KPS score is 100. A KPS score of 90 is very

[3] J. Rubenstein, *et al.*, Intensive Chemotherapy And Immunotherapy In Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202), 31 J. Clin. Oncol. 3061 (2013) (true and correct copy attached as Exhibit 4).

good; it means that the patient is able to carry on normal activity, with only minor signs or symptoms of disease.

18. A progress note for a May 24, 2017 visit provides further evidence of the improvement in Mrs. Pilliod's medical condition after the MT-R and EA consolidation treatment. For that visit, Dr. Rubenstein stated that she was "[o]verall doing great"; had "[n]o specific complaints"; and was in complete remission, with a "KPS 100" score and "no neurologic deficits" [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000029 to AP-07-000032)].

19. A brain MRI done in October 23, 2017 also shows that Mrs. Pilliod was in complete remission. The imaging report stated that there was "[n]o significant interval change" compared to a brain MRI report from February 25, 2017 "with no evidence of new or progressive disease" [UCSF Medical Center Records (AP-07-000097 to AP-07-000098)].

20. Mrs. Pilliod has remained in complete remission during 2018. Dr. Rubenstein's progress note for a March 28, 2018 visit stated that she was "[d]oing well after EA [treatment] without complaints" and that he assigned her a KPS score of "90-100" [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000039 to AP-07-000043)].

21. The most recent records available to me are from August 2018. A report for a brain MRI done on August 8, 2018 states: "No evidence of disease progression compared with brain MRI on 10/23/17" [UCSF Medical Center Records (AP-07-000098 to AP-07-000099)]. Dr. Rubenstein's progress note for the August 8, 2018 visit stated that she was "[o]verall doing well"; that there was "[n]o change" from the prior visit (on March 28, 2018, when he had given her a KPS score of 90-100); and that she was in complete remission [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000043 to AP-07-000047)].

22. At the August 8, 2018 office visit, Mrs. Pilliod was still on maintenance therapy with a drug called lenalidomide (also known as revlimid), which she had started in 2017 after finishing the EA consolidation treatment regimen [Dr. Rubenstein/UCSF Medical Center Records (AP-07-000032, AP-07-000035, AP-07-000043)].

23. Mrs. Pilliod was treated with the MT-R and EA consolidation regimen outlined in Rubenstein (2013). The "survival curves [in that study] show encouraging evidence of a stable

plateau," which means no more deaths or relapses, and the median overall survival for patients in that study (median follow-up of 4.9 years) had not yet been reached [Rubenstein (2013), at 3066 & 3064 Figure 2]. The favorable results for long-term survival reported in Rubenstein (2013) support my opinion that Mrs. Pilliod will continue to do well in the future.

24. The assertion in the Nabhan Declaration that Mrs. Pilliod is at high risk for disease recurrence, progression, and relapse is unreliable speculation. In my opinion, her continued complete remission status throughout 2018, following completion of MT-R and EA consolidation, is a more reliable predictor of her future well-being than is her initial presentation when she was diagnosed with PCNSL in 2015, as asserted by Dr. Nabhan.

25. Certain factors relating to Mrs. Pilliod's presentation and treatment have contributed to a more favorable outcome and prognosis for her. For example, according to Rubenstein (2013), patients who were BCL6 positive (i.e., whose PCNSL tumors expressed BCL6 (a gene re-arrangement)) had shorter survival than BCL6-negative patients. The medical records show that Mrs. Pilliod's tumor was BCL6 negative [Stanford Health Care Records (AP-03-004547, AP-03-005492)], which also supports my opinion regarding her prognosis.

26. In addition, Rubenstein (2013) identified treatment delay – a delay of over thirty days between diagnosis of PCNSL and the start of MT-R therapy – as leading to shorter progression-free survival for those patients as compared to patients whose MT-R therapy started within 30 days of their PCNSL diagnosis. As discussed above in paragraph 14, Mrs. Pilliod began her MT-R treatment on April 15, 2015, just six days after she was diagnosed with PCNSL (on April 9, 2015). This lack of treatment delay provides further support for my opinion regarding her prognosis.

27. In Rubenstein (2013), older patients (patients over 60 years old) had outcomes similar to outcomes of younger patients. This undermines the suggestion in the Nabhan Declaration that Mrs. Pilliod's advanced age at the time of her PCNSL diagnosis puts her at high risk for recurrence, progression, and relapse.

28. Even if Mrs. Pilliod were to relapse, she probably would benefit from another course of high dose methotrexate therapy, considering how well she responded to prior courses of

high dose methotrexate. Patients who have responded well to prior courses of high dose methotrexate tend to respond well to another course of high dose methotrexate after relapse, even after a second relapse [Pentsova (2014)[4]; Plotkin (2004)[5]].

29. In conclusion, Dr. Nabhan's prognosis for Mrs. Pilliod is based on speculation and is contrary to the most recent medical records, which show that she has been doing well in complete remission in 2017 and 2018 after receiving the MT-R and EA consolidation treatments discussed above. In my opinion, there is no basis to conclude that a trial within 120 days from October 9, 2018 is needed to allow Mrs. Pilliod to participate at a trial without impairing her interest in the litigation.

I declare under penalty of perjury of the laws of the State of California that the foregoing is true and correct.

Signed September 24, 2018 in West Virginia

David Gordon, M.D.

[4] E. Pentsova, *et al.*, Methotrexate Re-Challenge For Recurrent Primary Central Nervous System Lymphoma, 117 J. Neurooncol. 161 (2014) (true and correct copy attached as Exhibit 5).

[5] S. Plotkin, *et al.*, Treatment Of Relapsed Central Nervous System Lymphoma With High-Dose Methotrexate, 10 Clin. Cancer Research 5643 (2004) (true and correct copy attached as Exhibit 6).

EXHIBIT 1

CURRICULUM VITAE

NAME: DAVID HUGH GORDON, M.D.

BORN: Philadelphia, Pennsylvania
June 30, 1945

EDUCATION: College: Trinity College, Hartford, Conn.
B.S. (Biology) - 1967
Medical School: Case Western Reserve
Cleveland, Ohio - 1971

Post Graduate Training:
Straight Medical Internship - Hartford Hospital, Hartford, Conn., July 1971-June 1972.
First Year Medical Residency - Hartford Hospital, Hartford, Conn., July 1972-June 1973.
Second Year Medical Residency - University of Minnesota Hospitals, Minneapolis, Minn., July 1973-June 1974.
Hematology Fellowship- University of Rochester Medical Center, Rochester, N.Y. July 1974-June 1975.
Medical Oncology Fellowship - University of Rochester Medical Center, Rochester, N.Y., July 1975-June 1977.

PRACTICE: Southwest Oncology Associates, P.A. - July 1977-June 30, 1979.
San Antonio Tumor and Blood Clinic, P.A. - Vice President, July 1, 1979 - April 30, 1996.
San Antonio Tumor and Blood Clinic, Division of US Oncology, President, 1997 - 2012
San Antonio Tumor and Blood Clinic, Division of Cancer Care Network of South Texas, Executive Board Member, 2012 - September 2015

CERTIFICATION:
American Board of Internal Medicine. Certified June 1974
American Board of Internal Medicine, Medical Oncology Subspecialty. Certified October 1977.
American Board of Internal Medicine, Hematology Subspecialty. Certified October 1978.

LICENSURE: TEXAS E9664

UNIVERSITY APPOINTMENTS:

Instructor in Medicine - University of Minnesota, July 1973-June 1974.
Instructor and Trainee, Department of Medicine, Hematology Unit, University of Rochester, July 1974-June 1975.
Instructor and Trainee in Oncology in Medicine, University of Rochester, July 1975-June 1977.
Attending Physician, Monroe Community Hospital, Rochester, N.Y., June 1975-June 1977.
Clinical Instructor, Department of Medicine, University of Texas at San Antonio, November 1977-1980.
Clinical Assistant Professor, Department of Medicine, University of Texas at San Antonio, 1980-1983.
Clinical Associate Professor, Department of Medicine, University of Texas at San Antonio, 1983-1998.
Clinical Professor, Department of Medicine, University of Texas at San Antonio, 1998-2010.

HOSPITAL APPOINTMENTS

President, Medical Executive Board, Baptist Memorial Hospital System, 1989.
Chief of Staff, Baptist Memorial Hospital, 1988.
Associate Board of Trustees, Baptist Memorial Hospital System, 1988-1990.

MEDICAL SOCIETY APPOINTMENTS

Bexar County Medical Society, Board of Mediations, 1989-1991. (Chairman 1991).
Alternate Delegate to Texas Medical Association, Bexar County Medical Society, 1988-1989.
Board of Directors, Bexar County Medical Society. 1992-1994.
Vice President, Bexar County Medical Society, 1995.

OTHER PROFESSIONAL ACTIVITIES

Board of Directors, American Cancer Society, 1984, 1988-1999.
Associate Board of Directors, American Cancer Society, 1999 - 2001.
American Society of Hematology, Committee on Practice, 1989-1996.
Carrier Advisory Committee, Medicare, State of Texas, 1993-2015.
Director, Cancer Update, Annual Cancer Conference, Baptist Memorial Hospital System, 1990-2015.

MEMBERSHIPS: American Society of Clinical Oncology
American Society of Hematology
Fellow, American College of Physicians -
Member, 2002 - Present.
Phi Delta Epsilon Medical Fraternity
Texas Medical Association
Bexar County Medical Society
Texas Club of Internists

US ONCOLOGY (AMERICAN ONCOLOGY RESOURCES) RELATED ACTIVITIES
Pharmacy and Therapeutics Committee
Member, 1996-2000, 2001 - 2015
Vice President, 2001 - 2002
Member, Executive Committee, 2001 - 2015
National Policy Board
Member, 1997-1999, 2000-2001

US ONCOLOGY (AMERICAL ONCOLOGY RESOURCES) ACTIVITIES - RESEARCH
Supportive Care Committee, Chairman, 1996 - 2001
Medical Oncology/Supportive Care Committee, Co-Chairman, 2001 - 2002.
Research Steering Committee, Member, 1996 - 2002
Principle investigator for us oncology research studies:
Zoledronate Protocol No 4244603011. A randomized, double-blind, placebo-controlled multicenter trial to evaluate the safety and efficacy of zoledronate (4 mg and 8 mg) administered intravenously as an adjunct to anticancer therapy to patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer. 1999.
Zoledronate Protocol No 4244603011. Extension of above using extended duration of treatment with zoledronate. 2000.
Zoledronate Protocol No 4244603010. A randomized, double blind, multicenter, cooperative trial of IV zoledronate (4 mg or 8 mg) vs IV Aredia (90 mg) as an adjunct to standard therapies in the treatment of multiple myeloma and breast cancer patients. 1998 - present.
Randomized study of dacarbazine vs dacarbazine plus G3139 (BCL-2 antisense oligonucleotide in patients with advanced malignant melanoma. 2000.
Randomized study of dacarbazine versus dacarbazine plus G3131 BCL2 - antisense oligonucleotide in patients with advanced malignant melanoma, 2002.
Randomized, open label, multicenter study of darbepoetin alfa administered once every two weeks (q2w) compared with rHu EPO administered once every week (q w) for the treatment of anemia in subjects with malignancies, receiving multicenter chemotherapy, 2003.

PUBLICATIONS:

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Levick, S.; Jacobs, C.; Loukas, D.F.; Gordon, D.H.; Meyskens, F.L.; Uhm, K.: Naproxen Sodium in the Treatment of Bone Pain Due to Metastatic Cancer. *Pain*, Vol 35(3), December 1988, P 253-258.

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EXHIBIT 2

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ORIGINAL REPORT

Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related Outcome in Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy

Matthew J. Maurer, Hervé Ghesquières, Jean-Philippe Jais, Thomas E. Witzig, Corinne Haioun, Carrie A. Thompson, Richard Delarue, Ivana N. Micallef, Frédéric Peyrade, William R. Macon, Thierry Jo Molina, Nicolas Ketterer, Sergei I. Syrbu, Olivier Fitoussi, Paul J. Kurtin, Cristine Allmer, Emmanuelle Nicolas-Virelizier, Susan L. Slager, Thomas M. Habermann, Brian K. Link, Gilles Salles, Hervé Tilly, and James R. Cerhan

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H.T. and J.R.C. contributed equally to this work as co-senior authors.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Purpose
Studies of diffuse large B-cell lymphoma (DLBCL) are typically evaluated by using a time-to-event approach with relapse, re-treatment, and death commonly used as the events. We evaluated the timing and type of events in newly diagnosed DLBCL and compared patient outcome with reference population data.

Patients and Methods
Patients with newly diagnosed DLBCL treated with immunochemotherapy were prospectively enrolled onto the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource (MER) and the North Central Cancer Treatment Group NCCTG-N0489 clinical trial from 2002 to 2009. Patient outcomes were evaluated at diagnosis and in the subsets of patients achieving event-free status at 12 months (EFS12) and 24 months (EFS24) from diagnosis. Overall survival was compared with age- and sex-matched population data. Results were replicated in an external validation cohort from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien 2003 (LNH2003) program and a registry based in Lyon, France.

Results
In all, 767 patients with newly diagnosed DLBCL who had a median age of 63 years were enrolled onto the MER and NCCTG studies. At a median follow-up of 60 months (range, 8 to 116 months), 299 patients had an event and 210 patients had died. Patients achieving EFS24 had an overall survival equivalent to that of the age- and sex-matched general population (standardized mortality ratio [SMR], 1.18; $P = .25$). This result was confirmed in 820 patients from the GELA study and registry in Lyon (SMR, 1.09; $P = .71$). Simulation studies showed that EFS24 has comparable power to continuous EFS when evaluating clinical trials in DLBCL.

Conclusion
Patients with DLBCL who achieve EFS24 have a subsequent overall survival equivalent to that of the age- and sex-matched general population. EFS24 will be useful in patient counseling and should be considered as an end point for future studies of newly diagnosed DLBCL.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma in the United States and Europe and is an aggressive lymphoma with an expected survival of less than 1 year if untreated.[1,2] However, a significant number of patients are potentially cured with the current standard-of-care rituximab (anti-CD20 monoclonal antibody) plus anthracycline-based chemotherapy (immunochemotherapy), most commonly given as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3-6] Although the majority of patients treated with immunochemotherapy respond to treatment, 20% to 40% of patients will either fail to achieve remission or they will relapse. Most relapses occur within the first 12 to 18 months, and outcome for these patients is generally poor with salvage therapies, including platinum-based chemotherapy and stem-cell transplantations, resulting in long-term survival in only a minority of patients.[7-10] Although late relapses may occur, they

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are infrequent, with a recent report identifying only 7% of first relapses occurring more than 5 years after diagnosis in the immunochemotherapy era.[8] Traditionally, clinical studies of DLBCL have used progression-free survival and/or overall survival (OS) as outcomes. However, the event rate slows significantly approximately 12 months after diagnosis, and incorporation of late events can be complicated by competing risks, especially in older patients with comorbid health conditions.

On the basis of these clinical observations, we examined the type and timing of events and evaluated OS and cause-specific survival conditional on being alive and disease-free at 12 and 24 months from diagnosis in patients with DLBCL who were treated with immunochemotherapy. Given the competing risk of death in this generally older population (median age at diagnosis, 60 years), we also compared the OS rate to that expected from the general population, accounting for age and sex. We replicated our main results in independent studies from France. Finally, we assessed the impact of using event-free survival status at 24 months from diagnosis (EFS24) as a primary end point for the design of future treatment trials of DLBCL.

PATIENTS AND METHODS

This study was reviewed and approved by the human subjects institutional review board at the Mayo Clinic and the University of Iowa, and written informed consent was obtained from all participants. Patients were prospectively enrolled onto the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE)[11-13] or enrolled onto North Central Cancer Treatment Group NCCTG-N0489.[14] The MER cohort consisted of all patients with newly diagnosed DLBCL who received rituximab and anthracycline-based chemotherapy as their initial therapy. All diagnoses were confirmed by a study hematopathologist. Patients with primary mediastinal lymphoma were included; however, patients with primary CNS lymphoma, post-transplantation lymphoproliferative disorder, transformation of a previously diagnosed lymphoma, or DLBCL in association with HIV infection were excluded. Baseline clinical, laboratory, and treatment data were abstracted from medical records by using a standard protocol (MER) or per clinical trial protocol (NCCTG-N0489 [NCT00301821]). Loss to follow-up was low, since all patients were systematically contacted every 6 months for the first 3 years and then annually (MER)[11-13] or per clinical trial protocol (NCCTG-N0489).[14] Disease progression or relapse, re-treatment, and death were verified through review of pathology and medical records. Unplanned consolidative radiation therapy, but not radiation therapy as part of the initial treatment plan, was considered a re-treatment. Cause of death was determined by review of death certificates and medical records by using a standard definition developed for Eastern Cooperative Oncology Group ECOG-E4494.[4] Death as a result of disease included progressive/refractory disease not responding to treatment irrespective of other causes of death, cardiac deaths attributable to anthracycline toxicity, and deaths secondary to infections for patients actively receiving chemotherapy. Death unrelated to lymphoma included deaths that were considered independent of malignant lymphoma or chemotherapy treatments (eg, stroke, suicide, accidents).

Replication Study

Data for replication were obtained from an external set of patients with DLBCL who were treated with immunochemotherapy from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien 2003B (LNH2003B) program[15-19] and hospital-based registry in Lyon, France. The LNH2003B program of the GELA consisted of six prospective multicenter studies of patients with DLBCL older than age 18 years. Patients were stratified on age and age-adjusted International Prognosis Index for treatment allocation in four randomized phase III and two phase II studies (details in the Data Supplement). All patients had a pathology review confirming the DLBCL diagnosis. In this GELA program, during the first 2 years after treatment, assessment consisted of physical examination and laboratory tests every 3 months and computed tomography scans of the chest, abdomen, and pelvis every 6 months. Thereafter, physical examination and laboratory tests were done every 6 months and computed tomography scans every year for 5 years. The Lyon registry consisted of all patients with newly diagnosed DLBCLs treated with immunochemotherapy in routine clinical practice at the Léon Bérard Cancer Center between August 1998 and December 2008 and observed through 2010. Further details on these studies are in the Data Supplement.

Statistical Methodology

OS was defined as time from diagnosis until death as a result of any cause; cause-specific survival was summarized using common causes of death. Event-free survival (EFS) was defined as time from diagnosis until relapse or progression, unplanned re-treatment of lymphoma after initial immunochemotherapy, or death as a result of any cause. EFS indicators at predefined cut points (ie, EFS at 12 months [EFS12] or EFS at 24 months [EFS24]) were defined on the basis of EFS status at the indicated cut point after date of diagnosis. Kaplan-Meier curves were used to display survival curves. Event decomposition was performed by using a competing risk approach.[20] Expected survival accounting for age and sex was generated in R by using the general US (survexp.us)[21] and French (survexp.fr)[22] populations as reference groups for the US and French studies, respectively.[22-24] Observed versus expected OS was plotted by using a conditional approach[25] and summarized by using standardized mortality ratios (SMRs) of observed to expected deaths.[26] Simulation studies were performed to compare the power of continuous EFS to a dichotomous EFS24 end point (Data Supplement). All analyses were performed by using SAS v9.2 (SAS Institute, Cary, NC) and R v2.13.0.

RESULTS

Patient Characteristics

In all, 767 patients with newly diagnosed DLBCL who were treated with rituximab and anthracycline-based chemotherapy were enrolled onto the SPORE MER from 2002 to 2009 or the NCCTG-N0489 clinical trial from 2006 to 2007. Median age was 63 years (range, 18 to 92 years) and 53% were male (Table 1). At a median follow-up of 60 months (range, 8 to 116 months), 299 patients (39%) had an event and 210 patients (27%) had died. Kaplan-Meier estimates for the percentage of patients achieving EFS12 and EFS24 was 77% (95% CI, 74% to 80%) and 71% (95% CI, 67% to 74%), respectively.

Description of Events

An event decomposition was performed to elucidate the risk of relapse compared with other types of events, such as treatment-related death, relapse with indolent non-Hodgkin lymphoma, and death as a result of other causes. At the time of diagnosis, the vast majority of future events were a result of DLBCL relapse (Fig 1A) with a 5-year risk of relapse of 30% (95% CI, 26% to 33%). Future risk of other event types at the time of diagnosis was low, with 5-year risks no greater than 5% for other event types, including indolent non-Hodgkin lymphoma relapse. Examination of the relapse risk at diagnosis shows that 70% of DLBCL relapses occur within the first year from diagnosis (1-year risk, 21%; 95% CI, 18% to 24%) with a continued declining relapse rate as the time from diagnosis increased. Thus, once a patient completed therapy and achieved EFS12, the risk of future relapse in the following 5 years (Fig 1B) dropped to only 13% (95% CI, 9% to 17%). In patients achieving EFS24, the risk of future DLBCL relapse in the following 5 years improved to 8% (95% CI, 5% to 12%), which was the same as the risk of death as a result of unrelated causes (8%; 95%

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Table 1. Patient Characteristics

Characteristic	US Data Sets						French Data Sets						All Patients (N = 1,587)	
	MER (n = 680)		NCCTG-N0489 (n = 87)		All (N = 767)		Lyon, France (n = 220)		GELA (n = 600)		All (N = 820)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years														
Median	63		60		63		67		61		61		62	
Range	18-92		29-82		18-92		19-90		18-93		18-93		18-93	
≥ 60	387	57	42	48	429	56	130	59	286	48	416	51	845	53
Male sex	359	53	47	54	406	53	106	48	349	58	455	55	861	54
LDH > ULN	342	55	60	69	402	57	158	72	332	55	490	60	892	58
Stage III to IV	412	61	69	79	481	63	140	64	406	67	546	67	1,027	65
≥ 2 Extranodal sites	127	19	22	25	149	19	57	26	217	36	274	33	423	27
ECOG PS ≥ 2	120	18	9	10	129	17	49	22	103	17	152	19	281	18
IPI score														
0-1	242	36	23	26	265	35	61	28	202	34	263	32	528	33
2	186	27	24	28	210	27	58	25	129	22	185	23	395	25
3	168	25	29	33	197	26	61	23	141	24	192	23	389	25
4-5	84	12	11	13	95	12	52	24	128	21	180	22	275	17
EFS12														
Kaplan-Meier estimate	76		82		77		78		81		80		78	
95% CI	73 to 80		74 to 90		74 to 80		73 to 84		78 to 84		77 to 83		76 to 80	
EFS24														
Kaplan-Meier estimate	70		74		71		71		73		73		71	
95% CI	67 to 74		65 to 83		67 to 74		66 to 77		70 to 77		70 to 76		69 to 73	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS12, event-free survival at 12 months; EFS24, event-free survival at 24 months; GELA, Groupe d'Etude des Lymphomes de l'Adulte; IPI, International Prognostic Index; LDH, lactose dehydrogenase; MER, Molecular Epidemiology Resource; NCCTG, North Central Cancer Treatment Group; ULN, upper limit of normal.

CI, 4% to 12%; Fig 1C). Achieving additional event-free time from diagnosis resulted in only small gains in future DLBCL relapse risk (Data Supplement).

Comparison of Study Group Survival to That of the General Population

At diagnosis, patients had a significantly decreased survival compared with the age- and sex-matched general population, with an SMR of 2.88 (95% CI, 2.51 to 3.30; $P < .001$; Fig 2A). Survival improved as patients remained in a disease-free state, with patients achieving EFS12 having a subsequent SMR of 1.40 (95% CI, 1.10 to 1.76; $P = .0038$; Fig 2B); the SMR was no longer significant when patients achieved EFS24 (SMR, 1.18; 95% CI, 0.89 to 1.57; $P = .25$; Fig 2C). Similar results were seen in cause of death patterns (Fig 3), with little future lymphoma-related mortality in patients achieving EFS12 (Fig 3B) or EFS24 (Fig 3C). In contrast, most patients with an event in the first 12 or 24 months died as a result of lymphoma (Data Supplement). In a sensitivity analysis, results were similar when using a progression-free definition in which consolidative re-treatment was not considered an event (Data Supplement).

Replication of Survival Results

To replicate the survival findings, an external validation data set of 820 patients with newly diagnosed DLBCL who were treated with rituximab and anthracycline-based chemotherapy was assembled consisting of patients from the GELA LNH05-1B, LNH03-1B, LNH03-2B, LNH03-3B, LNH03-6B and LNH03-7B clinical trials and a hospital-based registry in Lyon, France. Event decomposition and cause of death data were not available. Median age was 62 years (range, 18 to 93 years) and 55% were male (Table 1). At a median follow-up of 42 months (range, 1 to 129 months), 290 patients (32%) had an event and 221 (24%) had died. Kaplan-Meier estimates for achieving EFS12 and EFS24 were 80% (95% CI, 77% to 83%) and 73% (95% CI, 70% to 76%), respectively. Results similar to those in the US data set were observed for patient survival when compared with age- and sex-matched survival in the French population. French patients had a larger survival deficit than the US patients at diagnosis (SMR, 4.99; 95% CI, 4.34 to 5.75; $P < .001$; Fig 4A) but showed improvement in survival as the duration of the disease-free period increased (EFS12 SMR, 2.06; 95% CI, 1.57 to 2.70; $P < .001$; Fig 4B). As seen in the US data set, there was no significant difference in subsequent survival compared with that for the general population in patients who were disease-free at 24 months (SMR, 1.09; 95% CI, 0.69 to 1.74; $P = .71$; Fig 4C).

Additional Analyses in the Pooled Data Sets

To increase power, we next pooled the US and French data sets. In the pooled data, survival after a relapse, re-treatment, or progression event (RRPE) was poor, with a median OS of 13 months (95% CI, 10 to 16 months) after an event other than death. Patients with an RRPE within 1 year from diagnosis had inferior survival (median OS, 8 months; 95% CI, 7 to 10 months) compared with patients with an RRPE between 12 and 24 months (median OS, 28 months; 95% CI, 15 to 50 months) or patients with an RRPE after 24 months (median OS, 36 months; 95% CI, 29 to 55 months; $P < .001$). However, 5-year survival rates were similar across the three groups (Data Supplement);

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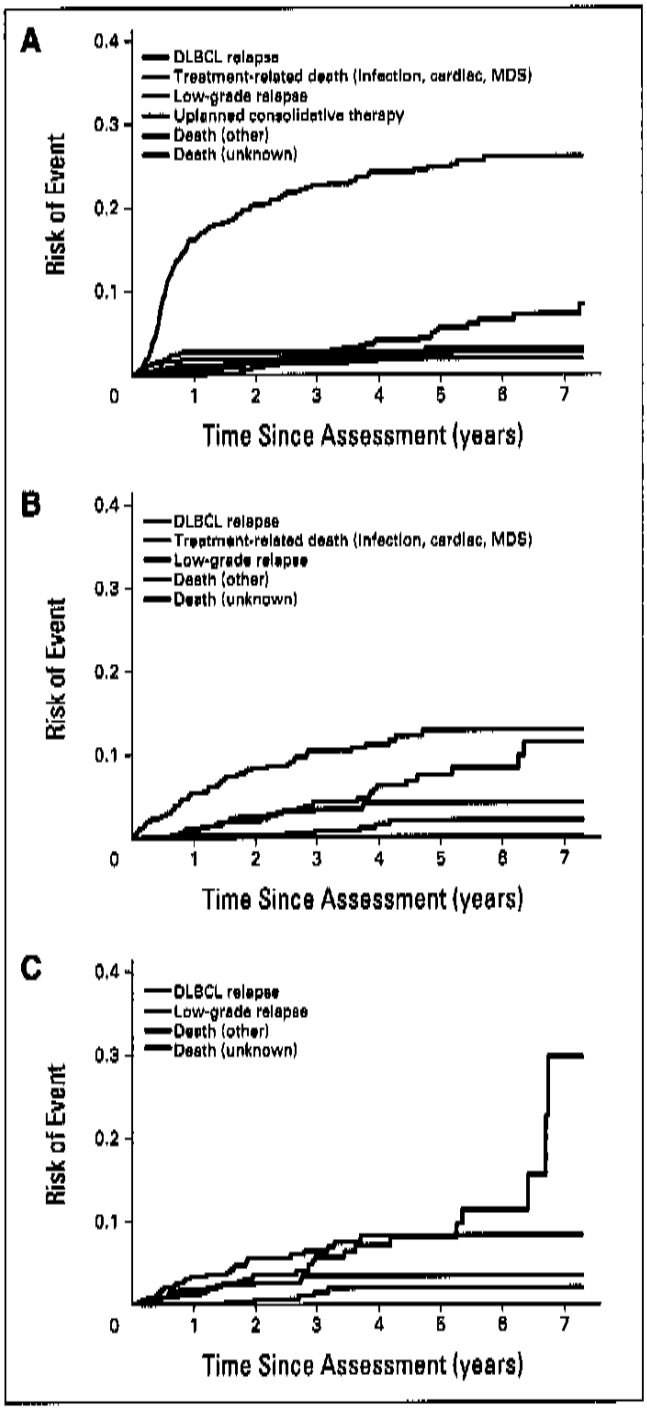

Fig 1. Event description in the US cohort at diagnosis, in patients achieving event-free survival at 12 or 24 months. (A) Assessment at diagnosis; (B) event free 12 months since diagnosis; (C) event free 24 months since diagnosis. DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome.

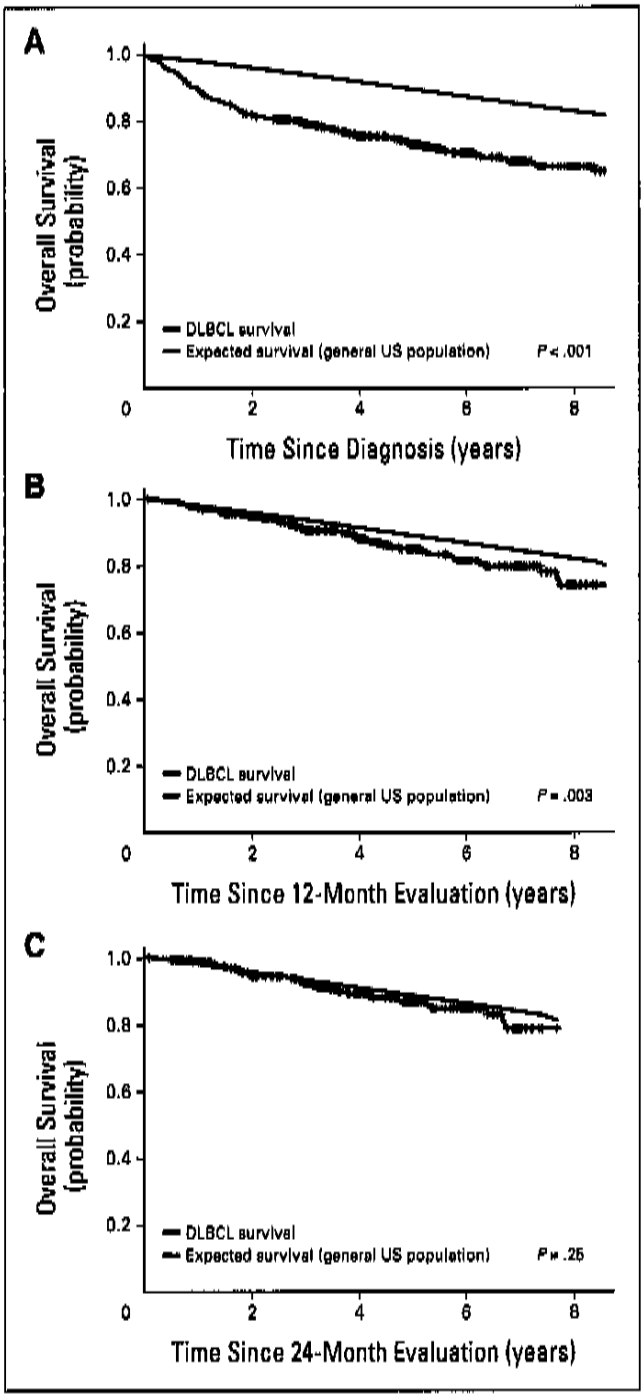

Fig 2. Overall survival versus expected survival in US cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

additional follow-up on these cohorts of patients will be needed to determine whether there is superior long-term survival for late-relapsing patients.

Pretreatment prognostic factors showed an influence on survival, with high-risk subgroups having greater SMR than low-risk subgroups (Fig 5A), and demonstrated continued impact on post-therapy prognosis for patients achieving EFS12 (Fig 5B). The only subgroup that did not show a significantly reduced survival compared with the age- and sex-matched general population was in patients achieving EFS12 with stage I to II disease (US SMR, 1.08; 95% CI, 0.71 to 1.59; $P = .76$; French SMR, 1.35; 95% CI, 0.64 to 2.48; $P = .43$). Pretreatment prognostic factors no longer identified any patient subgroups with reduced survival once patients achieved EFS24 (Fig 5C).

In sensitivity analyses, excluding primary mediastinal B-cell lymphoma and GELA patients who received rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) and consolidation with autologous stem-cell transplantation did not significantly change results (data not shown).

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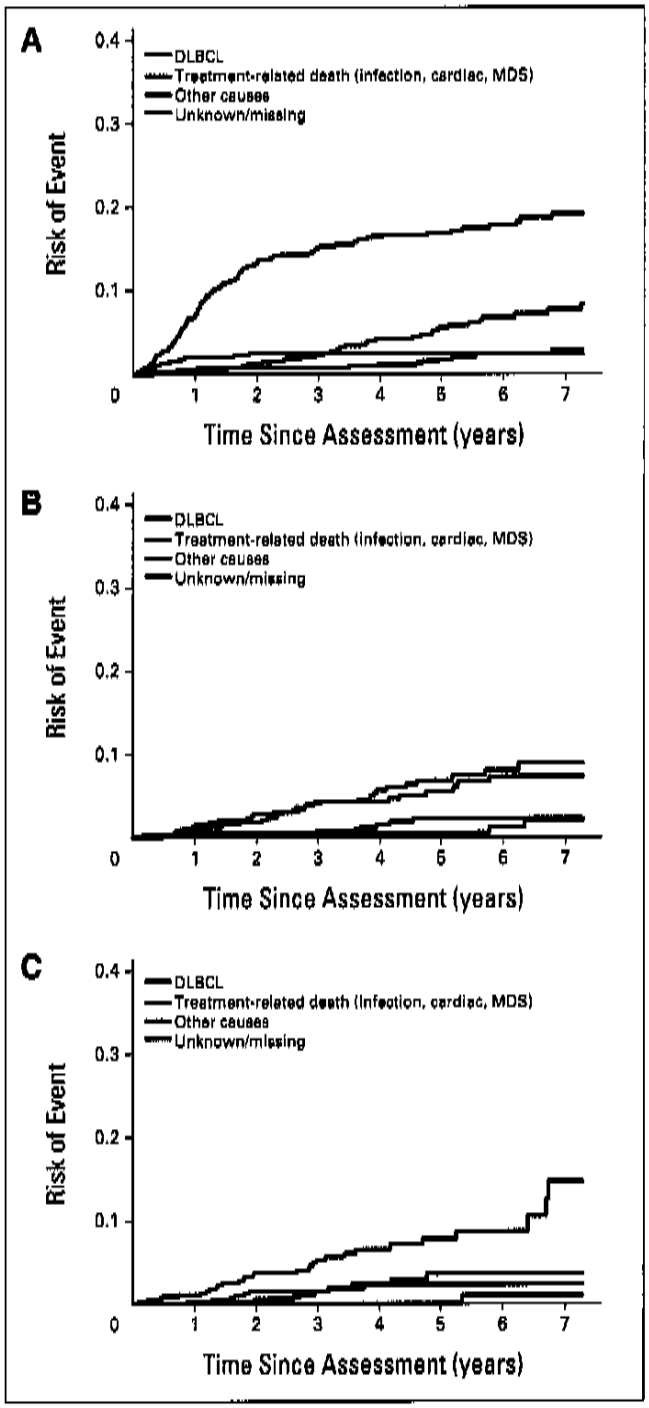

Fig 3. Cause of death in the US cohort at diagnosis, in patients achieving event-free survival at 12 or 24 months. (A) Assessment at diagnosis; (B) event free 12 months since diagnosis; (C) event free 24 months since diagnosis. DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome.

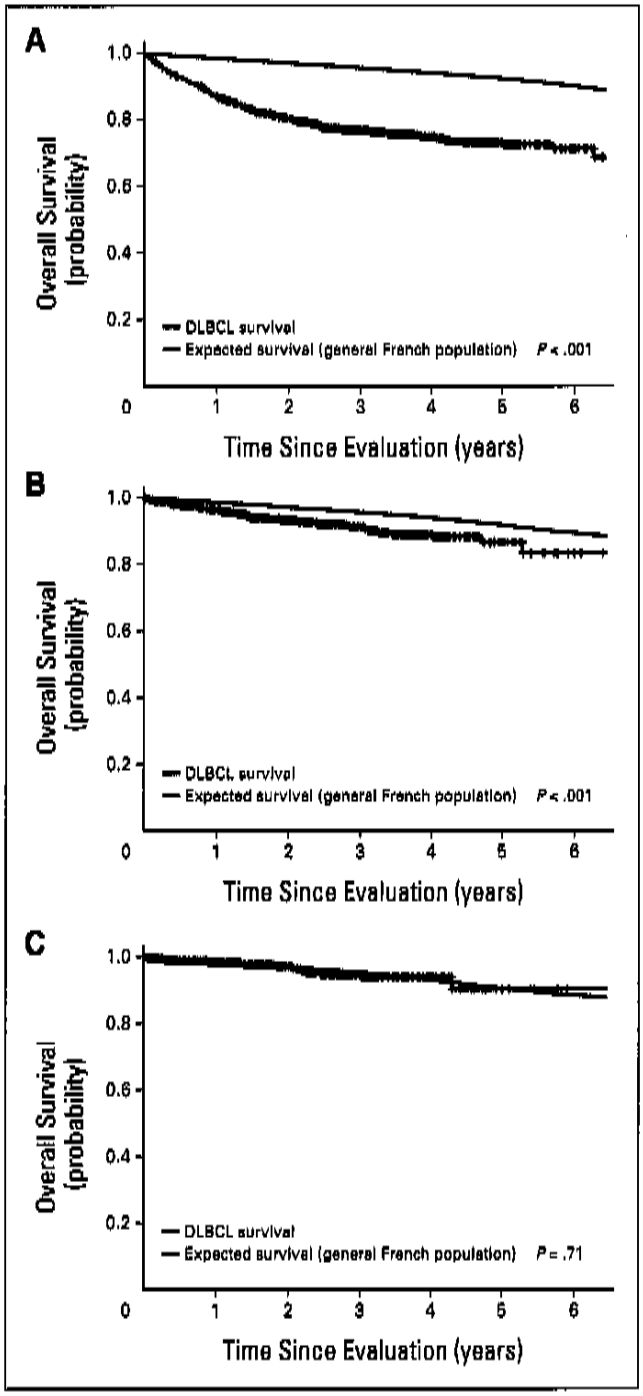

Fig 4. Overall survival versus expected survival in French cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

Simulation Study of EFS24 and Continuous EFS

Simulated clinical trials were performed to compare the power of EFS24 and continuous EFS to detect a difference in the DLBCL relapse rate of treatment arms in the presence of a competing risk of unrelated death (Data Supplement). Two primary effect models were assumed: one in which the treatment improved the risk of relapse only in the first year following diagnosis (ie, 12 months [12M]) and one in which the treatment improved the risk of relapse during the entire course of follow-up (all follow-up [ALLFU]; Data Supplement). Each simulated trial had an enrollment of 400 patients (200 in each arm) with an enrollment period of 3 years and a varied follow-up period of 24 to 60 months (median follow-up, 3.5 to 6.5 years). Under the 12M model, in which improvement is limited to the first 12 months when the relapse rate is highest, EFS24 (average power of 76% to detect a 50% reduction in DLBCL relapse between arms) was slightly more powerful than continuous EFS (average power of 69%; Data Supplement). Under the ALLFU model, continuous EFS (average power of 95% to

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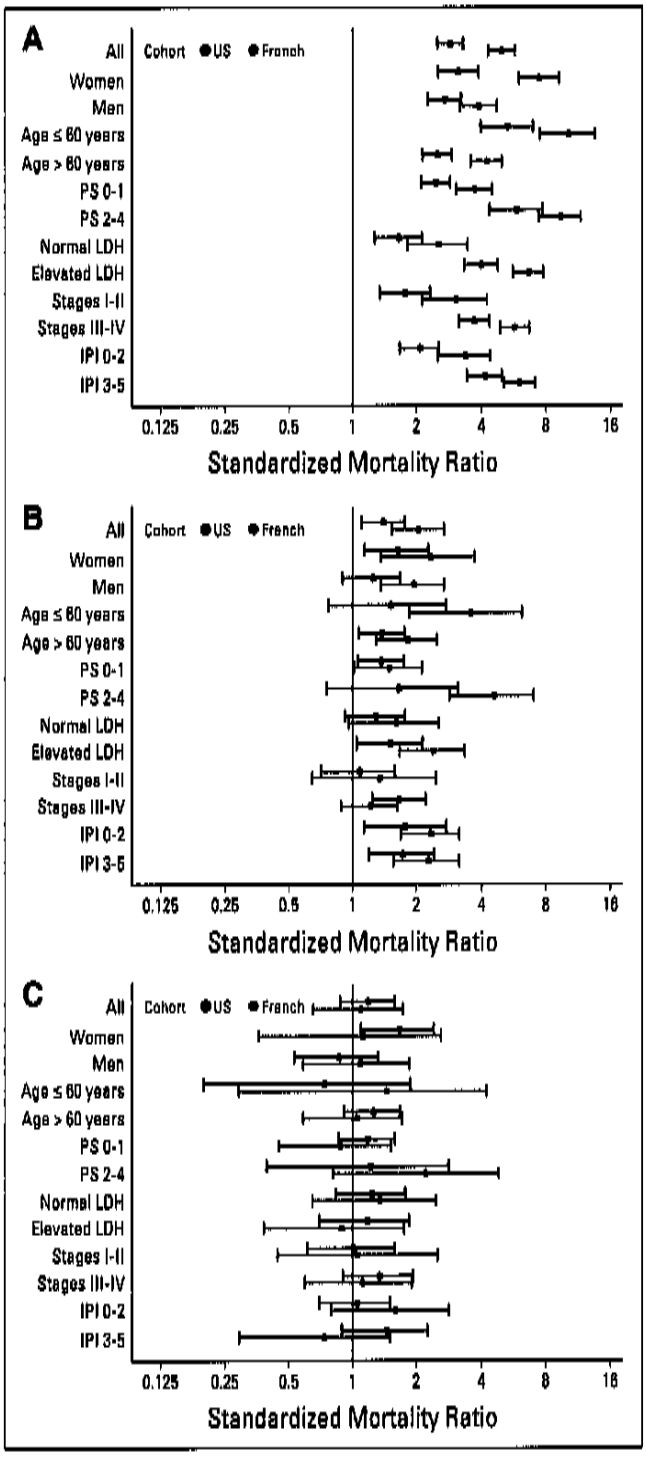

Fig 5. Forest plots of standardized mortality ratio in combined data set by diffuse large B-cell lymphoma subgroups at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) All patients since diagnosis; (B) EFS12 patients from 12 months since diagnosis; (C) EFS24 patients from 24 months since diagnosis. IPI, International Prognosis Index; LDH, lactate dehydrogenase; PS, performance status.

detect a 50% reduction in DLBCL relapse between arms) was slightly more powerful than EFS24 (average power of 91%). The models simulated were selected to be at the extreme ends of potential treatment effects. It is likely that the effect measured in future trials will lie somewhere in between, suggesting that there is comparable power between the two end points. Of note, the power for continuous EFS decreased with additional follow-up time under the 12M effect model and remained relatively consistent under the ALLFU effect model.

DISCUSSION

This study demonstrates that patients with DLBCL treated with standard immunochemotherapy who remain event-free 2 years after diagnosis have excellent long-term outcome with little lymphoma-related mortality in the follow-up period observed in this study. In other words, patients who have achieved EFS24 have subsequent survival comparable to that of the age- and sex-matched general population (ie, a normal life expectancy).

The strengths of the study include the large series of prospectively enrolled patients treated with immunochemotherapy, replication in an independent data set, and patients enrolled onto both registry and trial-based studies from the United States and Europe. This is one of the largest series of patients with DLBCL studied for outcome in the immunochemotherapy era and should have excellent generalizability. The major limitations of this analysis are the under-representation of very elderly patients (older than age 85 years) in our cohort and the lack of long-term (ie, > 10 years) follow-up since the immunochemotherapy era began in the early 2000s, and our study includes patients prospectively enrolled from the start of this treatment period.[27] In addition, these findings were in patients treated with anthracycline-based immunochemotherapy regimens, and extrapolation of results to other treatments would be speculative. We also did not assess the impact of management after relapse, which was beyond the scope of this study. It is important to note, as well as communicate to patients, that achieving EFS24 does not establish cure, since approximately 8% of patients event-free at 24 months had a subsequent relapse of DLBCL in the US data set. However; for the roughly 70% of newly diagnosed patients achieving EFS24, as well as perhaps stage I to II patients achieving EFS12, this does mean that the patient now has an OS from that point forward that is equivalent to that of the general non-DLBCL population. In other words, these patients now have a normal life expectancy, and they are now also at greater risk of dying from causes other than their DLBCL. For most patient groups, there is still a reduced survival in patients achieving the EFS12 end point; most of this added mortality in our series was from lymphoma resulting in death (results not shown). Importantly, these survival deficits appear to be resolved in patients once they achieve EFS24. Further follow-up will be needed to look for potential effects of long-term treatment on survival.

These results have important implications in planning new prospective clinical trials for DLBCL, and they support the use of EFS24 as the primary end point. Analysis of DLBCL can be challenging in that the majority of patients can be cured by their initial therapy, and the validity of time-to-event end points such as EFS is influenced by causes other than the intended element being studied (ie, DLBCL relapse/progression). Event decomposition in the US data shows that once patients achieve 24 months of follow-up, at least 50% of any future events will be deaths unrelated to DLBCL from patients in remission. Thus, in contrast to the general rule of thumb "the more follow-up the better," observing patients with DLBCL beyond 24 months for relapse provides little benefit, confirmed by our simulation studies. In addition, examination of the EFS curves in the

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practice-changing GELA LNH 98-5,[3] ECOG-E4494,[4] and MabThera International Trial (MiNT) group[6] trials shows that the separation of outcome between arms occurs within 24 months on each study. Given that the vast majority of DLBCL relapses occur in the first 24 months, any improvement in outcome is expected to manifest in the first 24 months and thus would be captured by the EFS24 end point. EFS24 is also an appealing end point for clinical trial design in DLBCL. It requires only 2 years of follow-up, and studies can be evaluated sooner than when using continuous EFS. It can potentially make trial design more accurate since the standard exponential model used for power calculations is a poor fit for the typical event distribution of DLBCL; the use of EFS24 also avoids potential violations of Cox proportional hazards models. Thus, when the primary goal is comparison of disease-related events, we recommend using EFS24 as the end point for outcome studies or clinical trials of patients with newly diagnosed DLBCL. Additional follow-up beyond 24 months is still needed for assessment of overall survival and to monitor for late complications such as progressive multifocal leukoencephalopathy or cardiomyopathy.

These data provide important insight into developing informed clinical strategies for post-therapy surveillance and management. The excellent outcome of patients achieving EFS24, and perhaps patients with low-stage disease who achieve EFS12, call into question the utility of routine surveillance imaging for patients in remission beyond these time points. Investigation of strategies involving prolonged postremission therapy will also benefit from a more precise understanding of expected outcomes from key landmark time points. Clinical risk prediction models for achieving EFS24 should be developed to identify patients at high risk of early relapse to help prioritize patients for clinical trials or alternative management strategies. Finally, these results will help physicians and patients develop a survivorship care plan, which will also need to address nonlymphoma health issues and potential late effects of therapy that are perhaps more likely to have an impact on life expectancy.

In conclusion, patients with newly diagnosed DLBCL who were treated with immunochemotherapy who are event-free 24 months after diagnosis have excellent outcome, with an OS equivalent to that of the age- and sex-matched general population in both US and French data sets. Consideration of EFS24 as an end point in clinical trials and biologic studies of newly diagnosed DLBCL is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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GLOSSARY TERMS

immunochemotherapy: a combination of immunotherapy (eg, anti-CD20) and chemotherapy.

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EXHIBIT 3

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ORIGINAL REPORT

Lymphoma Recurrence 5 Years or Later Following Diffuse Large B-Cell Lymphoma: Clinical Characteristics and Outcome

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Purpose
Patients with diffuse large B-cell lymphoma (DLBCL) usually relapse early following diagnosis but some relapses happen at 5 years or later. Few data exist regarding clinical characteristics and outcome of these patients.

Patients and Methods
We performed a retrospective analysis of all patients from two centers in Lyon, France, between 1985 and 2003 who had a biopsy-proven relapse 5 years or later following diagnosis of DLBCL. All available biopsies were reviewed and immunohistochemistry was completed.

Results
Among 1,492 patients with DLBCL, 54 were eligible. At diagnosis, 63% of patients had stage I-II, 82% had low/low-intermediate International Prognostic Index (IPI) score, 65% had extranodal involvement, 24% had an indolent component associated with DLBCL, 57% had germinal center phenotype, and 43% had non-germinal center phenotype. Median time from diagnosis to relapse was 7.4 years (range, 5 to 20.5 years). At time of relapse, 83% had DLBCL histology, and 17% had indolent histology. Having an indolent component at diagnosis was associated with indolent histology at relapse (P = .028). Five-year event free-survival (EFS) was 17% for patients with DLBCL relapse and 61% for patients with indolent relapse (P = .027). Five-year overall survival was 27% for patients with DLBCL and 75% for patients with indolent relapse (P = .029). For DLBCL relapse, 3-year EFS was 56% versus 18% with autologous stem-cell transplantation or not, respectively (P = .0661).

Conclusion
Patients with DLBCL who had a late relapse usually had localized stage, favorable IPI score, and extranodal involvement at diagnosis. The outcome of patients with DLBCL at time of relapse remains poor, and aggressive treatment such as autologous stem-cell transplantation should be pursued whenever possible. Biopsy at relapse is essential because some patients relapse with indolent histology.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) represents 30% of non-Hodgkin's lymphoma. Long-term disease-free survival is now a reality for at least 50% of patients and can reach more than 80% when lymphoma is localized at diagnosis.[1,2] Unfortunately, some patients eventually relapse, mainly in the first 2 to 3 years following treatment. Late relapses that occur after 5 years have been described but are considered rare events.[3-9]

Patients with late relapse seem to constitute a distinct subgroup with different disease behavior than patients with early relapse. Some would consider late-relapsing patients as having a good prognosis. However, few data exist regarding evolution of these patients, and prognosis at relapse is of primary importance in the choice of therapeutics. In addition, clinical characteristics at diagnosis of patients who have late relapses are not well defined. DLBCL usually relapses with DLBCL histology, but indolent histologies have been described over the years.[6,7,10-12] True incidence for indolent relapses and their evolution are not well known. To better understand clinical characteristics and prognosis of patients with DLBCL who had a late relapse, we

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decided to perform a retrospective study of all patients with DLBCL in Lyon, France, who presented with a relapse 5 years or later following diagnosis.

PATIENTS AND METHODS

Patients

Data on patients with DLBCL treated between 1985 and 2003 in Lyon, France, in two centers—Centre Hospitalier Lyon-Sud (CHLS) and Centre Léon-Bérard (CLB)—were retrieved from the respective center's database for each patient. All patients with a complete response (CR) or complete response unconfirmed (CRu) to initial treatment and who had a biopsy-proven relapse 5 years or later following diagnosis were included in this analysis. All non-Hodgkin's lymphoma histologies at relapse were included. Primary CNS lymphoma at diagnosis was excluded. Original patient records were reviewed to obtain the most precise information available regarding clinical presentation, disease course, and treatment. Efforts were made to complete missing information in the database.

Pathology

All pathology reports at diagnosis and at relapse were revised by expert hematopathologists (F.B. and C.C.-C.). All available pathology specimens were recovered in order to revise diagnosis and complete missing immunohistochemistry data. Only patients with initial diagnosis of DLBCL corresponding to WHO definition were included.[13] Patients with a history of indolent lymphoma and transformation were excluded. However, patients with DLBCL presenting with an indolent component at the same time, either in bone marrow or elsewhere, were included.

Standard immunohistochemical techniques were used on paraffin-embedded tissues fixed with formalin or Bouin's solution on an automated immunostainer (Benchmark; Ventana Medical Systems, Illkirch, France), according to the manufacturer's instructions. Appropriate positive and negative controls were run for each antibody. The immunohistochemical panel included B-cell markers (L26/CD20 and monoclonal CD79a [clone HM57],

Table 1. Patient Characteristics at Initial Diagnosis According to Histology at Relapse

Characteristic	All Patients		DLBCL Relapse		Indolent Relapse*		P
	No.	%	No.	%	No.	%	
No. of patients	54		45		9		
Age, years							
Median	57		57		58		
Range	25-76		25-76		35-71		
Sex (men:women)		70:30		71:29		67:33	1.00
Stage							
I-II		63		67		44	.27
III-IV		37		33		56	
B symptoms		22		23		22	1.00
Extranodal disease		65		62		78	.47
No. of extranodal sites							
0		35		38		22	.16 (0-1 v ≥ 2)
1		48		49		44	
≥ 2		17		13		33	
Extranodal sites							
Bone marrow	8		6		2		
Stomach	6		4		2		
Testis	4		4		0		
Nasal and sinus	4		4		0		
Tonsil	4		3		1		
Other†	25		18		7		
LDH above normal		39		43		22	.45
Performance status							
0-1		83		85		75	.61
2		17		15		25	
IPI score							
0-2		82		84		71	.59
3-5		18		16		29	
Treatment							
CHOP-like or ACVBP		89		87		100	.57
Other chemotherapy‡		9		11		0	
Rituximab		2		2		0	
Autologous stem-cell transplantation		2		2		0	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone.

*Only patients with indolent lymphoma are included in this subgroup. Patients with DLBCL who have an associated indolent component are included in the subgroup DLBCL relapse.

†Meningeal, epidural, bone, breast, small bowel, colon, liver, pancreas, peritoneal, lung, pleura, parotid, and skin.

‡Cyclophosphamide, doxorubicin, cisplatin; mechlorethamine, vincristine, procarbazine, prednisone; doxorubicin, bleomycin, vinblastine; cyclophosphamide, vincristine, doxorubicin, methotrexate, prednisone; cyclophosphamide, vincristine, prednisone.

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DAKO, Glostrup, Denmark), a T-cell marker (polyclonal CD3; DAKO), and monoclonal antibodies against CD5 (clone 4C7; Novocastra Laboratories, Newcastle, United Kingdom), CD10 (clone 56C6; Novocastra Laboratories), CD23 (clone 1B12; Novocastra Laboratories), CD43 (clone MT1; Novocastra Laboratories), CD138 (clone MI15; DAKO), bcl6 (clone PG-B6p; DAKO), bcl2 (clone 124; DAKO), and MUM-1/IRF4 (clone MUM-1p; DAKO). Expression of each marker was evaluated in the tumoral lymphoid cells. Germinal center (GC) and non-germinal center (non-GC) phenotype were determined by immunohistochemistry according to Han's algorithm,[14] using a cutoff level of 30%.

Bone marrow biopsy specimens that were considered infiltrated by lymphoma at the time of diagnosis were retrieved. They were reviewed by an expert hematopathologist (M.F.) to assess infiltration status. Infiltration when present was characterized by the size of lymphoma cells in the bone marrow.

Statistical Analysis

Event-free survival (EFS) was measured from the date of first relapse until second relapse or death of any cause. Overall survival (OS) was measured from the date of first relapse until death from any cause or last follow-up evaluation. Survival curves were estimated using the Kaplan-Meier method[15] and compared using the log-rank test.[16] Categoric data were compared using Fisher's exact test. Differences between the results of comparative tests were considered significant if the two-sided P value was $< .05$. All statistical analyses were performed using JMP 7.0.1 software (SAS Institute, Cary, NC).

RESULTS

A total of 1,492 patients with DLBCL were identified from databases: 1,107 from CHLS and 385 from CLB. Following initial treatment, 1,038 patients were in CR and 373 had a relapse, including 308 with a relapse at < 5 years following diagnosis. Thus, 65 patients presented with a relapse 5 years or later following diagnosis. Eleven patients were excluded for the following reasons: initial diagnosis was not DLBCL at time of review (five), diagnosis at relapse was not lymphoma (one), biopsy was not done at relapse (three), or records were missing (two). A total of 54 patients had a biopsy-proven relapse 5 years or later following diagnosis (3.6% of the total DLBCL patients): 44 from CHLS and 10 from CLB. Forty-five patients had a relapse with DLBCL histology and nine patients had indolent histology exclusively.

Patient Characteristics at Initial Diagnosis

Patient characteristics at initial diagnosis are presented in Table 1. Median age was 57 years and 70% of patients were men. Sixty-three percent had localized disease (37% stage I and 26% stage II) and 65% had extranodal disease. Main extranodal sites were bone marrow (eight), stomach (six), nose and sinus (four), testis (four), tonsils (four), skin (three), small bowel (three), and lung (three). Fifty percent had primary extranodal disease. Eighty-two percent had an International Prognostic Index (IPI) score of low (0-1) or low-intermediate (2).

Initial clinical characteristics were the same whether patients had DLBCL or indolent histology at relapse. Sixty-seven percent of patients who relapsed with DLBCL histology had stage I or II at diagnosis versus 44% for those with indolent relapse ($P = .27$). Presence of extranodal disease was evenly distributed between patients with DLBCL relapse (62%) or indolent relapse (78%). Other clinical characteristics such as time to relapse, B symptoms, performance status, IPI score, lactate dehydrogenase, β_2-microglobulin levels, and bulky disease were not predictive of histology at relapse (data not shown).

Table 2. Pathologic Characteristics at Diagnosis According to Histology at Relapse

Characteristic	All Patients	No. With DLBCL Relapse*	No. With Indolent Relapse	P
Pure DLBCL	41/54	37/45	4/9	.028
DLBCL with indolent component	13/54	8/45	5/9	
Indolent component associated with DLBCL				
MALT lymphoma	7	5	2	
Splenic marginal zone lymphoma	1	1	0	
Follicular lymphoma	5	2	3	
CD20+	46/46	37/37	9/9	1.00
Bcl-6 protein+	9/18	6/14	3/4	.58
CD10+	10/36	8/31	2/5	.60
MUM1+	11/23	11/20	0/3	.22
Bcl-2 protein+	19/29	15/25	4/4	.27
GC phenotype	12/21	9/17	3/4	.60
Non-GC phenotype	9/21	8/17	1/4	.60

Abbreviations: DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; GC, germinal center.
*No. with positive data for the No. of patients analyzed.

Pathologic characteristics at diagnosis are presented in Table 2. Twenty-four percent of patients (13) had a DLBCL histology associated with an indolent component: seven patients had mucosa-associated lymphoid tissue (MALT) lymphoma (including four from gastric MALT lymphoma), one had splenic marginal zone lymphoma, and five had follicular lymphoma. For patients with a gastric MALT component, no *Helicobacter pylori* infection was found. The other patients (76%) had DLBCL without an indolent component. Having an indolent component at diagnosis was associated with indolent histology at relapse ($P = .028$). Fifty-seven percent had a GC and 43% had a non-GC phenotype. No marker was predictive of histology at relapse (data not shown).

Initial Treatment

Because patients included in this analysis were treated over two decades, initial treatments were heterogeneous. However, of the 98% of patients who received a multidrug chemotherapy regimen, 94% of treatments included anthracyclines and 89% were CHOP-like (cyclophosphamide, doxorubicin, vincristine, and prednisone) or ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; Table 1). Of 22 patients treated with CHOP-like regimens, 14 received six or more cycles and four received three or four cycles followed by radiation therapy. For the remaining four patients, two received three and four cycles of CHOP-like chemotherapy alone; for the other two patients, number of cycles was not available. Five patients received chemotherapy regimens other than CHOP-like or ACVBP: four patients were treated with other regimens because the initial diagnosis was wrong, two were treated as Hodgkin's disease (MOPP [mechlorethamine, vincristine, procarbazine, prednisone] and MOPP/AVD [MOPP/doxorubicin, vinblastine, dacarbazine]) before the diagnosis was revised later at relapse, one patient was treated as ovarian cancer (CAP [cyclophosphamide, doxorubicin, cisplatin]) before diagnosis was revised as DLBCL, and one was treated as Burkitt lymphoma (COPADM [cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate]). One patient

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Table 3. Patient Characteristics at Relapse

Characteristic	All Patients No.	All Patients %	DLBCL Relapse No.	DLBCL Relapse %	Indolent Relapse No.	Indolent Relapse %
No. of patients	54		45		9	
Median age, years	66		66		66	
Time to relapse, years						
Median	7.4		7.5		6.7	
Range	5-20.5		5-20.5		5.2-16.9	
5-10		74		73		78
> 10		26		27		22
Stage						
I-II		48		49		44
III-IV		52		51		56
Extranodal disease		68		73		44
No. of extranodal sites						
0		32		27		56
1		57		59		44
≥ 2		11		14		0
Extranodal sites						
Bone marrow	10		8		2	
Bone	4		4		0	
Skin	4		3		1	
Sinus	3		2		1	
Other*	22		22		0	
LDH above normal		53		62		22
Performance status						
0-1		80		76		100
≥ 2		20		24		0
Treatment at relapse						
ASCT	15		14		1	
Induction regimen						
CHOP-like or ACVBP	2		1		1	
R-CHOP-like or R-ACVBP	2		2		0	
Ifosfamide-etoposide-mitoxantrone	4		4		0	
R-Ifosfamide-etoposide-mitoxantrone	1		1		0	
R-ICE	4		4		0	
R-DHAP	2		2		0	
Chemotherapy without ASCT	34		27		7	
CHOP-like or ACVBP	7		4		3	
R-CHOP-like or R-ACVBP	5		5		0	
Ifosfamide-etoposide	5		5		0	
Ifosfamide-etoposide-mitoxantrone	3		3		0	
DHAP	3		3		0	
R-DHAP	1		1		0	
R-GEMOX	2		2		0	
Rituximab alone	3		1		2	
Other chemotherapy	5		3†		2‡	
Radiation therapy alone	2		2		0	
Radiation + chemotherapy	7		6		1	
No chemotherapy/no radiation	3		2		1	
Response to treatment						
Complete response		65		61		88
Partial response		25		29		0
No response		10		10		12

Abbreviations: DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; ASCT, autologous stem-cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R, rituximab; ICE, ifosfamide, carboplatin, etoposide; DHAP, dexamethasone, cisplatin, cytarabine; GEMOX, gemcitabin, oxaliplatin; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

*Brain, eye, colon, liver, muscle/soft tissue, lung, pleura, testis, thyroid, tonsil, and tongue.

†High-dose methotrexate; rituximab, cyclophosphamide, vincristine, prednisone; cyclophosphamide/carboplatin.

‡CVP, chlorambucil.

was treated for unknown reason with CVP [cyclophosphamide, vincristine, prednisone] only. Only one patient received rituximab in combination with chemotherapy, and one patient received high-dose chemotherapy/autologous stem-cell transplantation (ASCT) in first CR. One patient did not receive chemotherapy and treatment consisted only of surgery. Radiation therapy was part of the treatment for nine patients. All patients were in CR following initial treatment, because it was an inclusion criteria. Half the patients were included in Groupe d'Etude des Lymphomes de l'Adulte (GELA) studies.

Patient Characteristics at Relapse

Patient characteristics at relapse are presented in Table 3. Median age at relapse was 66 years. Median time to relapse was 7.4 years (range, 5 to 20.5 years), and 26% of late relapses happened more than 10 years after diagnosis. Only 15% of patients with initial localized disease experienced relapse at the same site (Table 4). Forty-five patients (83%) had relapse as DLBCL, and nine patients (17%) had relapse as indolent histology exclusively (six patients had relapse as follicular lymphoma, two as nodal marginal zone lymphoma, and one as extranodal MALT lymphoma). Of the 45 patients with DLBCL relapse, 18% (8 patients) showed an associated indolent component: three with gastric MALT lymphoma, two with nodal marginal zone lymphoma, one with splenic marginal zone lymphoma, and two with follicular lymphoma. At time of relapse, of patients with DLBCL histology, 54% had a GC phenotype and 46% had a non-GC phenotype. Eighty-four percent of patients expressed bcl-2 protein. Cytogenetics were available for some patients, but none had analysis at both diagnosis and at relapse.

Treatment at Relapse

Treatments were different, depending on whether DLBCL or indolent lymphoma was present at relapse. Salvage regimens for patients with DLBCL relapses were diverse (Table 3): 17 patients received rituximab in combination with chemotherapy and 14 received high-dose chemotherapy with ASCT. Most of these 14 patients (12) received BEAM [carmustine, etoposide, cytarabine, melphalan] as conditioning regimen. The main reason for not receiving ASCT was age > 65 years at relapse (22 patients). Other reasons included early death (two), patient refusal (two), cardiac failure (one), chemoresistant disease (one), and unknown reason (three). Six patients received both ASCT and rituximab at relapse. Overall response rate was 90%, including 61% with CR.

Treatments for patients with indolent histology were heterogeneous: six patients received chemotherapy, two patients received rituximab alone, and one patient had surgery to remove lymphoma

Table 4. Immunophenotype from Tumoral Lymphoid Cells at Relapse

Immunophenotype	DLBCL Relapse*	Indolent Relapse*
CD20+	41/41	7/7
Bcl-6 protein+	18/24	2/3
CD10+	13/37	3/7
MUM1+	17/27	1/3
Bcl-2 protein+	27/32	4/5
GC phenotype	15/28	
Non-GC phenotype	13/28	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; GC, germinal center.
*No. with positive data for the No. of patients analyzed.

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tissue and was observed thereafter. Only one patient proceeded to ASCT. Seven of eight patients assessable for response had CR. One patient had progressive disease following CHOP-like chemotherapy.

EFS and OS

Five-year EFS was different, depending on whether patients had DLBCL or indolent relapse (17% *v* 61%; $P = .027$; Fig 1). Five-year OS was also different for patients with DLBCL or indolent relapse (27% *v* 75%; $P = .029$). EFS and OS were the same for patients with DLBCL relapse whether or not an associated indolent component was present (data not shown). For patients with DLBCL relapse, we evaluated the impact of ASCT on outcome (Fig 2). Three-year EFS was 56% versus 18% at 3 years ($P = .0661$), and 3-year OS was 83% versus 26% ($P = .0183$) with ASCT or not, respectively. Causes of mortality after ASCT were diverse: lymphoma progression (four), acute lymphocytic leukemia 7 years post-ASCT (one), cardiac failure 43 months post-ASCT (one), and infection 5 years post-ASCT (one). We did not find any difference in EFS or OS whether patients received rituximab at relapse or not, but few patients had received rituximab. In addition, time to relapse did not have any impact on outcome (data not shown).

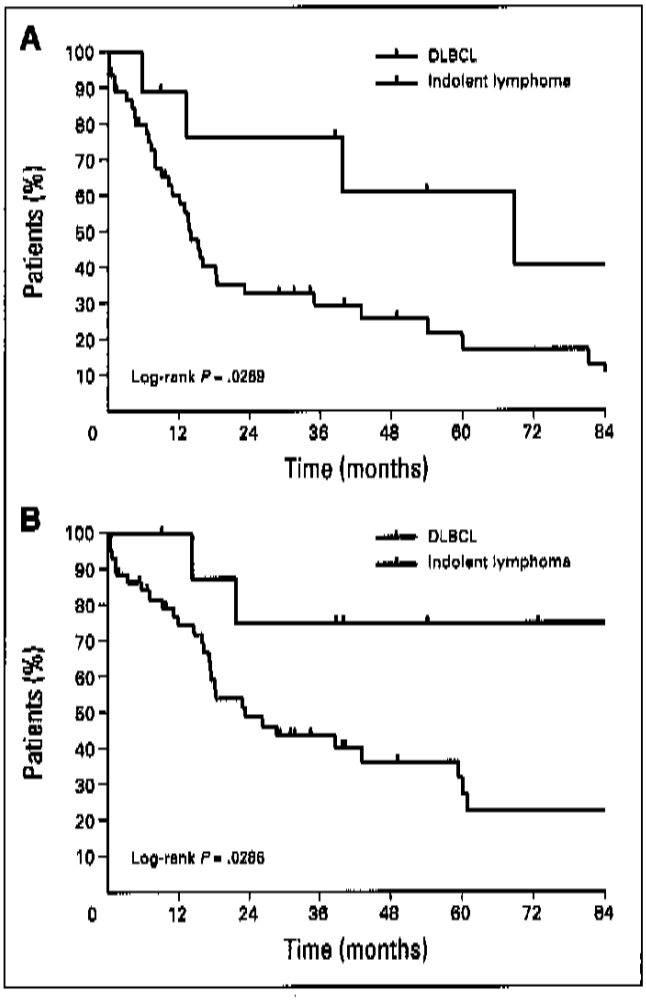

Fig 1. (A) Event-free survival and (B) overall survival of patients according to the histologic subtype at time of relapse. DLBCL, diffuse large B-cell lymphoma.

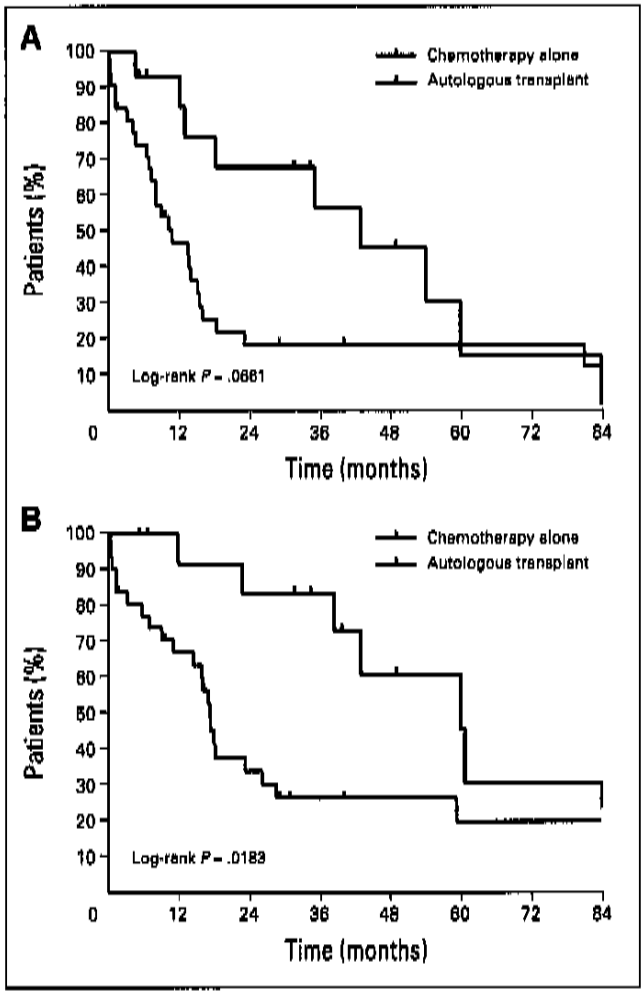

Fig 2. (A) Event-free survival and (B) overall survival of patients with diffuse large B-cell lymphoma at time of relapse according to the inclusion of high-dose therapy with autologous stem-cell transplantation in the treatment or not.

DISCUSSION

To the best of our knowledge, this study represents the largest report of patients with DLBCL who had a relapse 5 years or later following diagnosis. Some studies have been published about late relapse but most of them included patients with relapse occurring 24 to 30 months following diagnosis with few patients relapsing after 5 years.[4-8,17] A relapse after 5 years is a rare event and occurred in 3.6% of patients with DLBCL treated in Lyon from 1985 to 2003. This is in accordance with the incidence reported by others.[5]

Patients with late relapse seem to present clinical features at diagnosis that differed from those of the usual population of DLBCL. First, we found that 63% of patients had an initial localized disease. This is even higher, with 67% of early-stage disease, if we include only patients with DLBCL relapse. Second, we noticed that most patients in our series had favorable prognosis according to IPI since 82% of patients had a low or low-intermediate score. Third, 65% of patients had extranodal involvement and 50% had primary extranodal involvement. However, our late-relapse patients with initial good-risk disease were not undertreated; 98% of patients received combined chemotherapy, 94% received anthracycline, and most patients received an adequate number of cycles.

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Patients with DLBCL relapse usually had the same histology. However, relapse as indolent lymphoma following initial DLBCL has been described.[6,7,10-12,18] In our study, 83% of patients with initial DLBCL displayed a relapse as DLBCL, but 17% showed indolent histology at time of relapse. The pathophysiology behind this phenomenon is uncertain but we can make the assumption of an early transformation of indolent lymphoma at diagnosis. A study from our center by Ghesquières et al[19] reported 60 DLBCL patients with an indolent component at diagnosis and showed a high number of indolent relapses. In this study, we noticed a relationship between discordant histology at diagnosis and indolent relapse ($P = .028$). Because it is known that patients who have multiple biopsies will have discordant histology in 10% to 30% of cases,[20-22] we can hypothesize that our patients with pure DLBCL who relapsed with indolent lymphoma had an initial indolent component that was simply not detected. However, we cannot exclude that the indolent relapse in fact represents an unrelated second lymphoma, at least in some patients.

In other series, the initial treatment was not adequate and that may explain late relapses (a significant number of patients were treated without chemotherapy).[5,17] However, this seems unlikely in our series, as stated earlier. Only one late relapse was documented in patients treated with rituximab combined with chemotherapy in first-line therapy. However, because rituximab was introduced in 2001 for first-line therapy in DLBCL, the observation period is too short to make any conclusions about the influence of rituximab on the occurrence of late relapses. In the GELA 98-3 study, which described the benefit of rituximab combined with CHOP in elderly patients with DLBCL, relapse after 5 years was observed in 4% of the patients.[23]

As expected, patients who relapse with DLBCL histology do worse than patients who relapse with indolent histology (5-year OS from time of relapse, 27% *v* 75%; $P = .029$). It has been reported that DLBCL patients with late relapse had better outcome than those with an earlier relapse, but this was not obvious in our series: the outcome seems identical to what is usually described for relapsing DLBCL.[24,25] Old age at relapse is probably the main reason for this poor outcome since 24 patients (53%) were older than age 65 years. Low use of ASCT by itself is not enough to explain prognosis, since the main reason for not receiving it was age > 65 years. However, the group treated with ASCT had better results (3-year OS from time of relapse, 83% *v* 26%; $P = .0183$). Definitive conclusions regarding ASCT results cannot be made because of selection bias.

Studies that looked at late relapse in the past, even if numbers of patients with relapse beyond 5 years were smaller, showed interesting similarities with our results. A study from Ko et al[5] evaluated clinical characteristics and prognosis of 23 patients with relapse 5 years following diagnosis. The proportions of patients with initial early-stage disease (57%) and extranodal involvement (69%) were high. Prognosis from relapse was poor, with estimated 5-year EFS of 11% and 5-year OS of 33%. However, no patients had ASCT at relapse and no immunohistochemistry data were available. Lee et al[7] looked at relapse in a cohort of patients with advanced-stage DLBCL treated with MACOP-B [methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone]. Seventeen patients matched their definition of late relapse, which was 24 months following diagnosis, including 12 with relapse after 5 years. Ten of 17 patients had extranodal involvement at diagnosis, and histology at relapse was DLBCL for 10 patients and indolent lymphoma for six patients. Six-year OS was acceptable, with 42% for patients with DLBCL relapse.

One remaining question is fundamental: does late relapse represent a true clonally related relapse or a second lymphoma? Morphology and immunohistochemistry can help identify patients who experience a true relapse from those having a second lymphoma but these tools are largely imperfect. Molecular studies could answer this question but, unfortunately, this was impossible to do within our cohort. The number of patients with frozen tissue at diagnosis and at relapse was too small to make analysis interpretable. Additionally, most specimens at diagnosis were fixed with Bouin, which prevented us from performing molecular analysis. Three studies have previously looked at the possible occurrence of a new lymphoma: de Jong et al[17] studied 13 DLBCL patients with relapse 4 years or more following completion of therapy. They amplified and sequenced immunoglobulin heavy-chain gene CDR3 and CDR2 regions from tissue obtained at diagnosis and at relapse. They found 10 of 13 cases to be clonally related. They also noted that nine patients (69%) had GC immunophenotype, 10 (77%) had early-stage disease, and nine (69%) had extranodal involvement at diagnosis. No information regarding evolution was available. A smaller study from Nishiuchi et al[26] analyzed in a similar way three cases of DLBCL with relapse 5 years following diagnosis and found two of them to be clonally related. Finally, Lossos et al[27] analyzed eight cases of CNS recurrence 36 months or later following diagnosis. Of five assessable cases, three were found to be clonally related and two were unrelated. Regarding all the data, most cases seem to represent relapse, but a second lymphoma remains a possibility.

A subgroup of patients with initial early-stage DLBCL, favorable IPI, and extranodal involvement seems to be at risk of late relapse. One can say that because advanced-stage disease is usually more aggressive, those who will relapse will do so in the first 2 years following treatment, leaving unusual late relapse for patients with localized disease and favorable IPI. However, even if the subgroup of patients with late relapse shows distinct clinical characteristics, underlying biology is largely unknown.

Even if late relapse is unusual, its occurrence is well described. Most patients have initial early-stage disease, extranodal involvement, and favorable IPI. Biopsy at relapse is essential because the disease can recur as indolent lymphoma. Aggressive treatment with induction multiagent chemotherapy combined with rituximab and ASCT at relapse should be pursued whenever possible because outcome is poor.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202)

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Processed as a Rapid Communication manuscript. See accompanying editorial on page 3051; listen to the podcast by Dr Batchelor at www.jco.org/podcasts

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Purpose
Concerns regarding neurocognitive toxicity of whole-brain radiotherapy (WBRT) have motivated development of alternative, dose-intensive chemotherapeutic strategies as consolidation in primary CNS lymphoma (PCNSL). We performed a multicenter study of high-dose consolidation, without WBRT, in PCNSL. Objectives were to determine: one, rate of complete response (CR) after remission induction therapy with methotrexate, temozolomide, and rituximab (MT-R); two, feasibility of a two-step approach using high-dose consolidation with etoposide plus cytarabine (EA); three, progression-free survival (PFS); and four, correlation between clinical and molecular prognostic factors and outcome.

Patients and Methods
Forty-four patients with newly diagnosed PCNSL were treated with induction MT-R, and patients who achieved CR received EA consolidation. We performed a prospective analysis of molecular prognostic biomarkers in PCNSL in the setting of a clinical trial.

Results
The rate of CR to MT-R was 66%. The overall 2-year PFS was 0.57, with median follow-up of 4.9 years. The 2-year time to progression was 0.59, and for patients who completed consolidation, it was 0.77. Patients age > 60 years did as well as younger patients, and the most significant clinical prognostic variable was treatment delay. High *BCL6* expression correlated with shorter survival.

Conclusion
CALGB 50202 demonstrates for the first time to our knowledge that dose-intensive consolidation for PCNSL is feasible in the multicenter setting and yields rates of PFS and OS at least comparable to those of regimens involving WBRT. On the basis of these encouraging results, an intergroup study has been activated comparing EA consolidation with myeloablative chemotherapy in this randomized trial in PCNSL, in which neither arm involves WBRT.

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INTRODUCTION

Primary CNS lymphoma (PCNSL) is typically an aggressive non-Hodgkin lymphoma, usually of large B-cell histology, which historically has been considered to be associated with a significantly worse prognosis than systemic lymphomas of the same histology, if not incurable. To date, there is no standardized approach to the treatment of PCNSL.[1] Although there is consensus that high-dose methotrexate (HD-MTX) is the cornerstone of treatment, the median progression-free survival (PFS) with HD-MTX as monotherapy is modest, at only 12 to 13 months.[2,3] The Radiation Therapy Oncology Group demonstrated that a combined-modality approach using HD-MTX–based chemotherapy followed by whole-brain radiotherapy (WBRT) markedly extends median PFS to 24 months[4]; however, concerns regarding the irreversible neurocognitive effects of brain irradiation,[5] even at reduced doses,[6] have prompted the development of alternative consolidative strategies.

In CALGB (Cancer and Leukemia Group B) 50202, we asked the question of whether it is possible to treat patients with newly diagnosed primary CNS lymphoma with immunotherapy plus high-dose chemotherapy in the multicenter, cooperative group setting and achieve efficacy comparable to

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that of regimens using brain irradiation. We implemented a two-step, dose-intensive immunochemotherapy regimen designed to be tolerated by patients with PCNSL, particularly in the first few weeks after diagnosis, when performance status and neurologic function are most severely impaired. Induction therapy involves three components: HD-MTX, administered every 2 weeks; weekly rituximab; and temozolomide, prescribed monthly. Rituximab is administered during the first 6 weeks of therapy, an interval during which the blood-brain barrier may be most compromised.[7] Temozolomide reliably penetrates the blood-brain barrier, has established activity in CNS lymphomas as monotherapy and in combination with rituximab,[8-10] and has been demonstrated to provide superior health-related quality of life and toxicity profile compared with procarbazine in patients with brain tumors.[11,12]

To consolidate response and potentiate PFS, patients who obtained a complete response (CR) after induction chemotherapy received the second step of this regimen; infusional etoposide plus high-dose cytarabine as intensive consolidation with non–cross-resistant agents. Notably, the combination of etoposide plus cytarabine (EA) was previously demonstrated to be highly active as first-line salvage in recurrent/refractory CNS lymphoma.[13] The importance of high-dose cytarabine in the treatment of PCNSL is established.[14] Etoposide is effective in the treatment of CNS complications of lymphoid leukemia and other brain tumors and, when administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in aggressive lymphoma, may decrease the risk of secondary CNS lymphoma.[15,16]

PATIENTS AND METHODS

Eligibility

Patients were eligible provided they had histologic confirmation of CNS non-Hodgkin lymphoma (NHL), with central review of diagnostic specimens. Measurable disease based on gadolinium enhancement of brain or spine magnetic resonance imaging (MRI) and/or positive CSF cytology was also required. Patients were excluded for positive HIV serology, if pregnant or nursing, or for evidence of systemic NHL by computed tomography (CT) of chest, abdomen, and pelvis and bone marrow biopsy. Other exclusion criteria included baseline pleural effusions or ascites, Eastern Cooperative Oncology Group performance status (ECOG PS) > 2, absolute neutrophil count (ANC) < 1,500/mL, ALT/AST > 2× upper limit of normal, total bilirubin > 2 g/dL, and creatinine clearance < 50 mL/min. Each participant signed an institutional review board–approved informed consent document in accordance with federal and institutional guidelines.

On-Study Procedures

At enrollment, physical and neurologic examinations were performed in addition to laboratory studies, including complete blood count, differential and platelet count, and serum electrolyte and chemistries. MRI of brain and total spine, ocular slit lamp and CSF examination, and CT or MRI of chest/abdomen/pelvis as well as bone marrow aspirate and biopsy were performed.

Protocol Treatment

CALGB 50202 had two treatment modules (Fig 1). Remission induction chemotherapy consisted of HD-MTX, temozolomide, and rituximab (MT-R). HD-MTX was administered intravenously (IV) once every 2 weeks (for the first seven doses) at 8 g/m^2 over 4 hours, with leucovorin rescue every 6 hours, and adjusted for creatinine clearance, as described previously.[2] Rituximab 375 mg/m^2 was administered once per week for six doses, beginning on day +3 (patients with T-cell PCNSL did not receive rituximab). Temozolomide (150 mg/m^2) was administered once per day on days 7 to 11 each of the first 5 months. No intrathecal chemotherapy was administered. Consolidation

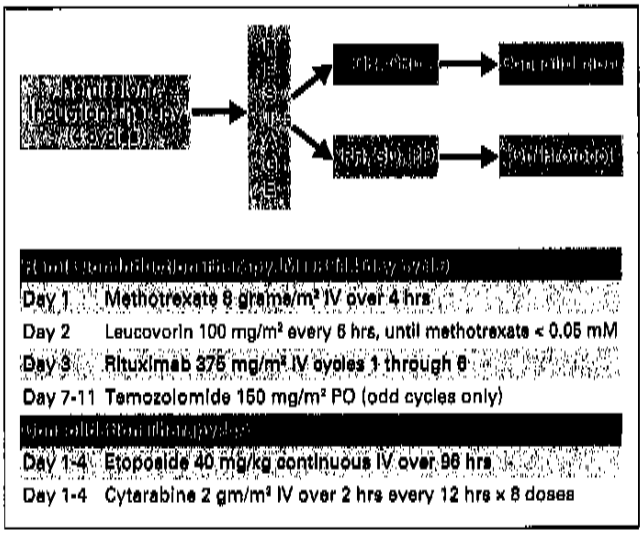

Fig 1. Protocol schema. Patients were restaged after 4 months of high-dose methotrexate-based therapy (seven doses of high-dose methotrexate, every 2 weeks; six doses of weekly rituximab; and 4 months of temozolomide over 5 days [MT-R]). Patients who achieved a complete response (CR) or CR/unconfirmed (CRu) received an additional course of high-dose methotrexate plus one of temozolomide. Three to 5 weeks later, patients received intensive consolidation with etoposide plus cytarabine (EA). High-dose EA chemotherapy doses were based on corrected body weight (kg), defined as ideal weight plus 0.25 (actual weight − ideal weight), as described previously.[17] IV, intravenous; PD, progressive disease; PO, orally; PR, partial response; SD, stable disease.

chemotherapy consisted of etoposide 5 mg/kg administered by continuous IV infusion every 12 hours for eight doses (total dose, 40 mg/kg), with cytarabine 2 g/m^2 IV over 2 hours every 12 hours for eight doses (total dose, 16 g/m^2), as described previously.[17]

Supportive Care

Hydration and urine alkalinization during methotrexate administration were achieved by administration of NaHCO3 (100 to 150 mEq/L) at 150 mL/h IV until urine output of ≥ 100 mL/h and urine pH > 7 for 4 hours before methotrexate and continued until completion of leucovorin rescue. During EA consolidation, patients showered twice daily, and corticosteroid eye drops, two drops per eye, were administered four times per day on days 1 to 6 to prevent cytarabine keratoconjunctivitis. Granulocyte CSF (5 mcg/kg/d) or granulocyte macrophage CSF 250 (mcg/m^2/d) were administered subcutaneously starting day 14 of therapy and continued until ANC reached ≥ 500/μL for 2 days or ≥ 1,500/μL for 1 day. Bacterial prophylaxis with fluoroquinolone antibiotics was initiated at ANC < 500/μL and continued until ANC reached ≥ 500/μL. Fungal prophylaxis (azole) was started day 6 of therapy and continued until ANC reached ≥ 500/μL. Herpes simplex virus and Varicella zoster virus prophylaxis consisted of acyclovir or valacyclovir. *Pneumocystis* pneumonia prophylaxis was provided with trimethoprim/sulfamethoxazole or dapsone. Febrile neutropenia and transfusion support were managed according to institutional guidelines.

Documentation of Response

At 4 months of remission induction therapy (after the seventh course of HD-MTX), patients were restaged by MRI of brain (plus spine and lumbar puncture if previously positive). Patients who achieved a CR or CR/unconfirmed received an additional (eighth) cycle of HD-MTX followed by a fifth course of temozolomide followed by remission consolidation therapy with EA. After consolidation therapy, patients were restaged with repeat brain MRI every 2 months for the first year, then every 4 months for years 2 and 3. Beginning at 3.5 years, patients were evaluated every 6 months until 6.5 years after induction. The International Primary CNS Lymphoma Collaborative Group response criteria were used, as described previously.[18]

Statistical Considerations

The study used a two-stage design to address the primary end point—CR rate—with exact binomial 95% CI. An interim analysis was conducted when

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response data were available from the first 27 patients, with a planned early stopping rule for a CR rate < 44%. With a target accrual of 45 patients, a successful trial was prospectively defined as a CR rate of at least 53% for the therapeutic approach to be acceptable for further investigation. Efficacy end points PFS, time to progression (TTP), and overall survival (OS) were defined as per the Revised Response Criteria for Malignant Lymphoma.[19]

Neurologic and other toxicities were closely monitored with the first 6, 10, 20, 30, and 45 patients. Rates ≥ 5% grade 4 neurotoxicity and ≥ 10% grade 5 other toxicities were prospectively defined as unacceptable, and if observed, the trial would be stopped. Toxicities were scored using the National Cancer Institute Common Toxicity Criteria, version 3.0.

Assessment of clinical prognostic factors was based on International Extranodal Lymphoma Study Group (IELSG) score[20] using the log-rank test. Assessment of candidate molecular prognostic markers *BCL6* and *MYC* was performed by immunohistochemistry in archival formalin-fixed paraffin-embedded tissue. The percent tumor cell nuclei staining for each marker was independently scored (nearest 10% increment) by two pathologists blinded to clinical outcome (E.D.H., M.O.N.) with near-100% reproducibility ($R^2 > 0.9$; $P < .001$). Cox proportional hazards models were fitted for outcomes using candidate molecular markers as continuous variables. If the model was statistically significant, the best cut point in the data was determined using an iterative procedure.

Patient registration and data collection were managed by the CALGB (Alliance) Statistics and Data Center, with data as of May 24, 2012, analyzed by CALGB statisticians. Data quality was ensured through review by CALGB (Alliance) statistical center staff and by the study chairperson. As part of the CALGB quality assurance program, members of the audit committee visit all participating institutions at least once every 3 years to verify compliance with federal regulations and protocol requirements. Review of medical records was performed for 13 (28%) of the 47 patients registered to this study.

Table 1. Patient Demographic and Clinical Characteristics (N = 44)

Characteristic	No.	%
Age, years		
Median	61	
Range	12-76	
Male sex	21	48
ECOG PS		
0	8	18
1	28	64
2	8	18
Elevated LDH*	12	29
Elevated CSF protein*	20	48
Deep brain lesions†	20	47
IELSG risk group‡		
0-1	13	33
2-3	23	58
4-5	4	10
Positive CSF cytology	10	24
Intraocular lymphoma	1	2
Large B-cell lymphoma§	43	98

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IELSG, International Extranodal Lymphoma Study Group; LDH, lactate dehydrogenase.
*Data regarding serum LDH and CSF protein concentration were available in 42 patients.
†Documentation of deep tumor location was made in 43 patients.
‡Complete IELSG prognostic characteristics were available in 40 of 44 patients.
§Large B-cell histology was diagnosed in 98% of patients; one patient had B-cell lymphoma, unspecified.

RESULTS

Patients and Disease Characteristics and Study

Forty-seven patients enrolled between October 2004 and November 2009 at 12 CALGB sites. Three patients were excluded from analysis because of failure to meet eligibility criteria or to receive protocol therapy (Table 1). Large B-cell lymphoma was diagnosed in 43 (98%) of 44 patients. The median age was 61 years, and 48% of patients were male. Among the 40 patients for whom complete IELSG PCNSL prognostic parameters were available, 27 (68%) had IELSG risk scores ≥ 2. Ten patients (24%) had positive CSF cytology, and one had intraocular lymphoma.

Response and Survival

After MT-R induction, nine patients (20%) experienced disease progression, one had stable disease, five (11%) achieved a partial response, and 29 (66%) achieved a CR, yielding a final CR rate of 66% (95% CI, 50% to 80%). The 2-year rate of PFS was 0.57; 2-year TTP was 0.59, and median TTP was 4.0 years. The 2-year TTP for those patients who completed the entire regimen was 0.77 (range, 0.56 to 0.89). The median PFS was 2.4 years, with one treatment-related death and one death resulting from lung cancer at 4.5 years. Median OS for the study population has not been reached, with estimated probability of OS at 4 years of 0.65 (range, 0.49 to 0.77; Figs 2A to 2C). To date, 17 patients have died, with median survival time among the 27 surviving patients of 4.9 years (range, 2.3 to 6.6 years).

Toxicity

As expected, 55% of patients experienced grade 4 neutropenia, and 50% of patients experienced grade 4 thrombocytopenia; 81% of these episodes occurred after remission consolidation chemotherapy with EA (Table 2). There were four cases of febrile neutropenia, (grade 3, three; grade 4, one); there was one grade 5 infectious complication (sepsis), which also occurred after EA. There was only one case of grade 3 renal failure (reversible) and no episodes of grade 3 or 4 cytarabine or other neurotoxicity. Summary of adverse events is provided in Appendix Table A1 (online only).

Clinical Prognostic Variables

We evaluated the relationship between established clinical prognostic variables and outcome in patients with PCNSL treated with the 50202 regimen (Figs 3A to 3D). ECOG PS > 1 and high IELSG score (4 to 5) were associated with shorter PFS. Unlike previous studies in PCNSL,[21,22] patients age > 60 years experienced outcomes similar to those of younger patients. The most significant clinical variable identified in this series was treatment delay. Although the median interval between diagnosis and initiation of protocol treatment for the entire 50202 cohort was 15 days, review of study throughput data revealed that 10 patients started MT-R therapy > 30 days after diagnosis (median, 39 days; range, 31 to 83 days). PFS for these patients was significantly shorter than for patients who started therapy soon after diagnosis (two-sided *t*-test $P = .05$). Among the cohort of patients for whom remission induction therapy was delayed > 30 days after diagnosis, two experienced disease progression during induction MT-R, three achieved only a partial response, and one had stable disease and went off study. Of the four patients with treatment delay who did achieve a CR, two subsequently experienced early disease progression, and only two remain in remission. Half of the patients with treatment delay succumbed to CNS lymphoma progression, whereas only 29%

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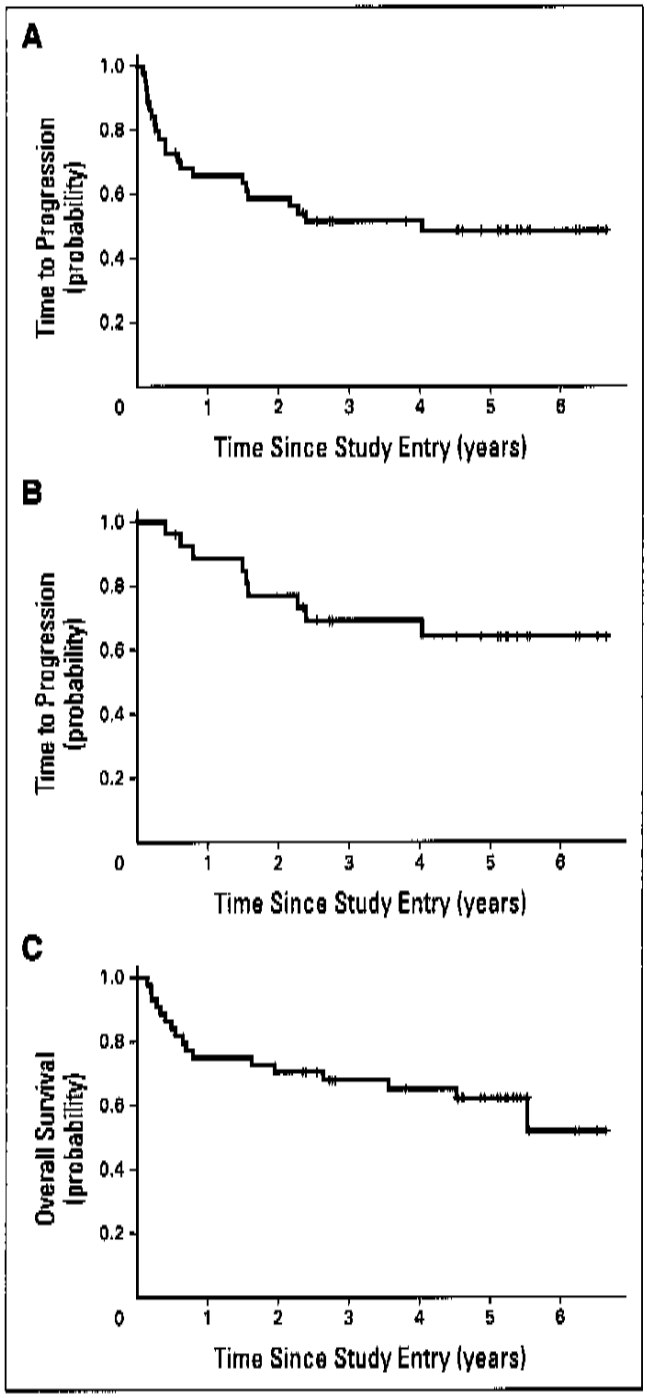

Fig 2. Outcome for all 50202 study patients; y-axis refers to cumulative probability of event. (A) Time to progression (TTP) for all patients; median TTP was 4.0 years (22 patients experienced disease progression). Estimated TTPs at 1, 2, 3, and 4 years were 0.66 (95% CI, 0.50 to 0.78), 0.59 (95% CI, 0.43 to 0.72), 0.52 (95% CI, 0.36 to 0.65), and 0.48 (95% CI, 0.33 to 0.63), respectively. (B) TTP for those patients (n = 27) who completed entire treatment protocol (induction plus consolidation). One- and 2-year probabilities of TTP from start of etoposide plus cytarabine consolidation were 0.85 (95% CI, 0.64 to 0.94) and 0.69 (95% CI, 0.47 to 0.83), respectively. (C) Overall survival (OS) for all patients; median OS has not been reached. Estimated OS at 1, 2, 3, and 4 years were 0.75 (95% CI, 0.59 to 0.85), 0.70 (95% CI, 0.52 to 0.80), 0.70 (95% CI, 0.52 to 0.80), and 0.65 (95% CI, 0.49 to 0.77), respectively. TTP is defined as time from date of study entry until progression or date of last follow-up while in remission, with censoring of deaths not resulting from progressive lymphoma. OS is defined as time from date of study entry until death resulting from any cause or date of last follow-up while in remission.

Table 2. Common Toxicities by Grade Occurring in Each Arm[a]

	Grade 3		Grade 4		Grade 5	
AE	No.	%	No.	%	No.	%
Hemoglobin						
MT-R	5	11	1	2	0	0
EA	3	12	0	0	0	0
Lymphopenia						
MT-R	3	7	1	2	0	0
EA	0	0	1	4	0	0
Neutropenia						
MT-R	7	16	4	9	0	0
EA	1	4	21	81	0	0
Thrombocytopenia						
MT-R	4	9	1	2	0	0
EA	1	4	21	81	0	0
Diarrhea						
MT-R	2	5	0	0	0	0
EA	2	8	0	0	0	0
Mucositis/stomatitis						
MT-R	0	0	0	0	0	0
EA	2	8	0	0	0	0
Nausea						
MT-R	2	5	0	0	0	0
EA	1	4	0	0	0	0
Febrile neutropenia						
MT-R	0	0	0	0	0	0
EA	3	12	1	4	0	0
Infection						
MT-R	3	7	0	0	0	0
EA	6	14	0	0	1	4
ALT						
MT-R	7	16	3	7	0	0
EA	0	0	0	0	0	0
AST						
MT-R	8	18	2	5	0	0
EA	0	0	0	0	0	0
High serum glucose						
MT-R	6	14	1	2	0	0
EA	0	0	1	4	0	0
Low serum potassium						
MT-R	11	25	1	2	0	0
EA	3	12	0	0	0	0
High serum potassium						
MT-R	3	7	0	0	0	0
EA	1	4	0	0	0	0
Low serum sodium						
MT-R	3	7	0	0	0	0
EA	0	0	0	0	0	0
Muscle weakness						
MT-R	3	7	0	0	0	0
EA	0	0	0	0	0	0
Pain						
MT-R	3	7	0	0	0	0
EA	1	4	0	0	0	0
Pneumonitis						
MT-R	3	7	0	0	0	0
EA	0	0	0	0	0	0
Maximum overall AE						
MT-R	24	55	12	27	0	0
EA	1	4	21	81	1	4

Abbreviations: AE, adverse event; EA, etoposide plus cytarabine; MT-R, methotrexate, temozolomide, and rituximab.

[a]Toxicities occurring in ≥ 5% of patients. No EA toxicity data were available for one patient who experienced disease progression and died within 10 days of intensive consolidation.

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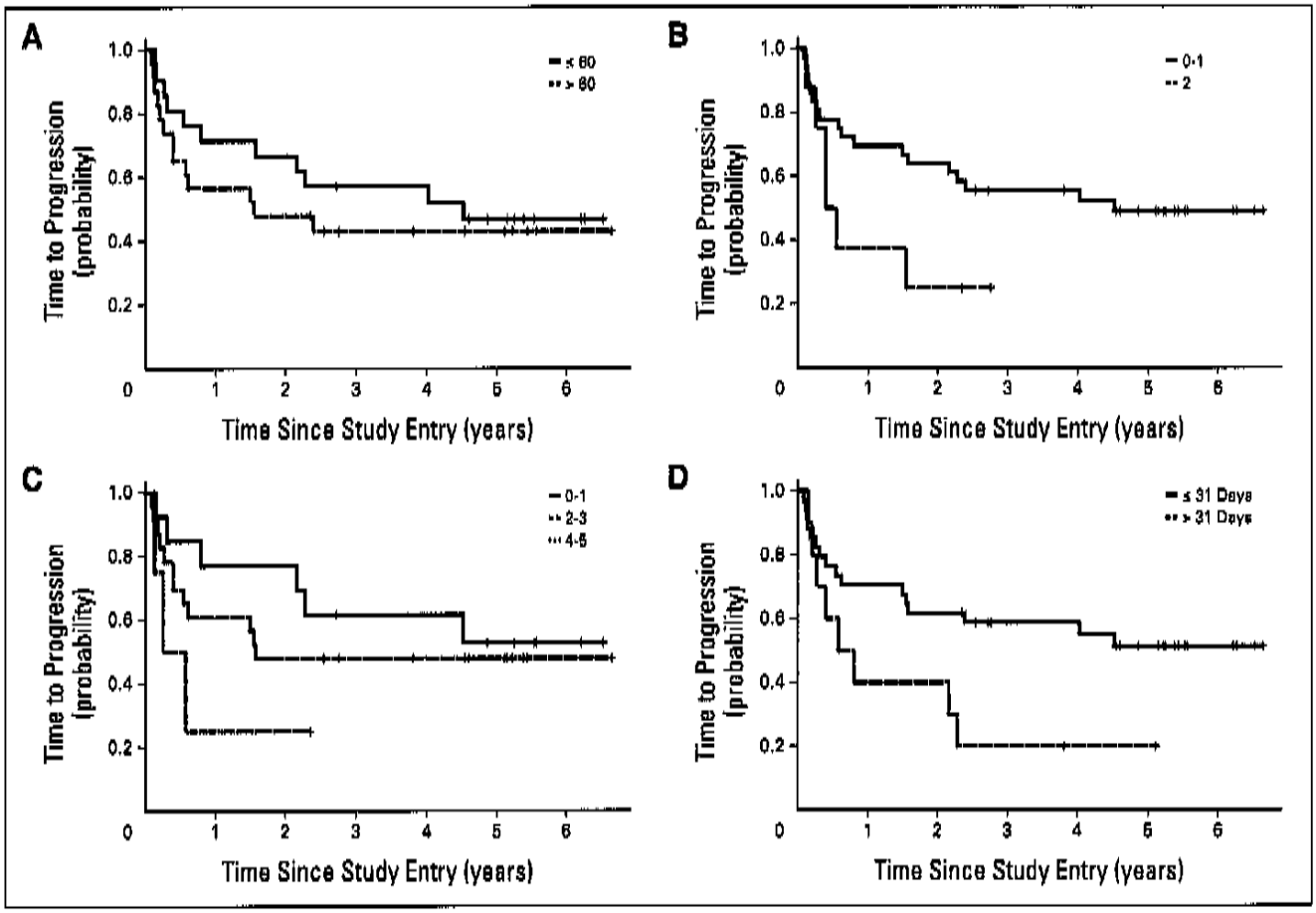

Fig 3. Clinical prognostic variables and their relationship to progression-free survival (PFS); median PFS survival was 2.4 years (22 patients who experienced disease progression plus two patients achieving complete response who succumbed to sepsis and lung cancer, respectively). Estimated PFS at 1, 2, 3, and 4 years were 0.64 (95% CI, 0.48 to 0.76), 0.57 (95% CI, 0.41 to 0.70), 0.50 (95% CI, 0.34 to 0.64), and 0.47 (95% CI, 0.32 to 0.61; not shown). (A) PFS was similar for patients age > 60 years (n = 23) and for younger patients (n = 21; P = .48). (B) PFS was shorter for patients with Eastern Cooperative Oncology Group performance status of 2 (n = 8; P < .06). (C) There was a trend between shorter PFS and highest International Extranodal Lymphoma Study Group risk score of 4 to 5 (P = .16). (D) Treatment delay was associated with shorter PFS. Patients with delayed initiation of remission induction therapy, beyond 30 days after diagnosis, experienced significantly shorter PFS compared with patients whose therapy began within 1 month of diagnosis (P = .050). Three-year PFS was 0.59 (95% CI, 0.40 to 0.73) for those without treatment delay and 0.2 (95% CI, 0.03 to 0.47) for those with treatment delay. PFS is defined as time from date of study entry until progression, death resulting from any cause, or date of last follow-up while in remission. There was no association between malignant CSF cytology at pretreatment staging and response rate or outcome.

of the patients (12 of 34) who were treated within 1 month of diagnosis have died. Notably, there was no association between ECOG PS or IELSG risk score and delay in remission induction therapy, supporting treatment delay as a previously unrecognized, independent clinical prognostic variable in PCNSL.

Molecular Prognostic Variables

Previous immunohistochemical analyses of prognostic molecules in PCNSL have been retrospective in nature and identified *BCL6* and *MYC* as candidate biomarkers.[23-26] Importantly, to date, there have been no prospective studies of molecular biomarkers in patients with PCNSL treated uniformly in the setting of a multicenter clinical trial. Furthermore, candidate prognostic biomarkers in PCNSL have not been examined in the context of rituximab and high-dose chemotherapy.

In CALGB 50202, diagnostic specimens were requested from all participating patients, and sufficient biopsy material was available for immunohistochemical staining from 26 patient cases (59%). High *MYC* expression (> 50% of lymphoma nuclei) was detected in 54% of patient cases, an increased proportion of patient cases compared with systemic diffuse large B-cell lymphoma,[27] but *MYC* expression in this series did not correlate with outcome. By contrast, high *BCL6* expression (≥ 30% of lymphoma nuclei) was detected in 19 patient cases (59%), consistent with previous reports.[28] High *BCL6* expression by lymphoma nuclei, correlated as a continuous variable with inferior TTP, PFS, and OS. The two-sided P values for these models were P = .045, P = .019, and P = .045, respectively (log-rank test). Because the global test was significant in all three cases, the most significant cut point for dichotomizing *BCL6* expression was evaluated using an iterative method and determined to be 60% (Figs 4A to 4C).

DISCUSSION

CALGB 50202 demonstrates for the first time to our knowledge the feasibility of high-dose chemotherapy consolidation administered in the multicenter, cooperative group setting for newly diagnosed

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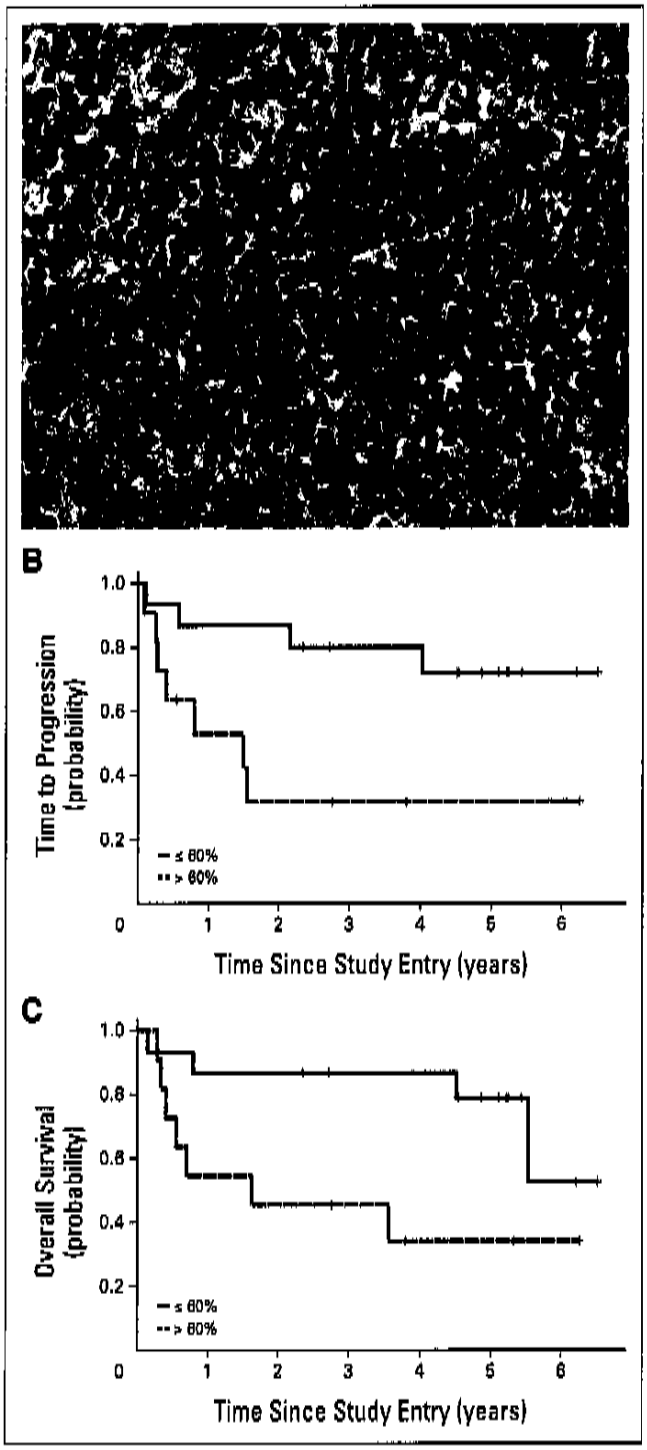

Fig 4. *BCL6* expression is associated with short time to progression (TTP) and overall survival (OS) in patients with primary CNS lymphoma (PCNSL) treated in the 50202 study. (A) Example of strong nuclear *BCL6* expression in a PCNSL case from patient treated in study (40× magnification). (B) High *BCL6* expression (ie, > 60% of lymphoma nuclei) is associated with short TTP (two-sided $P < .016$). (C) High *BCL6* is also associated with shorter OS (two-sided $P < .009$). For *BCL6*, monoclonal antibody Pg-B6p (Dako, Carpenteria, CA) was used. For *MYC* (not shown), monoclonal antibody Y69 (Epitomics, Burlingame, CA) was used. An automated immunostainer with iView diaminobenzidine detection (Ventana Medical Systems, Oro Valley, AZ) was used with CC1 heat-induced epitope retrieval for both assays.

PCNSL. The 0.57 rate of 2-year PFS exceeds those of other chemotherapy-alone studies[2,29,30] and is at least comparable to combined-modality approaches with reduced-dose WBRT.[31] The median TTP of all 50202 patients—4 years—is 2× longer than that achieved with combined-modality therapy in multicenter trials using standard-dose WBRT.[4,22] Survival for the cohort of patients who completed EA dose-intensive consolidation is particularly promising, confirming prior single-institution data.[32] The survival curves show encouraging evidence of a stable plateau, and the median OS for 50202 patients has not yet been reached, with a median follow-up of 4.9 years.

The CALGB 50202 regimen was generally well tolerated, with the exception of one treatment-related death caused by sepsis in a patient managed as an outpatient after EA chemotherapy; this event highlights the recommendation of detailed inpatient monitoring during the neutropenic and thrombocytopenic nadirs expected after the intensive consolidation phase of treatment. On the other hand, myelosuppression during the remission induction phase was mild; few patients required growth factor support; and there was only one case of grade 3 renal toxicity, despite high doses of methotrexate administered. Although there were no reported episodes of severe acute neurotoxicity, detailed post-treatment neurocognitive testing was not performed.

Remarkably, the PFS of patients age > 60 years treated in 50202 was similar compared with that of younger patients, a result that contrasts previous studies in PCNSL, which demonstrated that patients age > 60 years fare significantly worse.[21] Although preliminary, this observation suggests that many of the established prognostic features of PCNSL may be dependent on treatment-related variables, including radiotherapy.[5] It should also be noted that there may be subgroups of patients with PCNSL for whom radiotherapy may be necessary and who may potentially be identified in randomized studies.

In addition, our finding that the late initiation of remission induction therapy correlates with a population at higher risk of early disease progression, although novel, is supported by prior assertions that delayed diagnosis of PCNSL correlates with adverse outcome.[33,34] Among the factors that may contribute to delayed initiation of therapy after the diagnosis of PCNSL are the relative rarity of the diagnosis, a lack of familiarity with therapeutic options in community practice, the fact that many patients may choose to delay treatment to obtain a second opinion, and the assumption that PCNSL is an incurable disease. Whatever the cause of treatment delay, its association with adverse outcome has important implications for the management of these patients and provides evidence that the prompt initiation of therapy after diagnosis may translate to improved outcomes in PCNSL. This result also suggests that interventions that facilitate early diagnosis of PCNSL and intraocular lymphoma may also translate into improved outcomes for patients.

Finally, CALGB 50202 is the first clinical trial in PCNSL to our knowledge to prospectively evaluate molecular prognostic biomarkers expressed within diagnostic lymphoma specimens. As a lymphoma subtype, PCNSL tumors exhibited high *MYC* expression relative to systemic large-cell lymphoma, consistent with previous transcriptional evidence[35]; however, *MYC* was not prognostic. By contrast, our prospective data demonstrate that *BCL6* expression was predictive of shorter survival in patients with PCNSL treated with the 50202 regimen. This observation is in agreement with previous reports that

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expression of the *BCL6* oncoprotein correlates with adverse outcome in PCNSL.[23,26] Because the vast majority of B-cell PCNSL patient cases express MUM1, and prior studies have shown ongoing immunoglobulin gene somatic hypermutation, the concept of *BCL6*-positive PCNSL having an activated germinal center B-cell origin seems reasonable and may explain the adverse outcome of this phenotype.[28,36,37] Nevertheless, it should be pointed out that at least two retrospective, single-institution studies have suggested that *BCL6* expression correlates with improved outcome in PCNSL.[23,24] Possible explanations for these disparate findings are the retrospective nature of previous studies, the possibility that previous studies may not have considered the prognostic impact of high expression of the *BCL6* oncogene, and the possibility that the prognostic relevance of individual biomarkers may be dictated by treatment-related variables including brain radiotherapy and rituximab. In support of this explanation are recent prospective data demonstrating that the addition of rituximab to CHOP chemotherapy selectively improved survival in *BCL6*-negative systemic diffuse large B-cell lymphoma.[38] Although our study is the first to our knowledge to evaluate the significance of *BCL6* expression in PCNSL in the setting of rituximab, assessment of clinical and prognostic variables in this trial will require validation given the small size and number of biopsy specimens available, with consequent limited power. In any case, the observation that *BCL6* expression is predictive of adverse outcome in newly diagnosed PCNSL, if confirmed, suggests that this biomarker could prospectively be used in risk-adapted therapy and supports the rational application of *BCL6* antagonists in the treatment of this disease.[39]

Given the encouraging results of CALGB 50202 in terms of toxicity, response, and survival achieved in the multicenter setting, the MT-R regimen is being evaluated in a successor intergroup, randomized phase II trial—CALGB 51101 (Alliance)—which compares dose-intensive EA chemotherapy with myeloablative chemotherapy using carmustine plus thiotepa followed by autologous stem-cell transplantation.[40] Validation of *BCL6* and other molecular prognostic biomarkers and detailed neurocognitive testing are key correlative goals of this first randomized trial in PCNSL in which neither arm involves WBRT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: James L. Rubenstein, Eric D. Hsi
Administrative support: Sin-Ho Jung, Bruce D. Cheson
Provision of study materials or patients: James L. Rubenstein, Barbara Grant
Collection and assembly of data: James L. Rubenstein, Eric D. Hsi, Sin-Ho Jung, Barbara Grant, Bruce D. Cheson
Data analysis and interpretation: James L. Rubenstein, Eric D. Hsi, Jeffrey L. Johnson, Sin-Ho Jung, Megan O. Nakashima, Bruce D. Cheson, Lawrence D. Kaplan
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

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Table A1. AEs by Grade

Hematologic AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
Hemoglobin							
C2	3	12	0	0	0	0	26
MTX	5	11	1	2	0	0	44
Leukocytes (total WBC)							
C2	0	0	8	31	0	0	26
MTX	3	7	3	7	0	0	44
Lymphopenia							
C2	0	0	1	4	0	0	26
MTX	3	7	1	2	0	0	44
Neutrophils/granulocytes (ANC/AGC)							
C2	1	4	21	81	0	0	26
MTX	7	16	4	9	0	0	44
Platelets							
C2	1	4	21	81	0	0	26
MTX	4	9	1	2	0	0	44
Maximum hematologic AE							
C2	1	4	21	81	0	0	26
MTX	11	25	6	14	0	0	44

Nonhematologic AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
Cardiac arrhythmia, other							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Cardiac general							
Cardiopulmonary arrest, cause unknown							
C2	0	0	1	4	0	0	26
MTX	0	0	0	0	0	0	44
Hypertension							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Hypotension							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Constitutional symptoms							
Fatigue (asthenia, lethargy, malaise)							
C2	0	0	0	0	0	0	26
MTX	1	2	1	2	0	0	44
Insomnia							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Dermatology/skin							
Rash/desquamation							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
GI							
Dehydration							
C2	1	4	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Diarrhea							
C2	2	8	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Heartburn/dyspepsia							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44

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Table A1. AEs by Grade (continued)

Nonhematologic AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
Mucositis/stomatitis (functional)							
C2	2	8	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Nausea							
C2	1	4	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Vomiting							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Hemorrhage/bleeding							
Hemorrhage CNS							
C2	0	0	1	4	0	0	26
MTX	0	0	0	0	0	0	44
Hemorrhage, GI							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Petechiae/purpura							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Infection							
Febrile neutropenia							
C2	3	12	1	4	0	0	26
MTX	0	0	0	0	0	0	44
Infection (documented clinically)							
C2	5	19	0	0	0	0	26
MTX	3	7	0	0	0	0	44
Infection, other							
C2	1	4	0	0	1	4	26
MTX	0	0	0	0	0	0	44
Infection, normal ANC							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Infection, unknown ANC							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Lymphatics							
Edema, limb							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Metabolic/laboratory							
ALT, SGPT							
C2	0	0	0	0	0	0	26
MTX	7	16	3	7	0	0	44
AST, SGOT							
C2	0	0	0	0	0	0	26
MTX	8	18	2	5	0	0	44
Low serum albumin							
C2	0	0	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Alkalosis (metabolic or respiratory)							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Bilirubin							
C2	1	4	0	0	0	0	26
MTX	1	2	0	0	0	0	44

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Table A1. AEs by Grade (continued)

Nonhematologic AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
Low serum calcium							
C2	0	0	0	0	0	0	26
MTX	5	11	1	2	0	0	44
GGT							
C2	0	0	0	0	0	0	26
MTX	2	5	0	0	0	0	44
High serum glucose							
C2	0	0	1	4	0	0	26
MTX	6	14	1	2	0	0	44
Metabolic/laboratory, other							
C2	0	0	0	0	0	0	26
MTX	0	0	1	2	0	0	44
Low serum phosphate							
C2	0	0	0	0	0	0	26
MTX	3	7	0	0	0	0	44
High serum potassium							
C2	1	4	0	0	0	0	26
MTX	3	7	0	0	0	0	44
Low serum potassium							
C2	3	12	0	0	0	0	26
MTX	11	25	1	2	0	0	44
High serum sodium							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Low serum sodium							
C2	0	0	0	0	0	0	26
MTX	3	7	0	0	0	0	44
High serum uric acid							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Musculoskeletal/soft tissue							
Muscle weakness							
C2	0	0	0	0	0	0	26
MTX	3	7	0	0	0	0	44
Neurology							
Ataxia (incoordination)							
C2	0	0	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Confusion							
C2	0	0	0	0	0	0	26
MTX	1	2	1	2	0	0	44
Dizziness							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Mood alteration							
C2	0	0	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Neurology, other							
C2	0	0	1	4	0	0	26
MTX	0	0	0	0	0	0	44
Seizure							
C2	1	4	0	0	0	0	26
MTX	0	0	0	0	0	0	44
Syncope (fainting)							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44

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Table A1. AEs by Grade (continued)

Nonhematologic AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
Pain							
C2	1	4	0	0	0	0	26
MTX	3	7	0	0	0	0	44
Pulmonary/upper respiratory							
Hypoxia							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Pneumonitis/pulmonary infiltrates							
C2	0	0	0	0	0	0	26
MTX	3	7	0	0	0	0	44
Renal/genitourinary							
Renal failure							
C2	0	0	0	0	0	0	26
MTX	1	2	0	0	0	0	44
Vascular							
Thrombosis/thrombus/embolism							
C2	0	0	0	0	0	0	26
MTX	2	5	0	0	0	0	44
Maximum nonhematologic AE							
C2	10	38	1	4	1	4	26
MTX	26	59	8	18	0	0	44

Maximum Overall AE	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %	Total No.
C2	1	4	20	77	1	4	26
MTX	24	55	12	27	0	0	44

Abbreviations: AE, adverse event; AGC, absolute granulocyte count; ANC, absolute neutrophil count; C2, etoposide plus cytarabine consolidation; GGT, γ-glutamyltransferase; MTX, methotrexate; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvate transaminase.

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EXHIBIT 5

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Methotrexate re-challenge for recurrent primary central nervous system lymphoma

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Abstract The prognosis of primary CNS lymphoma (PCNSL) recurring after methotrexate is poor (objective response rates [ORR] = 26–53 %; 1-year overall survival [OS] = 35–57 %). Salvage PCNSL chemotherapies have been based on the use of different agents to avoid cross-resistance; however, methotrexate is the most active agent in PCNSL, and methotrexate re-challenge may be an effective strategy for recurrent disease. We report our experience with methotrexate re-challenge in PCNSL. We reviewed 39 patients with histologically confirmed PCNSL who responded to methotrexate at initial diagnosis, experienced disease relapse and received methotrexate re-challenge. At the time of re-challenge, median age was 66 and median Karnofsky performance score (KPS) was 70. Median time from initial diagnosis was 26 m. Twenty-six patients were at first relapse and 13 at second or later relapse. At re-challenge, methotrexate was given in combination with other agents to 33 patients and as a single agent to six. The objective response rate was 85 %, with a complete response in 29 (75 %) patients, partial response in four (10 %) and disease progression in six (15 %). At median follow-up of 26 m, the median progression-free survival was 16 m; 1-year OS was 79 % (95 % CI 63–89) and median OS was 41 m. KPS was a prognostic factor for progression free survival ($p = 0.04$). In this population selected by previous methotrexate response, methotrexate re-challenge was a safe and effective strategy, indicating chemosensitivity was retained. Efficacy compared favorably to other salvage treatments suggesting methotrexate re-challenge should be considered in recurrent PCNSL patients who previously responded to methotrexate.

Keywords Primary CNS lymphoma · Recurrence · Methotrexate

Introduction

Primary central nervous system lymphoma (PCNSL) is a relatively rare non-Hodgkin lymphoma arising within the brain, cerebral spinal fluid (CSF), spinal cord or eyes. In more than 90 % of patients, the histology corresponds to a diffuse large B cell lymphoma (DLBCL). Although traditional DLBCL chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and variations are ineffective in PCNSL, the use of high-dose methotrexate (MTX) based regimens, with or without radiotherapy, resulted in significantly improved efficacy, achieving response rates (RR) as high as 70–90 %, and median overall survival (OS) of 40–70 months. Unfortunately, relapses remain frequent, mostly occurring within the first 2 years after initial response, with late relapses also occasionally reported [1–4].

Salvage treatments for PCNSL have been poorly characterized in the literature, and available studies have reported variable outcomes with objective response rates (ORR) of 26–91 % and 1y OS of 35–71 %. Traditionally, salvage chemotherapies have been based on the use of agents different from MTX in order to avoid cross-resistance [5–12]. However, because MTX is by far the most active agent in PCNSL, MTX re-challenge has been proposed as a possible salvage strategy for recurrent

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disease [13], although to date such practice has not been widely adopted, as exemplified by salvage treatment patterns observed in a large recent trial in newly diagnosed PCNSL [14]. In this study, we report our experience with MTX re-challenge in recurrent PCNSL.

Patients and methods

This retrospective study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board. The MSKCC Department of Neurology database was used to identify patients with PCNSL who responded to MTX and then received MTX-based chemotherapy as a salvage treatment for recurrent disease between March 1998 and October 2010.

Additional inclusion criteria consisted of age $\geq$18, histological confirmation of PCNSL, radiographic evidence of brain involvement at recurrence, and absence of systemic involvement by lymphoma. All patients had pathology confirmed at MSKCC. Patients were included irrespective of the number of prior recurrences or therapies. Kaplan–Meier survival distributions were estimated to assess OS and progression-free survival (PFS). The OS was calculated from the date of initiation of MTX-re-challenge until death or last follow-up. PFS was calculated from date of initiation of MTX re-challenge to date of tumor progression or death. Potential prognostic factors were evaluated by a Cox proportional hazard model. Toxicity was assessed utilizing the common terminology criteria for adverse events (CTCAE) version 4.0. Responses were determined utilizing the International Primary CNS Lymphoma Group (IPCG) response criteria [15].

Table 1 Patient characteristics at the time of methotrexate re-challenge

$N = 39$	N	% or range
Sex		
Women	20	51 %
Men	19	49 %
Median age	66 years	41–82
Median KPS	70	50–100
Median time between initial diagnosis and MTX re-challenge	26 months	8.7–178
Positive CSF	4	10 %
Ocular involvement	7	18 %
Number of relapses prior to MTX re-challenge		
One	26	66 %
Two or more	13	34 %
Prior WBRT	16	41 %
Initial methotrexate treatment		
MPV	37	95 %
With high-dose cytarabine	22/37	
With rituximab	9/37	
Single-agent MTX (5 g/m2)	1	2.5 %
MTX, rituximab, temozolomide	1	2.5 %
Other prior treatments in patients with > 2 previous relapses	13	
Rituximab–temozolomide	9	68 %
Rituximab–IT MTX	1	8 %
Temozolomide	1	8 %
Rituximab–temozolomide–thiotepa	1	8 %
Ocular radiotherapy	1	8 %

KPS Karnofsky performance score, *MTX* methotrexate, *CSF* cerebrospinal fluid, *WBRT* whole-brain radiation therapy, *MPV* methotrexate, procarbazine, vincristine, *IT* intrathecal

Results

Patient characteristics

Thirty-nine patients with PCNSL were identified; 20 (51 %) were women (Table 1). All patients had a histological diagnosis of PCNSL confirmed by pathology review at MSKCC. A total of 38 patients (95 %) had a DLBCL, and in one patient (2.5 %) the lymphoma type could not be determined.

At the start of MTX re-challenge, the median age was 66 years (range 41–82 years) and the median Karnofsky performance score (KPS) was 70 (range 50–100). The median time from initial diagnosis to disease progression leading to MTX re-challenge was 26 months. Twenty-six patients (66 %) received MTX again at first relapse and 13 (34 %) at second or later relapse after failing other chemotherapy regimens. A total of 16 patients (41 %) had received whole brain radiotherapy (WBRT) prior to MTX re-challenge. Thirty-seven patients had received prior MTX in combination with procarbazine and vincristine. In nine of those patients, rituximab was added, and 22 also received high-dose cytarabine at consolidation. Single agent MTX was used in one patient and the remaining patient received MTX, rituximab and temozolomide as part of a CALGB protocol. One patient underwent high-dose chemotherapy with autologous stem cell transplant protocol (HDC-ASCT) as consolidation treatment.

Prior to initiation of MTX re-challenge, all patients underwent re-staging with MRI, ophthalmological evaluation, CSF cytology and body PET/CT. All patients had parenchymal brain lesions; seven patients (18 %) also had ocular involvement, and four (10 %) had a positive CSF cytology. Three patients received radiation to the orbits at the time of recurrence for progressive visual loss prior to

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MTX re-challenge therapy. No other patients received radiation therapy as part of MTX re-challenge.

Methotrexate re-challenge treatment

At re-challenge, MTX was given in combination with other agents to 33 patients (85 %; Table 2). A combination of rituximab, MTX, vincristine and procarbazine (R-MVP) was used in 17 patients, MVP was used in nine, single agent MTX in six, MTX, carmustine (BCNU) and etoposide in four, MTX and temozolomide in two, and MTX and etoposide in one. In 34 patients, the MTX dose was 3.5 g/m^2 infused over 2 h; in the remainder, doses varying from 2.5 to 8 g/m^2 were used. In twelve patients, a regimen identical to the initial therapy (rituximab, MTX, procarbazine, and vincristine) was used.

Toxicity

The MTX re-challenge treatment was generally well tolerated (Table 3). Grade 3/4 toxicities at re-challenge included pulmonary toxicity in two patients and reversible nephrotoxicity in four; hematotoxicity varied according to the combination used. Only one patient discontinued treatment due to toxicity (renal failure). No MTX-related acute neurotoxicity was documented, although formal neuropsychological evaluation was not consistently available to determine rates of chronic neurotoxicity.

Table 2 Methotrexate re-challenge treatment

MTX dose	*N*	%
3.5 g/m^2	34	87
Other doses (2.5–8.0 g/m^2)	5	13
Regimen utilized		
MPV + rituximab	17	44
MPV	9	23
Single agent methotrexate	6	15
MTX, BCNU, etoposide	4	10
MTX, temozolomide	2	5
MTX, etoposide	1	3
Consolidation treatment after MTX re-challenge		
Reduced WBRT	3	8
Ocular RT	1	3
HDC-ASCT	4	10
Rituximab maintenance	2	6

MTX methotrexate, *MPV* methotrexate, procarbazine, vincristine, *BCNU* carmustine, *WBRT* whole-brain radiation therapy, *RT* radiation therapy, *HDC-ASCT*: high-dose chemotherapy with autologous stem-cell transplant

Table 3 Toxicities observed during methotrexate re-challenge

Grade 3 or 4 toxicity (CTCAE v4)	*N*
Infection	5
Neuropathy	10
Thrombocytopenia	5
Neutropenia	7
ALT	6
AST	4
Renal toxicity	4
Pulmonary toxicity	2
Leukoencephalopathy	2
Fatigue	6
Hyponatremia	1
Deep venous thrombosis	1

Response, progression-free survival and overall survival

A complete response (CR) was achieved in 29 (75 %) patients, a partial response (PR) in four (10 %) and progression of disease in six (15 %); the ORR was 85 %. Among patients who achieved a CR, four underwent high dose chemotherapy with thiotepa, busulfan, and cyclophosphamide followed by autologous stem-cell transplantation (HDC-ASCT), three received reduced dose WBRT, one received ocular RT and two continued on rituximab maintenance. Among the four patients who achieved PR, two remain alive in a sustained PR after 23 and 61 months, and two others progressed.

The median PFS was 16 months (Fig. 1a), the 6 m-PFS was 82 % (95 % CI 66–91) and 1y PFS was 57 % (95 % CI 40–71). The median OS was 41 months and the 1 year OS was 78 % (95 % CI 63–89) (Fig. 1b). The median follow up of survivors was 26 months.

On univariate analysis, KPS at the time of MTX re-challenge was a prognostic factor for PFS ($p = 0.04$), with a trend in predicting OS ($p = 0.074$). There were no statistically significant differences in PFS or OS according to MSKCC RPA class, gender, age, time from initial diagnosis (continuous variable and above versus below median), previous exposure to WBRT, use of an MTX combination similar to a previously used regimen (vs. a different regimen), or number of previous relapses (one vs. more than one).

Discussion

We report a cohort of PCNSL patients who recurred despite an initial response to MTX-based chemotherapy, and who were re-challenged with a salvage MTX-based

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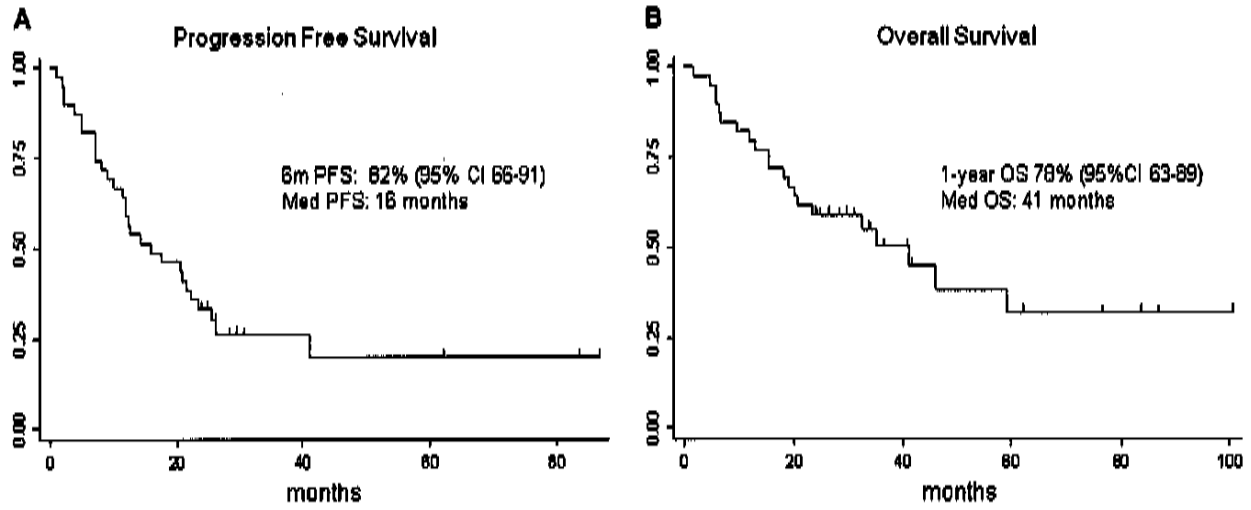

Fig. 1 Kaplan-Meyer estimates of progression free survival (a) and overall survival (b) for patients treated with MTX re-challenge for recurrent PCNSL

Table 4 Studies on treatment for relapsed or progressive primary CNS lymphoma

	N	ORR (%)	1y-OS (%)
Prospective studies			
Topotecan [9]	27	33	35
Temozolomide [18]	23	26	38
Rituximab [8]	12	36	Na
Temozolomide, rituximab [4]	16	14	71
Ara-C, VP-16 + HDC-ASCT (patients under age 65 only) [20]	43	47	60
Pemetrexed [12]	11	55	45
Retrospective studies			
Ara-C, VP-16, ifosfamide [6]	16	37	41
Procarbazine, CCNU, vincristine [11]	7	86	57
Temozolomide, rituximab [10]	15	53	55
Temozolomide [19]	17	59	35
WBRT [16]	27	74	50
WBRT [17]	48	77	54
MTX re-challenge [13]	22	91	Na
MTX re-challenge (this study)	39	85	78

Ara-C high-dose cytarabine, *VP-16* etoposide, *MTX* methotrexate, *HDC-ASCT* high-dose chemotherapy with autologous stem-cell transplant, *CCNU* lomustine, *WBRT* whole-brain radiation therapy, *Na* not available, *ORR* objective response rates, *1y-OS* 1-year overall survival

regimen. In comparison to other available treatments for recurrent PCNSL, these patients achieved favorable outcomes, with an ORR of 85 % and median OS of 41 months, suggesting that chemosensitivity to MTX was retained in spite of previous exposure to the drug. Importantly, an acceptable toxicity profile, with no significant cumulative side effects, was observed.

WBRT is often considered for salvage treatment of PCNSL in patients who have not been previously irradiated [16, 17]. However, WBRT may be associated with a high risk of neurotoxicity, especially in the setting of additional tumor-burden associated with recurrent disease, which by itself can also affect neurocognitive function. Therefore, developing salvage chemotherapy options remains of high interest. Only a few studies have reported outcomes with salvage chemotherapy for recurrent PCNSL (Table 4), mostly focusing on determining activity of single agents such as topotecan, temozolomide and rituximab [8, 9, 18, 19]. Interpreting these reports is difficult because of small sample sizes, and the studied populations have included variable proportions of patients with progressive disease primarily refractory to MTX, and patients with disease relapse developing after initial response to MTX. As a whole, such studies have found only modest efficacy, highlighting the need to develop new options for both progressive and recurrent disease.

A single retrospective study has examined the role of MTX re-challenge in recurrent PCNSL [13]. That study evaluated 22 patients who had failed single agent MTX, including two patients with isolated ocular involvement. Patients were re-treated with single agent MTX, with doses varying from 3 to 8 g/m^2. A favorable toxicity profile was observed, and the ORR was 91 %. However, the OS of those patients from the time of MTX re-challenge was not provided, and therefore it is difficult to establish the efficacy of the regimen in comparison to other salvage strategies. Our results confirm the observed activity in a larger and more heavily pre-treated population, including patients with multiply relapsed disease and patients who had failed prior WBRT.

In spite of high complete response rates to MTX re-challenge, patients with recurrent PCNSL remain at high

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risk of relapse. In some of our patients, the MTX re-challenge was used as a salvage induction chemotherapy in preparation for additional consolidation treatments such as HDC-ASCT and reduced dose WBRT, which likely contributed to prolonged disease control and survival. Interesting results have been observed in recurrent PCNSL patients treated with salvage cytarabine and etoposide (CYVE), followed by a myeloablative regimen consisting of cyclophosphamide, thiotepa and busulfan, and stem-cell rescue [20]. However, the CYVE regimen was highly toxic, with frequent and fatal hematologic toxicities in 7 % of patients. Our results suggest that MTX re-challenge may be a suitable alternative to CYVE in patients with relapsed disease as a pre-transplant induction chemotherapy. Likewise, the cytoreduction afforded by the MTX re-challenge allowed for the use of consolidation reduced-dose WBRT (23.4 Gy) in some patients, a treatment strategy currently under investigation for newly diagnosed disease [3, 21, 22]. This may constitute an interesting consolidation alternative in patients with recurrent PCNSL who are not transplant candidates.

The current study is inherently limited by its retrospective nature, varying MTX regimens employed, lack of prospective neuropsychological evaluations, and the fact that results only apply to those patients who have responded previously to MTX, who nonetheless account for the vast majority of PCNSL patients. Although confirmation in the prospective setting is warranted, this remains the largest study of PCNSL patients treated with MTX-based therapy at recurrence, and our findings suggest that induction MTX re-challenge should be considered in all patients with recurrent PCNSL who previously responded to MTX.

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Conflict of interest None.

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EXHIBIT 6

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Review

Treatment of Relapsed Central Nervous System Lymphoma with High-Dose Methotrexate

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ABSTRACT

Purpose: **Over the past decade, high-dose methotrexate has emerged as the single most effective agent in the initial treatment of primary nervous system lymphoma. However, the majority of patients who respond initially to treatment relapse. The optimal management of these patients has not been determined. We performed a multicenter, retrospective study of high-dose methotrexate in patients with relapsed central nervous system lymphoma.**

Experimental Design: **Patients with relapsed disease were eligible if they achieved a complete response to initial treatment with methotrexate-based chemotherapy or received methotrexate after gross total resection or interstitial radiation. All of the patients were retreated with a regimen containing high-dose methotrexate (≥3 g/m^2).**

Results: **Twenty-two patients with a median age of 58 years were included in the study. Overall response rates were 91% to first salvage (20 of 22 patients) and 100% to second salvage (4 of 4 patients). Median survival was 61.9 months after first relapse (95% confidence interval, 42.1–∞) and 91.9 months overall (95% confidence interval, 47.2–∞). Toxicity was primarily hematologic with 10 episodes of grade 3 or 4 toxicity during 566 cycles of chemotherapy.**

Conclusions: **These results indicate that high-dose methotrexate remains effective for relapsed central nervous system lymphoma in patients who initially respond to methotrexate and raise the possibility of deferring more toxic salvage regimens in this select group of patients.**

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INTRODUCTION

The introduction of high-dose methotrexate (HD-MTX) into the treatment of primary nervous system lymphoma has substantially improved the survival of patients with this disease (1–3). Between 50 and 65% of patients achieve a complete radiographic response after treatment with regimens containing HD-MTX, and an additional 20 to 35% of patients achieve a partial radiographic response (4–7). Complete responses (CRs) are not durable in most patients, and the majority subsequently relapse (4–7). In addition, 10 to 15% of patients have lymphoma refractory to first-line therapy. The prognosis for patients with relapsed or refractory central nervous system (CNS) lymphoma is poor. Without treatment, median survival is 2 months (8).

Small series of cases of treatment for relapsed or refractory primary nervous system lymphoma have been published (9–14). Salvage chemotherapy extends survival compared with no therapy but the number of long-term survivors is small. New approaches to the treatment of relapsed and refractory disease are needed. We report a retrospective evaluation of patients with recurrent primary nervous system lymphoma treated with high-dose intravenous MTX at four institutions.

PATIENTS AND METHODS

Patients. The records of immunocompetent patients with CNS lymphoma treated between 1996 and 2003 at Massachusetts General Hospital, Johns Hopkins University, University of Alabama at Birmingham, and Wake Forest University School of Medicine were reviewed. All of the patients had pathologically confirmed non-Hodgkin's lymphoma, involving the brain parenchyma, vitreous fluid, and/or cerebrospinal fluid (CSF). Patients who were treated with MTX-based chemotherapy as first-line treatment were assessed for response to treatment. Those who achieved a CR to therapy, defined as resolution of contrast-enhancing tumor after initial treatment, were included in the study. A subset of patients who received MTX-based chemotherapy after gross total resection or interstitial radiation was also included in the study. The evaluation of patient records was approved by the institutional review board (IRB) at Massachusetts General Hospital.

Treatment. The administration of HD-MTX has been described in detail elsewhere (5). Patients received hydration with oral or intravenous sodium bicarbonate until urine output exceeded 100 mL/h and urine pH exceeded 7.0. Intravenous MTX (≥3g/m^2) was administered with 1:1 dose reduction for each point of glomerular filtration rate below 100 mL/min. For example, a patient with a glomerular filtration rate of 85 received a 15% dose reduction. Patients with glomerular filtration rate <50 mL/min were excluded from receiving MTX. Urine output greater than 100 mL/h and urine pH >7 were maintained until MTX was adequately cleared from the serum. Rescue with

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leucovorin calcium was initiated 24 hours after the start of MTX infusion and continued until MTX was cleared.

Response to chemotherapy was monitored by contrast-enhanced cranial magnetic resonance imaging for parenchymal disease, by CSF cytopathology for leptomeningeal disease, by slit-lamp examination with or without vitreal biopsy for intraocular lymphoma, and by contrast-enhanced spinal magnetic resonance imaging for neurolymphomatosis. Time between evaluations was determined by the treating physician. Response to treatment after reinduction was defined as CR if there was complete resolution of the enhancing tumor without evidence of ocular or leptomeningeal disease, mixed response if there was a CR in brain parenchyma but persistent disease in the eyes, partial response if there was at least a 50% reduction in the volume of enhancing tumor, and progressive disease if there was an increase in the size of enhancing tumor or the appearance of new lesions. All other responses were defined as stable disease.

Patients were treated every 2 weeks until they achieved a CR in brain without evidence of ocular or nerve disease, achieved a partial response but failed to improve with continued therapy, or experienced progressive disease. Those who achieved a CR were then treated monthly for a period of time determined by the treating physician.

Statistical Considerations. Time to relapse was defined as the interval of time between documentation of CR after initial treatment to documentation of relapsed disease. Patients were assigned multiple times to relapse (*e.g.*, time to first relapse, time to second relapse) if they achieved multiple CRs after salvage therapy. Overall survival was defined as the time from initial diagnosis of CNS lymphoma to death or last follow-up. Survival after relapse was defined as the time from first relapse to death or last follow-up. Toxicity data were collected by a review of medical records.

The primary end points in this analysis were best radiographic response after salvage therapy, time to death from initial CNS diagnosis, and time to death from first salvage. Time to death from initial CNS diagnosis is a left-truncated event time, because it necessarily exceeds the time to initial relapse from initial CNS diagnosis. Secondary end points included time to relapse after first salvage therapy, time to relapse after second salvage therapy, and toxicity. Time to relapse after first salvage therapy is a right-truncated event time, because it necessarily precedes the time to death or last follow-up. The Kaplan–Meier method was used to estimate curves for overall survival and survival after relapse. Cox proportional-hazards models were fitted to estimate hazard ratios and to perform regression analysis. The estimation and regression analyses were adjusted for truncation where necessary. Age and ocular involvement were used as predictors in univariate regression models for each of the end points. Number of cycles of chemotherapy until initial response, time to initial response, and time to first relapse were used as predictors of second response, time to second relapse, and time to death from initial response. The number of cycles of chemotherapy until second response was used in the analysis of time to second relapse.

RESULTS

The records of patients with relapsed CNS lymphoma at the four participating institutions were reviewed. Twenty patients had achieved a CR after initial MTX-based therapy. Two patients had no evidence of residual disease after gross total resection or interstitial radiation and received MTX (Table 1). All of the patients were treated with MTX-based chemotherapy on relapse. There were 13 males and 9 females with a median age of 58 years. Previous medical histories included testicular non-Hodgkin's lymphoma in remission (three patients), rheumatoid arthritis (one patient), immune thrombocytopenic purpura (one patient), and recur-

Table 1 Patient characteristics and initial treatment with MTX

Patient	Age/Gender	Extent of disease	Initial MTX regimen	Cycles to CR
1	80/M	Brain	HD-MTX*	11
2	35/F	Brain	HD-MTX	7
3	78/M	Brain	HD-MTX	2
4	64/M	Brain	HD-MTX	4
5	52/F	Brain	HD-MTX → SRS	14
6	62/F	Brain	HD-MTX → WBRT	3
7	40/F	Brain	HD-MTX	6
8	67/M	Brain + nerve	HD-MTX	8
9	50/F	Brain + ocular	HD-MTX	8
10	72/F	Brain + ocular	CHOD → M-CHOD	6
11	62/M	Brain + CSF	M-CHOD	5
12	31/F	Brain → ocular	Ocular RT → HD-MTX	4
13	60/M	Brain	Interstitial RT → HD-MTX	7
14	44/M	Ocular → brain	Ocular RT → HD-MTX	8
15	30/M	Brain	STR→ MTX, Ara-C→stem cell rescue	n/a
16	64/M	Ocular → brain	Ocular RT → HD-MTX	6
17	57/M	Brain	GTR → HD-MTX	n/a
18	42/F	Brain	HD-MTX	6
19	49/M	Brain + ocular	WBRT → HD-MTX + ocular RT	6
20	59/F	Brain	HD-MTX	3
21	57/M	Brain	HD-MTX	14
22	56/M	Brain	HD-MTX	6

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; M-CHOD, methotrexate, cyclophosphamide, vincristine, Adriamycin, and dexamethasone; RT, radiation therapy; STR, subtotal resection; Ara-C, 1-β-D-arabinofuranosylcytosine; GTR, gross total resection.

* HD-MTX, ≥3.5 g/m^2.

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rent Bell's palsy (one patient). At initial diagnosis, 15 patients had disease confined to the brain only, 2 had disease confined to the vitreous, 3 had disease in the brain and vitreous, and 1 each had disease in the brain/CSF and brain/nerve (Table 1). Initial staging for all of the patients included HIV serology and lumbar puncture for cytology and flow cytometry. Computed tomography scans of the thorax, abdomen, and pelvis were obtained in selected patients.

Initial Treatment with Methotrexate. All of the patients received HD-MTX. Two of the 22 patients had surgical resections before chemotherapy, 5 received focal radiation before chemotherapy, and 3 received other chemotherapeutic agents besides MTX (Table 1). In these 22 patients, the median number of cycles to CR was 6 (range, 2–14), and the median time to first relapse was 24.4 months (range, 2–100 months).

First Salvage with Methotrexate. Recurrent disease was documented in brain in 17 patients, in vitreous in 1, in nerve in 1, in brain/ocular in 1, and in brain/CSF in 2. Nineteen patients received cycles of HD-MTX at 8 g/m^2, two patients at 3.5 g/m^2, and one patient at 3 g/m^2. No patients received whole-brain radiation, intrathecal chemotherapy, or other chemotherapy agents. One patient received stereotactic radiosurgery to a small residual focus of enhancing tumor. The median number of cycles to response was four (range, 1–14). CR was achieved by 16 (73%) of 22 patients, mixed response by 1 (5%) of 22 patients, partial response by 3 (14%) of 22 patients, and progressive disease by 2 (9%) of 22 patients. The overall response rate for first salvage was 91%.

Second Salvage with Methotrexate. Seventeen patients were at risk for recurrent disease at the completion of first salvage therapy; 7 patients relapsed and 1 was lost to follow-up. The median time to second relapse for these patients was 25.8 months [95% confidence interval (CI), 13.5–∞]. Four patients received HD-MTX for second salvage, one patient received whole-brain radiation followed by temozolomide, one patient received topotecan, and one patient refused treatment. For patients who received HD-MTX, the median number of cycles to response was 4.5 (range, 2–6). CR was achieved by two (50%) of four patients and partial response by two (50%) of four. The overall response rate for second salvage was 100%. The two patients who achieved a CR relapsed at 1.5 and 15 months. Both were treated with topotecan and whole-brain radiation for recurrent lymphoma.

Survival. Seven patients have died, and one has been lost to follow-up. Median survival from initial diagnosis was 91.9 months (95% CI, 47.2–∞) and from first salvage was 61.9 months (95% CI, 42.1–∞; Fig. 1).

Univariate and Multivariate Analysis. Results of univariate logistic regression models and analysis by Cox proportional hazards regression models revealed no variables with significant prognostic value. However, there was a trend toward significance for a relationship between increasing number of cycles during initial treatment and longer time to first relapse (hazard ratio 1.18, $P < 0.1$) and between ocular involvement and longer survival after salvage (hazard ratio 3.37, $P = 0.14$).

Toxicity. HD-MTX was well tolerated by the majority of patients. The median number of cycles for this selected cohort of patients was 25 (range, 9–58). Toxicity was primarily hematologic with four episodes of neutropenia (one grade 1, two grade 2, and one grade 4), seven episodes of thrombocytopenia (five grade 1, one grade 2, and one grade 3), two episodes of anemia (one grade 1 and one grade 2), four episodes of azotemia (one grade 1, three grade 2), four episodes of hepatotoxicity (grade 3), two episodes of allergy (grade 1), three episodes of thrombosis/embolism (two grade 3 and one grade 4), two episodes of mucositis (one grade 1 and one grade 2), two episodes of diarrhea (one grade 1 and one grade 2), and one episode of infection (grade 3). In a total of 566 cycles, there were ten episodes of grade 3 or 4 toxicity.

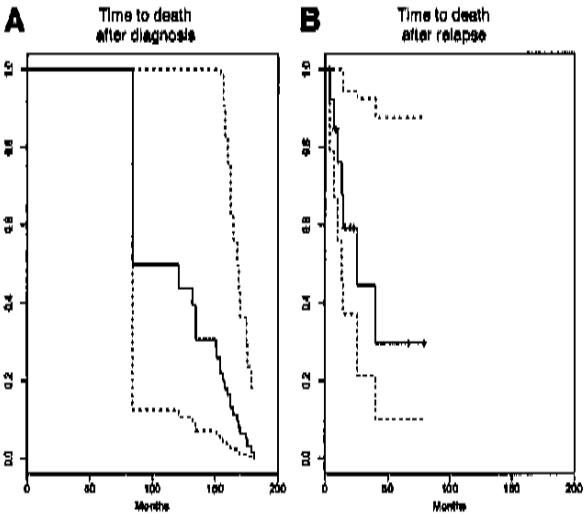

Fig. 1 Kaplan–Meier survival curves for time to death after diagnosis (*A*) and time to death after first relapse (*B*). *Dashed lines*, the 95% CI.

DISCUSSION

We studied the efficacy and tolerability of HD-MTX as salvage therapy for a subset of patients with relapsed CNS lymphoma who initially responded to MTX therapy. The objective response rates were 91% after first salvage (20 of 22 patients) and 100% after second salvage (4 of 4 patients). Time to relapse after first salvage with HD-MTX was similar to the time to relapse after initial treatment (25.8 months *versus* 24.4 months, respectively; Fig. 2). Because only patients who experienced relapse before the end of follow-up were included in this group, the median time to relapse for this sample may be an underestimate for all patients with CNS lymphoma. However, this bias should be slight because we have obtained at least 33 months of follow-up on each subject. Median survival was 61.9 months after salvage and 91.9 months after CNS diagnosis.

These findings expand on prior reports of chemotherapy for primary CNS lymphoma. In one series, 10 of 16 patients with relapsed disease after combined-modality therapy achieved a CR after salvage therapy (6). Similarly, 5 of 10 patients treated with cytarabine and etoposide in anticipation of intensive chemotherapy and stem-cell rescue achieved a CR, and 3 of 10 achieved a partial response for a response rate of 80% (14). However, not all patients treated previously with chemotherapy respond to salvage therapy. Among patients treated with MTX after blood–brain barrier disruption, those who received prior chemotherapy were substantially less likely to achieve CR than those who did not (33 *versus* 69%, respectively; 7). In this study, the initial response to chemotherapy was not noted. Thus, it is not known how many of these patients had progressive rather than relapsed disease.

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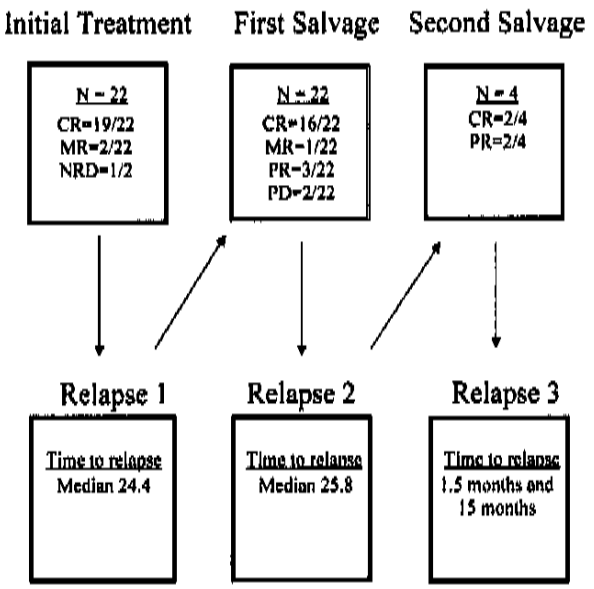

Fig. 2 Flow chart summarizing the number of patients treated, response to treatment, and time to recurrence. All times are in months. (*MR*, mixed response; *NRD*, no residual disease; *PR*, partial response; *PD*, progressive disease).

In the present study, survival after diagnosis and survival after relapse, compared favorably with previous reports. In studies of whole-brain radiation (9), intra-arterial carboplatin (10), topotecan (11), procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNA), vincristine (PCV; ref. 12), temozolomide (13), and intensive chemotherapy followed by stem-cell rescue (14), median survival after salvage ranged from 2+ months to 12+ months. For patients treated initially with combined-modality therapy, median survival after relapse was 27 months (6). Meta-analysis of 24 studies revealed a median survival of 14 months after salvage for patients with relapsed or refractory disease treated with a variety of regimens (8).

At the present time, there are no evidence-based guidelines to determine the optimal duration of treatment with HD-MTX. Many schedules discontinue treatment after a predetermined number of cycles or reduce the frequency of chemotherapy once maintenance is complete. Although patients who achieve a CR have no evidence of enhancing disease on magnetic resonance imaging, previous studies have documented microscopic disease in the absence of contrast-enhancing lesions (15). It is not known whether relapse is due to the failure of current maintenance schedules to achieve disease control or due to the emergence of clones resistant to MTX. Future studies of CNS lymphoma are needed to address the optimal duration of treatment with HD-MTX and to identify combined chemotherapy regimens with superior antilymphoma activity.

These data must be interpreted in the context of the study design. First, patients were highly selected to include those who achieved a complete response to initial therapy with HD-MTX. This may have led to selection of a subset of patients with tumors that were particularly sensitive to chemotherapy and, thus, were predisposed to have longer survival times. However, because 50–65% of patients with primary CNS lymphoma achieve CR with MTX monotherapy the results reported herein are potentially applicable to more than one half of all patients with primary CNS lymphoma. Second, previous studies of salvage chemotherapy often included patients with recurrent and refractory disease. Including both populations leads to lower response rates and shorter survival because patients with refractory disease do worse than those with recurrent disease.

In conclusion, salvage therapy with HD-MTX appears to be effective for patients with CNS lymphoma who relapse after initial CR to MTX. Given the low toxicity associated with HD-MTX, we believe it is reasonable to consider deferring treatment with whole-brain radiation therapy or more toxic chemotherapy regimens until these patients have been given a trial of HD-MTX. Finally, we feel that prospective studies of patients with recurrent or refractory disease are warranted, given the high rate of relapse in CNS lymphoma and the lack of established agents to treat this condition.

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DECLARATION

DECLARATION OF MARTIN CALHOUN

Martin Calhoun hereby declares as follows:

1. I am of the attorneys representing the defendants in *Pilliod v. Monsanto Company, et al.* and have represented defendants in other Roundup® lawsuits pending in Judicial Council Coordinated Proceeding ("JCCP") No. 4953 and in other jurisdictions. I submit this declaration in support of Defendants' Opposition to Motion for Trial Preference.

2. I am over the age of 18. I make the statements set forth herein based on my personal knowledge and my review of Mr. and Mrs. Pilliod's medical records. If I were called to testify, I could and would competently testify to the statements in this declaration.

3. I am a partner in the law firm Hollingsworth LLP. I have been a practicing defense attorney since 1991 and have extensive experience conducting discovery in complex products liability cases and preparing to defend such lawsuits before and at trial.

4. Preparing for a single-plaintiff Roundup® trial is a massive undertaking. Trial preparation becomes even more complicated and time-consuming if the trial involves two plaintiffs with different medical histories who each allege different NHL sub-types caused by different individual exposures to Roundup®-branded herbicides.

5. Because the *Pilliod* case is not currently set for trial, defendants have not yet pursued any discovery in this case (except for recently beginning the process of requesting medical records from various treating health care providers, promptly after the Pilliods served Plaintiff's Fact Sheets and medical records releases on defendants).

6. Extensive fact discovery remains to be conducted in the *Pilliod* case before defendants will be ready for trial, including issuing written discovery requests; obtaining voluminous medical records from various treating health care providers; and taking depositions of Mr. and Mrs. Pilliod, their treating physicians, and other fact witnesses.

7. Defendants also will need substantial time for expert disclosures and discovery, including identifying the right general and plaintiff-specific expert witnesses for the *Pilliod* lawsuit; deposing any plaintiff's expert witnesses; and defending the depositions of defendants' expert witnesses. In addition to the *Sargon* briefing regarding general causation that has been

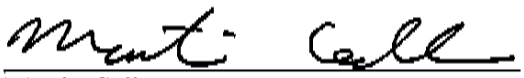
scheduled by the Court for the entire JCCP, substantial time will be required for *Sargon* briefing in the *Pilliod* case regarding experts who address issues other than general causation, dispositive motions briefing, and motion *in limine* briefing. Moreover, defendants will need a significant amount of time to prepare for trial.

8. In my opinion, it is completely unrealistic to expect that the work required to adequately defend against the two separate plaintiffs' claims at trial can be done within approximately two months (from the October 9, 2018 hearing on the Motion for Trial Preference to the December 2018 trial date requested in the motion) – or even within the 120 days contemplated by CCP § 36(f).

9. A true and correct copy of *In re Toyota Motor Cases*, No. 4621, 2012 WL 965830 (Los Angeles County Super. Ct. March 5, 2012) is attached as Exhibit 1.

I declare under penalty of perjury of the laws of the State of California that the foregoing is true and correct.

Executed this 25th day of September, 2018 in Washington, D.C.



Martin Calhoun

EXHIBIT 1

2012 WL 965830 (Cal.Superior) (Trial Order)
Superior Court of California.
Los Angeles County

Coordination Proceeding Special Title TOYOTA MOTOR CASES.
This document relates to: All Cases.

No. 4621.
March 5, 2012.

Orders Denying Motions for Preference, Setting Trial Dates, Selecting Bellwethers and Tentative Orders Regarding Scheduling Bellwether Trials and the D.A. Case

Anthony J. Mohr, Coordination Trial Judge.

Date: January 26, 2012

Time: 8:30 a.m.

Dept: 309-CCW

Coord. Trial Judge: Hon. Anthony J. Mohr

On January 26, 2012, at 8:30 a.m. in Department 309 of this Court, the following matters in *Toyota Motor Cases* (JCCP No. 4621) came on for hearing:
(1) Status Conference;

(2) Plaintiff Uno's Motion for Preference in *Uno v. Toyota Motor Sales, U.S.A., Inc., et al.* (L.A. County Superior Court, Case No. KC057888) [1];

(3) Plaintiffs' Motion for Preference in *Rincon v. Levin, et al.* (Ventura County Superior Court, Case No. 56-2010-00381196-CU-PA-VTA) [2]; and

(4) Plaintiffs' Motion for Severance in *Rincon v. Levin, et al.* (Ventura County Superior Court, Case No. 56-2010-00381196-CU-PA-VTA). [3]

Brian R. Strange, Mark P. Robinson, Jr., Garo Mardirossian, Todd A. Walburg, Moses Lebovits and John P. Kristensen appeared on behalf of the Plaintiffs' Executive Committee, Plaintiffs' Co-Lead Class Counsel, and the Plaintiffs' Steering Committee. John D. Arya, Mark V. Berry, Anne Hanna, Stephanie A. Jones, Sean D. Beatty and Allen L. Lanstra appeared personally, and Thomas J. Nolan appeared telephonically, on behalf of the Toyota Defendants.

SELECTION OF BELLWETHER TRIALS

IT IS ORDERED that Plaintiffs are permitted to withdraw *Jorge v. Toyota* (L.A. Super. Ct., Case No. BC469915) as a proposed bellwether case, and in its place substitute in *Dushane v. Toyota* (L.A. Super. Ct., Case No. BC439156), as a new proposed bellwether case.

IT IS FURTHER ORDERED that Plaintiffs are permitted to withdraw *Torrens v. Toyota* (L.A. Super. Ct., Case No. YC065630) as a proposed bellwether case, and in its place substitute in *Ezal v. Toyota* (San Luis Obispo Sup. Ct., Case No. CV090425), as a new proposed bellwether case.

THE COURT ORDERS THAT the parties rank in order of preference their respective proposed bellwether cases, and provide the information requested by the Court in the message posted on Case Anywhere on January 27, 2012 (make, date and model of vehicle involved in each case; trial time estimate, preferably in hours, for each case). Pursuant to the Court's request, the parties have provided the following ranked lists:

Plaintiffs' Proposed Bellwether Trial Cases

1. *Uno v. Toyota Motor Sales, U.S.A., Inc., et al. ("Uno")*, which involves a 2006 Toyota Camry. Plaintiffs' time estimate is approximately 180 hours or 40 court days of trial;

2. *Houllf v. Toyota Motor Sales, U.S.A., Inc., et al. ("Houlf")*, which involves a 2008 Toyota Tundra. Plaintiffs' time estimate is approximately 70 hours or 15 court days of trial;

3. *Dushane v. Toyota Motor Sales, U.S.A., Inc., et al. ("Dushane")*, which involves a 2005 Toyota Prius. Plaintiffs' time estimate is approximately 180 hours or 40 court days of trial;

4. *Ezal v. Toyota Motor Sales, U.S.A., Inc., et al. ("Ezal")*, which involves a 2005 Toyota Camry. Plaintiffs' time estimate is approximately 180 hours or 40 court days of trial.

Toyota's Proposed Bellwether Trial Cases

1. *Feras Al Jamal, et al. v. Toyota Motor Sales, U.S.A., Inc., et al. ("Al Jamal")*, Los Angeles County Superior Court (originally filed in Riverside County Superior Court), RIC 10019862, filed October 8, 2010, and involving a 2005 Toyota Camry. Based on the number of parties and witnesses, Toyota preliminarily estimates 35-40 court days (175-200 hours) for trial, excluding jury selection and deliberations.

2. *Mercury Insurance Company v. Toyota Motor Sales, U.S.A., Inc., et al.*, Los Angeles County Superior Court (originally filed in Los Angeles County Superior Court), 11K03341, filed February 16, 2011, and involving a 2007 Toyota Camry. Based on the number of parties and witnesses, Toyota preliminarily estimates 15-20 court days (75-100 hours) for trial, excluding jury selection and deliberations.

3. *David Grainger, et al. v. Toyota Motor Sales, U.S.A., Inc., et al.*, Los Angeles County Superior Court (originally filed in Los Angeles County Superior Court - Central District), BC434646, filed March 25, 2010, and involving a 2010 Toyota Camry. Based on the number of parties and witnesses, Toyota preliminarily estimates 35-40 days (175-200 court hours) for trial, excluding jury selection and deliberations.

4. *Gloria Flores, et al. v. Toyota Motor Sales, U.S.A., Inc., et al.*, Los Angeles County Superior Court (originally filed in Contra Costa County Superior Court), C10-00681, filed March 18, 2010, and involving a 2002 Toyota Camry. Based on the number of parties and witnesses, Toyota preliminarily estimates 35-40 days (175-200 court hours) for trial, excluding jury selection and deliberations.

IT IS FURTHER ORDERED that *Uno* will be the first bellwether trial, with jury time-qualification commencing on a date between November 1, 2012 and November 30, 2012, the specific date to be determined by the Court. Trial will commence after January 1, 2013, the specific date to be determined by the Court.

IT IS FURTHER ORDERED that in the event that Uno settles or is dismissed more than two (2) weeks before October 15, 2012, *Houlf will* assume the trial schedule set forth above for *Uno*. The Court finds that discovery can be completed in sufficient time to allow for trial this fall.

IT IS FURTHER ORDERED that the third bellwether trial will be *Ali Jamal,* the first selection of the Toyota defendants. In the event that *Uno* and *Houlf settle* or are dismissed more than two (2) weeks before October 15, 2012, *Al Jamal* will assume the trial schedule set forth above for *Uno*.

IT IS FURTHER ORDERED that if plaintiffs dismiss or otherwise dispose of a case selected by Toyota, Toyota's next case will move up a position, and Toyota may select another case to fill the then open fourth position.

THE D.A. CASE

THE COURT FURTHER ORDERS that the case *of People of the State of California v. Toyota Motor Sales, U.S.A., Inc., et al.* (the "D.A. Case") will commence at the same time as the first bellwether trial and will "run in the background" of the bellwether trials.[4] In that connection, IT IS HEREBY ORDERED AS FOLLOWS:

1. IN GENERAL:

1. The District Attorney, his staff and his counsel shall not argue or otherwise make presentations to the juries in any private bellwether actions. In the presence of the juries, the District Attorney, his staff and his counsel shall not: (i) appear at counsel's table, (ii) examine witnesses, (iii) argue to the Court, or (iv) otherwise conduct themselves in a manner that suggests involvement related to the private bellwether actions in any way.

2. The juries shall not be informed that the District Attorney is bringing a case against the Toyota defendants. No reference shall be made to the D.A. Case ill front of the juries, nor may documents referencing the D.A. case be published to the juries or allowed in the jury room. The parties and counsel will conduct themselves, both in the courtroom and in public areas of the courthouse, so as not to communicate information about the D.A. Case to jurors. Unless specifically allowed by the Court, reference shall not be made in the presence of the jury to law enforcement actions, public enforcement actions, or public injunction actions brought against the Toyota defendants. The parties and counsel shall not make statements to the press or public statements outside of the proceedings concerning their involvement and participation in the D.A. case, as well as its trial concurrently with, the private bellwether actions.

3. The Court reserves the right to issue further orders to protect the parties against undue prejudice and to maximize efficiency.

II. DESIGNATION OF TESTIMONY

4. In connection with the D.A. case, the parties will be permitted to object to testimony and exhibits that the jury saw and heard during the private bellwether actions as well as designate as evidence in the D.A. case testimony and exhibits that the jury saw and heard during the private bellwether actions. As a tentative protocol: 1) such designations shall be lodged and served on trial counsel 30 calendar days after judgment has been entered in the private action, and objections to designations on relevance, completeness or other grounds shall be lodged and served 45 calendar days after judgment

has been entered, unless a different schedule is ordered by the Court. 2) The parties will meet and confer in good faith to agree on joint transcript and exhibit designations. Remaining objections will be resolved by the Court. 3) After the Court has resolved objections to party designations for a particular private bellwether action, those designations may be amended only with the Court's permission. 4) Upon service and lodging of the amended designations, the opposing party or parties shall have 15 calendar days to serve and lodge objections. 5) The parties will meet and confer in good faith to agree on joint transcript and exhibit designations. Remaining objections will be resolved by the Court.

III. WITNESS TESTIMONY SEPARATE FROM THE PRIVATE BELLWETHER ACTIONS

5. Examination of witnesses will first proceed in the private bellwether action until counsel have finished for purposes of that case. Only after the jury has been removed from the courtroom will any examination or cross-examination of the witness proceed in the D.A. Case.
26. While the D.A. Case is running concurrently with another action, evidence presented in the DA case (outside the jury's presence) will be limited to the model/year vehicle at issue in the private action (*e.g.*, 2006 Toyota Camry in *Uno*) and the subject matter of the private bellwether action. Witness examinations in the D.A. Case outside the jury's presence shall not duplicate examination that has occurred in the jury's presence during the private bellwether action.

7. A party is not prohibited from later calling a witness who has previously been examined in any of the private bellwether cases or in the D.A. Case while running in the background of the private bellwether cases.

THE UNO PLAINTIFFS' MOTION FOR TRIAL PREFERENCE

Plaintiffs Yasuharu and Jeffrey Uno have moved for trial preference. They succeed to decedent Noriko Uno's claims after she was killed in an automobile accident on August 28, 2009. Noriko was driving her 2006 Toyota Camry when Plaintiffs allege that the vehicle experienced a A event causing the vehicle to speed up uncontrollably. Noriko lost control, hit a telephone pole and died at the scene.

Plaintiff Yasuharu was not in the car when the accident occurred. But that fact is not relevant. He is 69 years old and in ailing health. (Decl. of Mardirossian, ¶ 12.) He suffers from end-stage renal disease and Plaintiffs claim he will die soon. On this basis, Plaintiffs move for trial preference under Cal. Civ. Proc. Section 36(d). Plaintiffs also move for preference under Cal. Civ. Proc. section 36(e), claiming that preference is in the "interests of justice."

The problem with this motion is the lack of admissible evidence of Yasuharu's medical condition, including but not limited to evidence that he will die soon.

Cal. Civ. Proc. section 36(d), states:

> (d) In *its discretion, the court may* also grant a motion for preference that is accompanied *by clear and convincing medical documentation that concludes that one of the parties suffers from an illness or condition raising substantial medical doubt of survival of that party beyond six months,* and that satisfies the court that the interests of justice will be served by granting the preference.

(Emphasis added.)

The only evidence offered to demonstrate that Plaintiff Yasuharu may not live more than six months is the inadmissible opinion of his counsel, Mr. Mardirossian. (*See* Decl. of Mardirossian, ¶ 12.) Mr. Mardirossian attaches Yasuharu's medical records to his declaration, but there is no evidence that he is able to authenticate these records. Worse, even if

the records are admissible, none of them contains a medical opinion regarding the estimated life span of including his current condition, dependency on dialysis, unlikely chances of receiving a kidney transplant in his lifetime, and increasing frailty raises substantial doubt that Plaintiff Yasuharu Uno will survive beyond six months." *Ibid.* Mr. Mardirossian is not a physician and has no basis for this statement. Defendants properly object to the inadmissible opinion. Defendants' Evidentiary Objections to this portion of the Declaration of Garo Mardirossian, ¶ 5 is sustained. Moreover, a review of Yasuharu's medical records shows no medically-based opinion related to his estimated life span. While the records show that Mr. Yasuharu is undergoing dialysis and is on the waiting list for a kidney transplant at Loma Linda Transplant Institute, the records do not address his projected life span. (*See* Decl. of Mardirossian, Ex. A.) Plaintiffs have not provided any medical opinion related to the records they attach and counsel and the court are unqualified to render their own. Without some qualified interpretation of the medical records there is no evidence showing that Plaintiff Yasuharu will die within six months. Plaintiffs cannot meet the "clear and convincing" standard set forth in Cal. Civ. Proc. section 36(d).

Plaintiffs also move the court for trial preference under Cal. Civ. Proc. section 36(e), which states:

> (e) Notwithstanding any other provision of law, the court may in its discretion grant a motion for preference that is supported by a showing that satisfies the court that the interests of justice will be served by granting this preference.

(Emphasis added.)

While the court is not compelled to give preference to Plaintiffs' case, it has discretion about whether to permit Plaintiffs' request for trial preference. Defendant insists that 120 days is not enough time to conduct discovery into the cause of the alleged UA event (Opposition, 8:13-20), and without proper discovery it will be prejudiced by a preferential trial date. (*See Dick v. Superior Court* (1986) 185 Cal.App.3d 1159, 1166: "A second critical factor which the court must take into account in ruling on a motion for trial preference is any prejudice to the defendant resulting from the accelerated trial date.") Toyota and the plaintiffs' steering committees have been planning for the first bellwether trial to begin, or at least to begin jury time qualification, by late autumn of 2012. To upset that trajectory and require the parties, especially Toyota, to proceed to trial without conducting adequate discovery would be unfair.

For these reasons, the court DENIES the Uno motion for preference. However, the denial is without prejudice. It appears that, properly presented, there may be evidence that Plaintiff Yasuharu is in declining health and that it would be appropriate to allow Plaintiffs some expedited trial date. Moreover, the plaintiffs' steering committee is willing to select the Uno case as its first bellwether trial. Therefore, on the court's own motion and as stated above, the court selects the Uno action as plaintiffs' first bellwether trial, to commence as noted earlier in this order. In that connection, the court authorizes case specific discovery as well as discovery with respect to the 2006 Toyota Camry, which, the court is told, is the model and year of the vehicle Noriko Uno was driving when she was killed. The court understands that the parties may wish to conduct discovery beyond these topics (and other topics that already have been authorized in the coordinated proceedings). Any additional discovery (e.g., interrogatories, requests for admissions) must be approved in advance by the court before it is served.

FINAL STATUS CONFERENCE IN ALL CASES

In a coordination of this magnitude, the court anticipates that each trial may require several "final status conferences." The first, in Uno, will occur on September 17, 2012, at 1:30 PM. Counsel in the D.A. Case may attend and participate. By then the court expects the following (and incidentally, the following will apply to final status conferences in all jury trials in this coordination, bellwether or not,):

1. Twenty-one days before the final status conference, counsel must file and serve any in limine motions it wishes to make. That gives opposing counsel the appropriate time to oppose them if they wish to do so. While reply memoranda are not forbidden, they are discouraged, because the court finds they are of little use in connection with in limine motions.

2. Counsel are to submit proposed jury instructions. We will settle as many as possible during the final status conference(s).

3. Counsel are to submit proposed verdict forms. We will settle as much as we can of these during the final status conference(s).

4. Counsel are to submit a joint witness list on which the names of all potential witnesses are "blended" and alphabetized. No caption, attorney, or law firm names are to appear on the list. No later than the first day of jury selection, counsel are to have eighteen copies available to distribute to the prospective jurors in the "six pack."

5. Counsel are to exchange exhibit lists. Counsel must indicate which exhibits they object to as well as the grounds. The court will attempt, as much as possible, to rule on objections before the trial begins.

6. There is no need to submit proposed neutral statements to be read to the prospective jurors. Each side will have a chance to present a five minute "mini-opening" before voir dire begins.

7. The jurors will be allowed to submit written questions during the course of the trial.

Counsel should meet and discuss whether they would like to give a questionnaire to the prospective jurors once we time qualify them. If so, please prepare a questionnaire. To the extent you do not agree on questions, let me know what they are, and I will rule on them

THE RINCON MOTION FOR TRIAL PREFERENCE AND SEVERANCE

Plaintiffs are Rosa, Adriana and Karla Rincon. Rosa was driving a van with Adriana and Karla and their deceased son/brother Bernardino Jr., when they were struck by Defendant Levin. Mr. Levin alleges-by way of a cross-complaint against Toyota-that his 2009 Toyota Camry experienced a UA event and caused the accident. All of the plaintiffs were injured in the accident.

Adriana is under 14 years old. Based on that fact, Plaintiffs move for trial preference under Cal. Civ. Proc. Section 36(b). Anticipating that Mr. Levin and Toyota will not be prepared to try the substantive issue of what caused the alleged UA event, Plaintiffs also move for severance from the Levin v. Toyota cross-complaint. This is Plaintiffs' third attempt at severance. (*See* Decl. of Tamel, Ex. A, 2:1-8; Ex. C, 1:1-14.) Cal. Civ. Proc. section 1008(b) only permits a motion for reconsideration based upon a showing of new facts, circumstances, or law.

Plaintiffs argue that this latest motion for trial preference does present new facts or circumstances. (Severance Motion, 6:22-25; Decl. of Burkes, ¶ 13.) They are wrong. They could have moved for preference at any time since being added onto this coordinated proceeding because, Adriana and Karla had been under 14 years of age since the Rincons filed this action.[5] There is no new fact or circumstance which led to Plaintiffs' need for trial preference; at least Plaintiffs mention none in their motion. The court DENIES Plaintiffs' motion for severance because there are no new facts or law justifying their untimely motion for reconsideration.

Even if we consider this motion afresh, it appears that severing the case would not result in an efficient use of time. Moreover, it would make it all but futile for Mr. Levin to mount a defense against the Rincons' action.

With respect to the motion for preference, Cal. Civ. Proc. section 36(b) provides as follows:

> A civil action to recover damages for wrongful death or personal injury shall be entitled to preference upon the motion of any party to the action who is under 14 years of age unless the court finds that the party does not have a substantial interest in the case as a whole.

While Cal. Civ. Proc. section 36(b) is mandatory by its terms, special consideration is given to coordinated cases. This is evident from Cal. Civ. Proc. section 404.7, which provides:
Notwithstanding any other provision of law, the Judicial Council shall provide by rule the practice and procedure for coordination of civil actions in convenient courts, including provision for giving notice and presenting evidence.

California Rules of Court, Rule 3.504(b) (formerly Rule 1504) states:

To the extent that the rules in this chapter conflict with the provisions of law applicable to civil actions generally, the rules in this chapter prevail, as provided by [CCP] 404.7.

California Rules of Court, Rule 3.541(b)(2) (formerly Rule 1541(b)(2) and in the same chapter as Rule 3.504 above) states in pertinent part:

> The judge may, for the purpose of coordination and to serve the ends of justice ... (2) schedule and conduct... a trial... to the efficient use of judicial facilities and resources.

Taken together, courts have interpreted Cal. Civ. Proc. section 36(b) as non-mandatory in coordinated cases due to its conflict the California Rules of Court on the same topic. In *Abelson v. National Union Fire Insurance Company of Pittsburgh* (1994) 28 Cal.App.4th 776, the court noted the non-mandatory nature of Cal. Civ. Proc. section 36, due to the same type of conflict. The *Abelson* court recognized that conflicts between section 36 and the coordination rules may exist and noted that the trial court had discretion on whether to follow section 36 in coordinated cases:
Rule 1504 provides: "(a) Except as otherwise provided in these rules, all provisions of law applicable to civil actions generally apply regardless of nomenclature to an action included in a coordination proceeding if they would otherwise apply to such action without reference to this rule. *To the extent that these rules conflict with such provisions, these rules shall prevail* as provided by section 404.7 of the Code of Civil Procedure."

Adelson, supra, 28 Cal.App.4th at 788 (emphasis added.)

In this case, the court and counsel have already dealt with scheduling certain coordinated cases for trial and selecting bellwether cases. Rule 3.541(b)(2) permits the Court to schedule trials in furtherance of justice and for the efficient use of judicial facilities and resources. According to *Adelson,* Rule 1504 and Cal. Civ. Proc. section 404.7, the court's coordinated power trumps the otherwise mandatory application of Cal. Civ. Proc. section 36.

While the court is not compelled to give preference to Plaintiffs' case, it has discretion with respect to whether to allow Plaintiffs a trial preference. (*See* Cal. Civ. Proc. section 36(e): the court has discretion to grant preference when doing so would be in the "interests of justice.") Plaintiffs argue only one fact related to why the court should exercise its discretion in setting this case for trial preference: Mr. Levin's age. They note that Mr. Levin is 85 years old and insinuate that this may prevent him from testifying at trial. Indeed, Levin's own counsel appears to have cited Mr. Levin's age in an attempt to imply that it is a factor for speeding up this case. (Decl. of Burkes, Ex. A.)[6] However, Plaintiffs cite no

evidence showing that Mr. Levin is in poor health or may otherwise be incapable of waiting for trial in the normal course. Rather, Defendant offers evidence that he is in good health. (*See* Decl. of Bionstad, Ex. A "Levin Depo.," 59:23-60:17.) Moreover, Defendant makes a good argument that preference would not be in the "interests of justice" since Mr. Levin would be prejudiced in presenting his best defense, which is that rather than his own negligent driving, the 2009 Camry experienced a UA event, causing the accident and Plaintiffs' injuries. Defendant says that 120 days is not enough time to conduct discovery into the cause of the UA events, and that without proper discovery, his due process rights will be v7 iolated. (*See Roe v. Superior Court* (1990) 224 Cal.App.3d 642, 643, n.2, *citing Peters v. Superior Court* (1989) 212 Cal.App.3d 218, 227.) Case law has not definitively determined whether truncated discovery due to preferential trial setting constitutes a due process violation. The *Peters* court never reached the issue because the petitioner lacked standing. The *Roe* court noted that the issue was still amenable to debate and did not answer the question. All that aside, at the least it would be unfair to require Mr. Levin to try his case without adequate preparation, and thus the "interests of justice" would not be served by giving Plaintiffs preference. [7]

There is no question, however, that the Rincons' case would proceed to trial more quickly had Mr. Levin not implicated Toyota. The court believes that the proper result is to bifulrcate this trial, vary the order of proof, and set it for trial soon. Accordingly, the court rules as follows:

The first phase of the trial will involve the damages claims on behalf of the Rincon plaintiffs and will commence on July 9, 2012, at 10:30 a.m. The final status conference is set for June 8, 2012, at 2 P.M. Counsel are referred to the orders with respect to the final status conferences in the Uno case in connection with what they must accomplish for the final status conference.

Following a jury verdict in phase 1, the court will schedule a date for the balance of the Rincon trial.

Dated: MAR 05 2012

<<signature>>

ANTHONY J. MOHR

Coordination Trial Judge

Footnotes

1 The moving party shall prepare a separate Notice of Ruling or Proposed Order regarding this motion and circulate to the parties for approval before submission to the Court.

2 The moving party shall prepare a separate Notice of Ruling or Proposed Order regarding this motion and circulate to the parties for approval before submission to the Court.

3 The moving party shall prepare a separate Notice of Ruling or Proposed Order regarding this motion and circulate to the parties for approval before submission to the Court.

4 The court acknowledges that Toyota continues to maintain that the D.A. Case is subject to Defendants' due process and other rights, including but not limited to the right to have discovery completed before trial commences, the right to not be subjected to undue prejudice, and the right to a fair trial, and thus that the D.A. Case cannot and should not "run in the background" of the private bellwether actions.

5 In fact, it seems that Karla Rincon turned 14 years old on October 22, 2011. (*See* Levin's Opposition to Motion for Preference, fn. 1. There appears to be a typo in Mr. Levin's footnote as he indicates that Karla Rincon turned 14 on XX/XX/1997. It appears that she was *born* on that date, which would make her 14 on XX/XX/2011.)

6 Mr. Levin's counsel wrote to Toyota on January 3, 2011, to inform Toyota that it would be deposing Mr. Levin. In the letter Mr. Levin's counsel stated "Given that Mr. Levin is 85 years old and his testimony is critical to this matter, we intend to proceed with the deposition as noticed by the plaintiffs." (Decl. of Burkes, Ex. A.)

7 Defendant also argues that the court should deny the motion because Adriana and Karla do not have a substantial interest in the action. This argument fails because, as Defendant admits, Adriana's claims are for $18,000 in damages as well as unspecified damages resulting from her emotional distress claims related to witnessing the death of her brother Bernardino, Jr. (Opposition, 11:3-13.)

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PROOF OF SERVICE

Coordination Proceeding Special Title (Rule 3.550)
Roundup Products Cases
Alameda County Superior Court
Case No. JCCP 4953

I am employed in the County of Los Angeles, State of California. I am over the age of 18 and not a party to the within action. My business address is 555 South Flower Street, 30th Floor, Los Angeles, California 90071.

On September 25, 2018, I served a true and correct copy of the document described as **DEFENDANTS' OPPOSITION TO MOTION FOR TRIAL PREFERENCE; DECLARATIONS OF DAVID GORDON, M.D. AND MARTIN CALHOUN; EXHIBITS** on the interested parties by electronic transfer to Case Anywhere via the Internet, pursuant to the Court's Case Management Order No. 2 Authorizing Electronic Service dated March 23, 2018.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this Proof of Service was executed on September 25, 2018 at Los Angeles, California.

Marianne Hendrix