



First in Human Phase 1 trial (LS1681) of Abraxane®/Rituximab 160nm nanoparticle (AR160) in Relapsed/Refractory B-cell Lymphomas Including Transformed Follicular Lymphoma: A Final Report

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INTRODUCTION

Nanotechnology for cancer therapy aims to increase drug delivery to tumor sites while lowering toxicity. AR160 is a novel 160 nm nano-immunoconjugate consisting of commercial grade nab-paclitaxel (NP) nanoparticles non-covalently coated with rituximab (R) for targeted delivery into tissues expressing CD20. The drug delivery system and clinical grade product was developed in the laboratory of Svetomir N. Markovic, M.D., Ph.D., Mayo Clinic Rochester.¹ Single agent rituximab at a dose of 375 mg/M² in relapsed aggressive lymphomas is not utilized because of limited activity in patients with multiple relapses. Taxanes have modest clinical activity as a single agent with overall response rates of 23% and 17% when administered at doses of 200 mg/m² and 140 mg/m².^{2,3} We hypothesized that utilizing the targeted ability of rituximab that the AR160 taxane nanoparticle would have activity in relapsed B-cell NHL and offer a new class of agents for relapsed B-cell NHL.

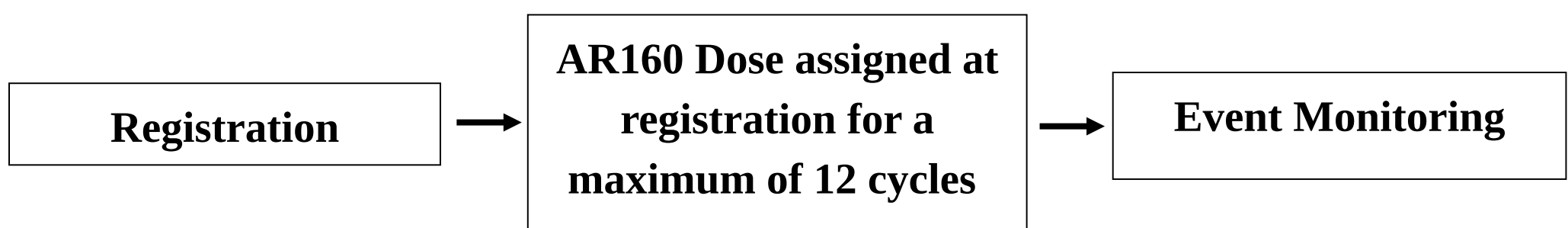
METHODS

- A phase 3 + 3 phase I clinical trial was conducted in patients with relapsed refractory non-Hodgkin lymphoma to determine the maximum tolerated dose of AR160 administered intravenously on days 1, 8, and 15 of a 28-day cycle.
- AR160 was prepared on site in the Mayo Clinic Cancer Center Research Pharmacy, and the product was reconstituted by mixing the two agents delivering as one combined infusion at a specific concentration (HDF).
- The starting doses were significantly lower than standard doses. Disease evaluations were conducted every 2 treatment cycles using CT based criteria (Lugano 2014) or PET. Patients were treated until disease progression or tolerability.

PATIENT ELIGIBILITY

- Age ≥ 18 years
- Histologic confirmation of relapsed/refractory CD20+ B-cell NHL
- Measurable disease (at least 1 lesion ≥ 1.5 cm in diameter
- ECOG performance status 0-2
- ANC ≥ 15000/mm³, platelet count ≥ 75,000/mm³, hemoglobin ≥8.0g/dL, total bilirubin ≤1.5xULN, calculated creatinine clearance ≥ 30 ml/min (Cockcroft-Gault formula)
- Patients were required to have had prior systemic treatment with no other therapy of clinical benefit
- Patients with aggressive lymphoma were required to have a stem cell transplant if transplant eligible
- Life expectancy ≥ 3 months
- Last treatment ≥ 4 weeks
- No active CNS lymphoma

TREATMENT



Agent	Dose	Route	Days	ReRx
AR160	assigned at time of registration	IV over 60 minutes (only 1 st dose; subsequent doses infused over 30 minutes)	1, 8 and 15	Every 28 days*

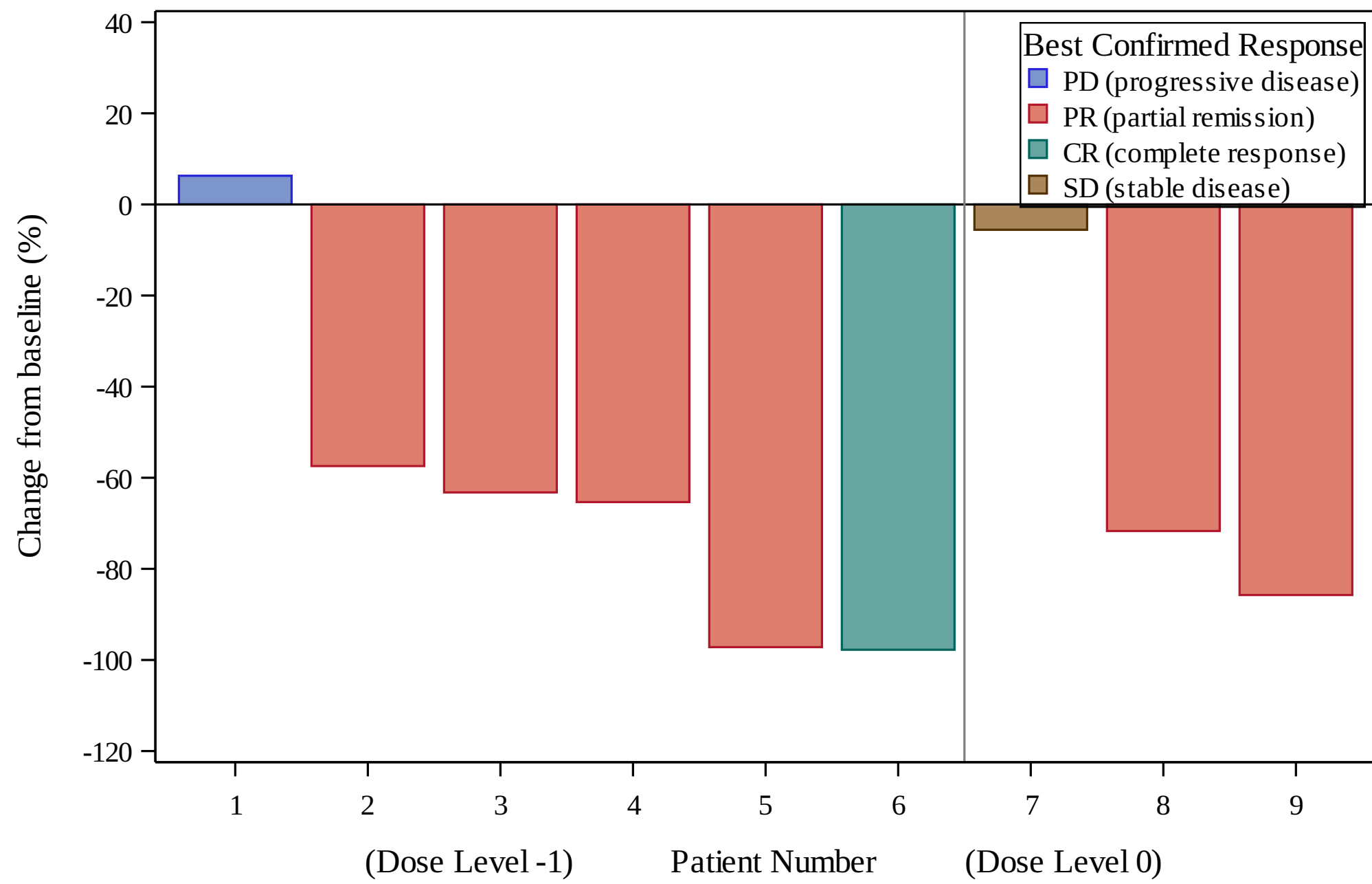
Dose Level	Dose (ABRAXANE)	Dose (Rituximab)
-1	75mg/m ²	30mg/m ²
0*	100mg/m ²	40mg/m ²
1	125mg/m ²	50mg/m ²
2	150mg/m ²	60mg/m ²

TABLES AND FIGURES

TABLE 1: Patient Histology and Response

Histology	Number	Response
Follicular lymphoma (FL) grade 1-2	2	PR, PR
FL relapse from transformation	1	PR
High-grade B-cell lymphoma with MYC and BL2 rearrangements transformed from FL	1	PD
High-grade B-cell lymphoma with MYC and BCL2 rearrangements	2	PR, CR
Transformed FL from DLBCL	1	PR
High-grade B-cell NHL NOS	1	PR
Mantle Cell Lymphoma	1	SD

Figure 1: LS1681 CT Best Confirmed Response

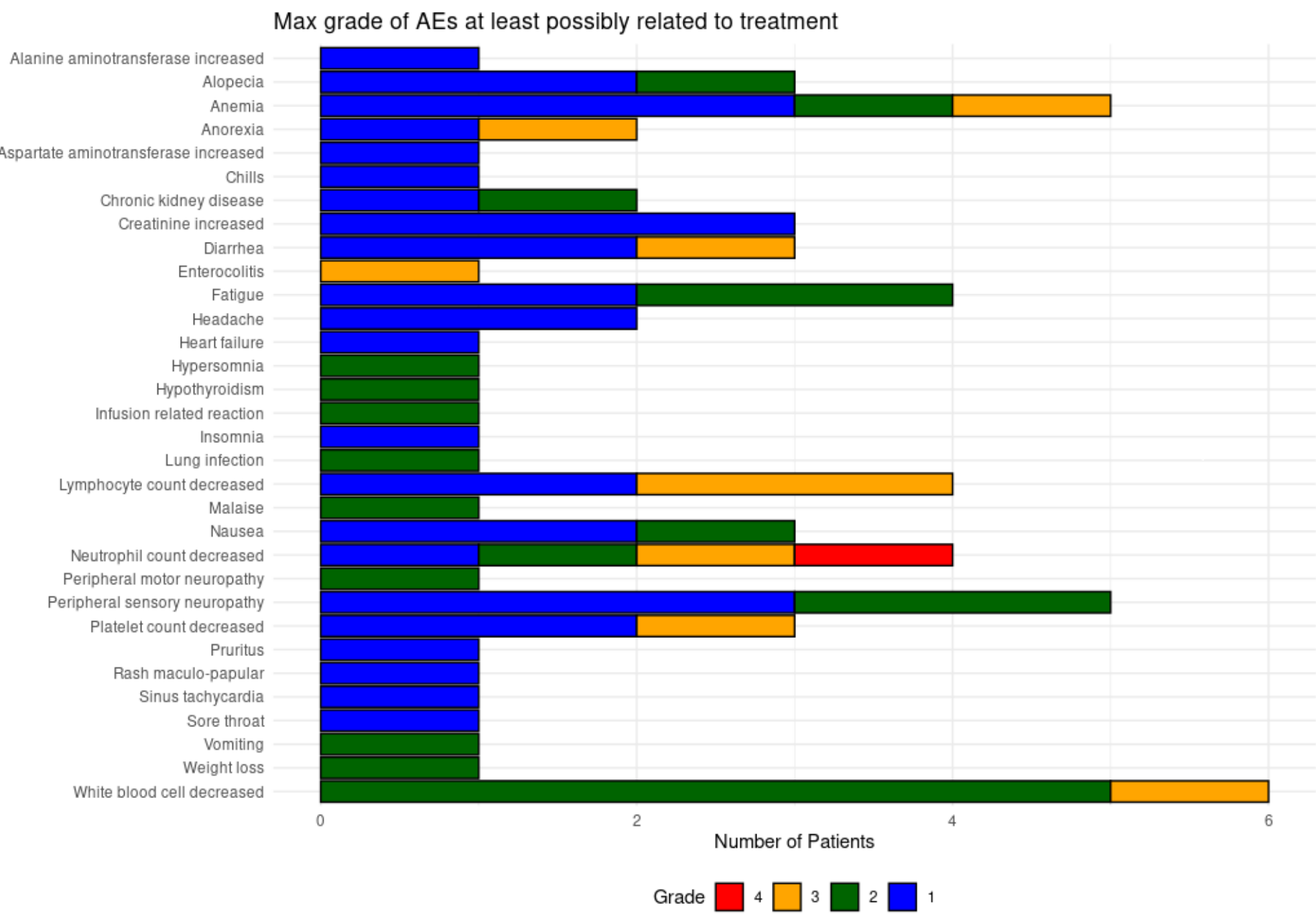


Results of tumor responses as measured by CT scans. The bar graph shows the best confirmed response for each patient.

TABLE 2: Grade 1+ Adverse Events

Summary of Grade 1+ Adverse Events Max Grade per Patient Per Event Adverse Events at Least Possibly Related to Treatment Number of Evaluable Patients Arm: A=9		
Patients with a maximum:	Arm	N (%)
Total		
Grade 1 Event	A	0 (0.0%)
Grade 2 Event	A	3 (33.3%)
Grade 3 Event	A	4 (44.4%)
Grade 4 Event	A	2 (22.2%)
Grade 5 Event	A	0 (0.0%)
Hematologic Adverse Events		
Grade 1 Event	A	0 (0.0%)
Grade 2 Event	A	4 (44.4%)
Grade 3 Event	A	3 (33.3%)
Grade 4 Event	A	2 (22.2%)
Grade 5 Event	A	0 (0.0%)
Non-Hematologic Adverse Events		
Grade 1 Event	A	3 (33.3%)
Grade 2 Event	A	3 (33.3%)
Grade 3 Event	A	3 (33.3%)
Grade 4 Event	A	0 (0.0%)
Grade 5 Event	A	0 (0.0%)
Note: Summaries are based on available patient data		

FIGURE 2: Max grade of Adverse Events



Bar graph of the number of patients experiencing each AE. Grade 1 (blue), grade 2 (green), grade 3 (orange) and grade 4 (red).

RESULTS

- 9 patients (7 males and 2 females) with a median age of 61 (range 55-84 years) were enrolled.

- Median number of prior treatments: 4 (range 3-16).

- Three patients were treated at dose level 0. Neutropenia necessitated dropping to dose level -1.

CONCLUSIONS

- AR160 is a novel drug delivery system incorporating significantly lower doses of paclitaxel and rituximab

- AR160 demonstrates promising clinical activity in patients with low-grade and high-grade previously treated B-cell lymphomas

- 6 of 9 patients with relapse or progressive disease were alive with subsequent therapies

- This principle of treatment is applicable to other disorders.

- Further clinical testing is warranted in these patient populations.

REFERENCES

¹Nevala WK, Butterfield JT, Sutor SS, Knauer DJ, Markovic SN. Antibody-targeted paclitaxel loaded nanoparticles for the treatment of CD20+ B-cell lymphoma. Sci Reports. 2017, March 1; 7:45682

²Younes A, Sarris A, Melnyk A, et al. Three-hour paclitaxel infusion in patients with refractory and relapsed non-Hodgkin lymphoma. J Clin Oncol. 1995;13:583-587.

³Wilson WH, Chabner BA, Bryant F, et al. Phase II study of paclitaxel in relapsed non-Hodgkin lymphoma. J Clin Oncol. 1995;13:381-386.