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Clinical Study Report to the Investigators

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E2404

Bevacizumab and CHOP (A-CHOP) in Combination for Patients with Peripheral T-Cell or Natural Killer Cell Neoplasms

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1 Summary

E2404 is a phase II trial of bevacizumab and CHOP (A-CHOP) in combination for patients with peripheral T-cell or natural killer cell neoplasms. Patients were treated with 6-8 cycles of ACHOP followed by 8 doses of maintenance bevacizumab. The primary endpoint of this study was the 1 year progression free survival (PFS) rate, which was defined as the proportion of patients who were progression free and alive at 1 year from registration. A 1-year PFS rate of 30% was considered non-promising and 50% considered promising. A one-stage design was used. The study was to accrue 43 patients in order to have 39 eligible. ACHOP would be considered promising for further study if 16 of 39 patients were progression free at 1-yr. This design has 90% power at a one-sided 0.09 significance level.

The study was activated in July 2006, and was suspended in March 2009 and then closed in August 2009. A total of 46 patients have been enrolled and 39 were determined eligible and included in the analysis. Sixteen out of 39 cases stayed alive and progression free at 1-year post registration; the results met the pre-specified decision rule, and the treatment is considered promising. With a median follow-up of 3.0 years, the median PFS is estimated as 0.64 year and median OS as 1.85 years. As of 4/30/2012, toxicity data is available on all 44 patients who started treatment, and 23 patients experienced grade 4 and 1 patient (24029) had grade 5 toxcities. An additional case (24037) has lethal toxicity acquired only through AdEERs (not on case report form). Only 9 out of 39 eligible patients completed protocol therapy, others were off study due to reaons including deisease progression, adverse events, other diease, patient withdrawal.

2 Introduction

Peripheral T cell (PTCL) and natural killer (NK) cell lymphomas are rare diseases with a poor outcome. Traditionally, PTCL have been treated with regimens used for DLBCL (diffuse large B cell lymphoma) with anthracycline containing regimens, however outcomes are poor with a 3 year survival of approximately 30%. Within NHL subtypes, VEGF overexpression has been seen more with PTCL and is associated with a poor outcome. Since angiogenesis plays an important role in the biology of PTCL a rationale therapeutic strategy is to study the inhibition of angiogenesis by blocking VEGF. Bevacizumab (Avastin (A), Genentech, So San Francisco, CA, USA) is a humanized monoclonal antibody against VEGF, which is currently approved for the treatment of several solid tumors, including colon, lung, renal cell and brain. We hypothesized that the addition of bevcizumab to standard CHOP chemotherapy (cyclosphosphamide, doxorubicin, vincristine, prednisone) would prolong the PFS in patients with previously untreated PTCL.

3 Objectives

The primary objective was to evaluate the 12 month progression-free survival. Secondary objectives are: To evaluate the overall response rate (complete remission [CR, CRu or Functional CR] + partial remission) after 3 cycles, 6 cycles and 8 cycles. To evaluate overall survival. To evaluate the toxicity of induction and continuing bevacizumab phases. To collect serum for banking.

4 Eligibility Criteria

Each of the criteria in the following checklist must be met in order for a patient to be considered eligible for this study.

- Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease, unless verified by CT scan or other appropriate imaging. Patient must have at least one objective measurable disease parameter. NOTE: For patients who are enrolling after receiving 1 cycle of CHOP, the baseline CT has to be done < 4 weeks before starting that cycle and does NOT have to be repeated just before study entry.

- Patients must have Peripheral T-cell or Natural Killer Cell Neoplasms excluding Anaplastic ALK positive T-Cell Large Cell Lymphoma and Cutaneous T-Cell Lymphomas. HTLV-1 positive tumors are eligible. All stages of disease are eligible.
- Patients must not have had evidence of other active malignancies other than carcinomas in situ of the cervix or basal cell carcinoma of the skin within 6 months prior to registration.
- Patients may have received one previous cycle of CHOP for PTCL.
- Patients may not receive any non-study chemotherapy or radiation therapy while receiving study treatment.
- Patients must not have historical or radiographic evidence of CNS metastasis including previously treated, resected or asymptomatic brain lesions or leptomeningeal involvement. In addition, patients with a history of active seizures or a history of CVA within 6 months prior to registration are excluded.
- Patients must not have had a major invasive surgical procedure, open biopsy or significant traumatic injury within 4 weeks prior to registration. Patients must not anticipate a need for a major surgical procedure during the course of the study. Patients must not have had a minor surgical procedure within 7 days of starting protocol therapy. Peripheral lymph node core biopsy, bone marrow biopsy, fine needle aspiration, skin biopsy and central line placement are NOT considered minor surgical procedures.
- Patients must not have evidence of bleeding diathesis or coagulopathy, or must be receiving a stable dose of anticoagulation therapy with stable INR for at least 2 weeks prior to registration. Heparin flushes for line patency is allowed. Patients on anticoagulation therapy should be monitored closely with PT/INR and/or PTT and levels should be kept within the acceptable range for the underlying thrombotic disease.
- Patients with a history of deep venous thrombosis or pulmonary embolism must be receiving a stable dose of anticoagulation therapy for at least 2 weeks prior to registration.
- Patients must not have been using any anti-platelet drugs. The use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAID) is allowed.
- Patients must have an ECOG performance status 0-2.
- Patients must have adequate organ function as evidenced by the following laboratory studies (within 2 weeks prior to registration).
- Patients must have a urinary protein creatinine (UPC) ratio < 1 within 2 weeks prior to registration.
- Patients must not have clinically significant cardiovascular disease or peripheral vascular disease.
- Patients must not have a non-healing ulcer (unless involved with lymphoma) or bone fracture.
- Patients must not have an active infection requiring parental antibiotics.
- Patients must not have known HIV infection.
- Patients must have a left ventricular ejection fraction > 50% to be eligible.
- Patients must not have any history of abdominal fistula, gastrointestinal perforation or intraabdominal abscess within 6 months prior to registration.
- Patients must be age > 18 years.
- Women must not be pregnant or breast feeding.
- Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

5 Treatment

Figure 1 shows the schema of the study. Patients should begin treatment within 7 days of registration. Patient received 3 to 8 cycles of ACHOP (1 cycle =21 days). Patients will be assessed for response after cycle 3, cycle 6, and cycle 8 (if given). Patients in CR, CRu or functional CR during cycle 3 and cycle 6 assessments will go to continuing maintenance bevacizumab (MA) therapy after cycle 6. Patients in SD after cycle 3 who remain in SD after cycle 6 should discontinue protocol treatment. Patients in PR after cycle 3 who remain in PR after cycle 6 will go to continuing bevacizumab therapy. The following groups of patients will receive an additional 2 cycles of ACHOP (Cycles 7 and 8): 1) those who are in PR after cycle 3 who are then in CR, CRu or functional CR after cycle 6, and 2) those who are in SD after cycle 3 who are then in PR after cycle 6. Patients in PR, CR, CRu or functional CR after cycle 8 will go to continuing bevacizumab therapy.

6 Statistical Considerations

6.1 Design

The primary endpoint of this study is the 1 year progression free survival (PFS) rate. A 1 year PFS rate of 30% is considered non-promising and 50% is considered promising. A one-stage design is used because of the limited treatment options available for these patients. A total of 39 eligible patients will be entered on study and followed for 1 year. Assuming an ineligible rate of 10%, 43 patients will be required. If at least 16 patients are alive and free of progression at 1 year, the treatment will be considered promising. The probability of concluding that the regimen is effective is 0.90 assuming true underlying 1 year PFS rate of 50% and is 0.09 if the true underlying 1 year PFS rate is 30%. With 39 eligible patients, the 90% confidence interval for the 1 year PFS rate will be no wider than 28%.

6.2 Analysis

Baseline patient characteristics were listed with descriptive statistics (median, range, percentage). PFS was defined as the time from registration to progression, relapse or death. Overall survival (OS) was measured from registration to death from any cause. Response criteria were based on the "international workshop to standardize criteria for non-Hodgkin's lymphomas" [1]. Toxicity and secondary primary cancers were evaluated for all patients that received any protocol therapy regardless of eligibility. Toxicities were assessed using the *NCI Common Terminology Criteria for Adverse Events (CTCAE)* version 3.0. The response rate was reported for overall response and CR/CR unconfirmed (CRu) with 95% confidence interval (CI). Th e Kaplan – Meier method was used to estimate the survival distribution. Comparisons between histology groups were conducted among eligible patients with a log-rank test. Analysis was performed using SAS 9.2 and R 2.11.1

7 Results

7.1 Accrual

This study was activated on July 7, 2006 and was suspended on March 4, 2009 with an accrual of 45 patients. After study suspension, an additional patient who has been consented prior to the suspension date entered this study, for a total of 46 patients. The study was terminated on August 27, 2009. Accrual by ECOG-ACRIN institution is summarized in Table 1. The data cut-off date for this analysis was April 5, 2012. Patient status is listed in Table 2.

7.2 Disposition of Cases

Out of 46 patients enrolled, 2 cases (24045, 24046) never started treatment with the reasons listed in Table 2. Among 44 cases who started protocol treatment, central review is available on 43 case with 34 cases were reviewed based on submitted diagnostic materials and 9 cases (24001, 24012, 24016, 24017, 24023, 24025,

24032, 24037, 24038) were reviewed based on local pathology report. One case (24014) has missing central pathology review. As the results, 4 cases (24017, 24020, 24029, 24043) were determined with "other" histology. Excluding these 4 cases and the case (24014) with missing central pathology review, the study has 39 eligible cases for the analysis. No other ineligibility was identified.

7.3 Patient Demographics and Disease Characteristics

Patients' baseline demographic and characteristics were listed in table 3. Eighteen of 39 (46%) patients had stage IV disease, and eight of 39 (20%) had lymph node masses > 5 cm. B symptoms were present in 44% of the patients and 10 of 39 (26%) had > 1 extranodal site of involvement. The most common subtypes were PTCL-NOS and AITL. All seven anaplastic large cell lymphoma (ALCL) tumors were ALK-negative. Six of seven patients with ALCL had an International Prognostic Index (IPI) < 2, compared to eight of 15 with PTCL-NOS, and 10 of 17 with AITL.

7.4 Treatment

Table 4a lists last treatment received by patients and table 4b lists the distribution of off-treatment treasons. Of the 39 patients, 10 received fewer than six cycles (range 2 – 5) of ACHOP, 29 had 6 – 8 cycles and 18 received maintenance bevacizumab (MA). Table 4c lists reasons for not completing 6 cycle of ACHOP. Only nine of 39 patients completed all planned therapy as per study design. The inability to complete all cycles was largely due to toxicity (20.5%) and disease progression (33.3%).

7.5 Adverse Events

Table 5a show grade 3 or above toxicities, that were (1) definitely, (2) probably; and (3) possibly related to treatment. All patients who received any study treatment, regardless of eligibility status, were evaluated for adverse events. As of 4/30/2012, toxicity data is available on all 44 patients who started treatment. Two lethal events were listed in table 5b. Case 24037 had lethal toxicity that was only reported through AdEERs, not on case report form. This case had CRfor a while, then developed Acute Monoblastic Crisis Leukemia. Adverse event was coded as "Leukemia secondary to oncology chemotherapy", possibly due to CHOP therapy. Cardiac toxicities were reported previously [2].

7.6 Secondary Primary Cancer

All patients, regardless of eligibility status, were checked for secondary primary cancer. Four secondary primary cancers have been reported (Table 6).

7.7 Responses

Table 7 lists responses overall and by IPI group (Low (0-2) vs. High (>=3)) after ACHOP therapy. Thirty-five out of 39 patients (90%) (95% CI: 76 – 93%) responded to ACHOP, with 19 out of 39 (49%) achieving a CR/CRu (95% CI: 58 – 87%). Three of 39 (8%) had PD while on treatment.

7.8 1-Year Progression-Free Survival

The study was designed to detect 1-year PFS rate of 50% (promising) vs. 30% (non-promising). Out of 39 eligible patients who entered the study and followed for a year, if at least 16 patients are alive and free of progression at 1-year, the treatment will be considered promising. We have 39 eligible patients out of total 46 enrolled. And 16 out of 39 cases stayed alive and progression free at 1-year post registration (listed below). So the results met the pre-specified decisionl rule, the treatment is considered promising. See below for the 16 cases that stayed alive and progression free at 1-year post registration.

ID	Best Response	Progresion Status	Surival Status	Event Status*	PFS
24001	CR	No	Alive	0	3.50992
24004	PR	Yes	Alive	1	1.15537
24005	CRu	Yes	Dead	1	1.65366
24006	CR	No	Alive	0	1.53593
24009	PR	Yes	Alive	1	2.0178
24013	PR	Yes	Dead	1	1.10335
24019	PR	No	Alive	0	1.55236
24022	CR	No	Alive	0	1.36071
24028	CR	No	Alive	0	1.82341
24031	CR	No	Alive	0	1.25941
24033	CRu	No	Alive	0	1.55236
24035	CR	No	Alive	0	1.63176
24036	PR	Yes	Dead	1	1.10609
24037	CR	Yes	Alive	1	1.60986
24038	CR	No	Alive	0	1.27858
24042	CR	No	Alive	0	2.81725

For the rest 23 cases, there were two cases (24002, 24008) that were lost of follow-up before 1-year (list below). One case (24010) progressed within a year and was last known alive, and the rest 20 cases were all died with/without progressed within a year from study registration.

ID	Best Response	Progresion Status	Surival Status	Event Status*	PFS
24002	SD	No	Lost of Follow-up	0	0.31211
24003	CRu	Yes	Dead	1	0.22724
24007	PR	Yes	Dead	1	0.49281
24008	PR	No	Lost of Follow-up	0	0.4627
24010	CR	Yes	Alive	1	0.75838
24011	PR	Yes	Dead	1	0.57769
24012	PR	Yes	Dead	1	0.64339
24015	PD	Yes	Dead	1	0.22177
24016	PR	Yes	Dead	1	0.34497
24018	PR	Yes	Dead	1	0.29295
24021	PR	Yes	Dead	1	0.43532
24023	CR	Yes	Dead	1	0.52841
24024	CR	Yes	Dead	1	0.36687
24025	CR	Yes	Dead	1	0.62149
24026	PR	Yes	Dead	1	0.48186
24027	CR	Yes	Dead	1	0.47091
24030	PD	Yes	Dead	1	0.17248
24032	CRu	No	Dead	1	0.16975
24034	PD	Yes	Dead	1	0.06845
24039	PR	No	Dead	1	0.34497
24040	CR	Yes	Dead	1	0.43806
24041	PR	Yes	Dead	1	0.78029
24044	PR	Yes	Dead	1	0.25188

*1: event, 0: censored

7.9 Progression-Free Survival /Overall Survival Curve

With a median follow-up of 3.04 year, the 1-year PFS rate was 44% from KM estimate. Th e median PFS and OS rates were 7.7 and 22 months, respectively [Figure 1(A) and 1(B)]. Th e 1-year PFS rate varied markedly by histologic subtype: 15% in PTCL-NOS, versus 57% in AITL and 71% in ALK-negative ALCL (p = 0 .02) [Figure 1(C)]. The 1-year OS rate was also significantly diff erent in the various histologic types, including: 67% in PTCL-NOS, 88% in AITL and 86% in ALK-negative ALCL (p = 0.05). Since patients were not followed after they developed PD, details on second-line therapy at relapse are not available.

8 References

[1] Cheson BD, Horning SJ, Coiffi er B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17:1244.

[2] Advani RH , Hong F , Horning SJ , et al . Cardiac toxicity associated with bevacizumab (Avastin) in combination with CHOP chemotherapy for peripheral T cell lymphoma in ECOG 2404 trial. Leuk Lymphoma 2012; 53:718-720.

[3] Ganjoo K, Hong F, Horning SJ, Gascoyne R, Natkunam Y, Swinnen L, Habermann T, Kahl BS, Advani R. Bevacizumab and CHOP (A-CHOP) in Combination for Patients with Peripheral T-Cell or Natural Killer Cell Neoplasms: An Eastern Cooperative Group Study (E2404). Leukemia and Lymphoma. 2013 Jun 20. [Epub ahead of print].

9 Tables

Table 1: Accrual by ECOG-ACRIN Institution

Institution Name	Step 1
CWRU - MetroHealth Medical Center	1
Carle Clinic CCOP	3
Cook County Hospital MBCCOP	4
Iowa CCOP	2
Johns Hopkins University	6
Mayo Clinic	6
Metro-Minnesota CCOP	3
Penn State Hershey Cancer Institute	1
Pennsylvania, University of	1
Sioux Community CA Consortium CCOP	2
St. Vincent Hosp Reg Ca Ctr CCOP	1
Stanford University	11
Vanderbilt University	2
Wichita CCOP	3
Total	46

Table 2: Case Status

Cases Entered	46
Ineligible	6
Never Started Assigned Therapy	2*

Reason for ineligibility: (n=6)

Path review showed no lymphoma after one cycle of treatment (24017);
Second biopsy and second opinion after registration does not show signs of cancer (24045);
Other pathological ineligible (24020, 24029, 24043);
Missing pathology review (24014).

Reason for not starting assigned therapy: (n=2)

Not eligible (24045);
Patient refused treatment (24046).

*Case 24045 pathologically ineligible, did not start assigned therapy

Table 3: Baseline Patient Demographic and Characteristics

	N	%
Gender		
Male	28	71.79
Female	11	28.21
Age (Median, range)	60 (21-81)	
Race		
Caucasian	36	92.31
Other	3	7.69
Ethnicity		
Missing	1	2.56
Hispanic or latino	2	5.13
Non-hispanic	36	92.31
Disease Stage		
Stage II	6	15.38
Stage IIE	1	2.56
Stage III	10	25.64
Stage IIIE	1	2.56
Stage IIIS	3	7.69
Stage IV	18	46.15
PS		
0	14	35.9
1	20	51.28
2	5	12.82
No. of extra-nodal sites		
0	16	41.03
1	13	33.33
2	9	23.08
4	1	2.56
Mediastinal Mass		
No	35	89.74
Yes	4	10.26
Any lymph node greater than 5cm		
No	31	79.49
Yes	8	20.51
B symptom		
No	22	56.41
Yes	17	43.59
Prior Radiation Therapy		
No	39	100
Prior surgery		
No	33	84.62
Yes	6	15.38
Elevated LDH		
Missing	1	2.56
No	20	51.28
Yes	18	46.15
Spleen involvement		
Missing	2	5.13
No	30	76.92
Yes	7	17.95
IPI	1	2.56

Table 3: Baseline Patient Demographic and Characteristics

	N	%
Missing		
0	2	5.13
1	9	23.08
2	13	33.33
3	11	28.21
4	1	2.56
5	2	5.13
Histology		
Peripheral T-cell lymphoma, unspecified (PTCL-NOS)	15	38.46
Angioimmunoblastic T-cell lymphoma (AITL)	17	43.59
Anaplastic large-cell lymphoma-primary systemic type (ALCL)	7	17.95

Table 4a: – Last Treatment Received

Last cycle of treatment received	N	%
Cycle 2 ACHOP	3	7.69
Cycle 3 ACHOP	3	7.69
Cycle 4 ACHOP	3	7.69
Cycle 5 ACHOP	1	2.56
Cycle 6 ACHOP	6	15.38
Cycle 7 ACHOP	1	2.56
Cycle 8 ACHOP	4	10.26
Cycle 1 continuation BEV	3	7.69
Cycle 2 continuation BEV	1	2.56
Cycle 3 continuation BEV	1	2.56
Cycle 4 continuation BEV	1	2.56
Cycle 5 continuation BEV	2	5.13
Cycle 7 continuation BEV	1	2.56
Cycle 8 continuation BEV	9	23.08
Total	39	100

Table 4b: Off-Treatment Reason Distribution

Off-Treatment Reasons	N	%
Treatment completed per protocol criteria	9	23.08
Disease progression, relapse during active treatment	13	33.33
Adverse events/side effects/complications	8	20.51
Patient withdrawal / refusal after beginning protocol therapy	4	10.26
Patient off treatment for other complicating disease	1	2.56
Other	4	10.26
Total	39	100

Table 4c: Reasons for Not Completing 6 Cycle of ACHOP

ID	Last Treatment	Off-Treatment Reason
24002	Cycle_3_ACHOP	Other
24003	Cycle_3_ACHOP	Adverse events/side effects/complications
24007	Cycle_4_ACHOP	Patient withdrawal / refusal after beginning protocol therapy
24010	Cycle_2_ACHOP	Adverse events/side effects/complications
24015	Cycle_2_ACHOP	Adverse events/side effects/complications
24018	Cycle_5_ACHOP	Disease progression, relapse during active treatment
24030	Cycle_3_ACHOP	Disease progression, relapse during active treatment
24032	Cycle_4_ACHOP	Patient withdrawal / refusal after beginning protocol therapy
24034	Cycle_2_ACHOP	Disease progression, relapse during active treatment
24044	Cycle_4_ACHOP	Disease progression, relapse during active treatment

Table 5a: Treatment-Related Toxicities

	Treatment A (n=44)		
	Grade		
	3	4	5
Toxicity	(n)	(n)	(n)
Hemoglobin	2	1	-
Leukocytes	4	10	-
Lymphopenia	8	4	-
Neutrophils	4	19	-
Platelets	2	3	-
Ventricular arrhythmia NOS	-	1	-
Hypertension	4	-	-
Hypotension	1	-	-
Left ventricular systolic dysfunction	4	-	-
Cardiomyopathy, restrictive	-	1	-
Fatigue	5	1	-
Weight loss	1	-	-
Death NOS	-	-	1
Colitis	1	-	-
Constipation	1	-	-
Dehydration	1	-	-
Diarrhea w/o prior colostomy	1	-	-
Muco/stomatitis by exam, oral cavity	1	-	-
Muco/stomatitis (symptom) oral cavity	1	-	-
Perforation, colon	1	-	-
Abdomen, hemorrhage NOS	1	-	-
Nose, hemorrhage	1	-	-
Febrile neutropenia	8	-	-
Infection w/ gr3-4 neut, colon	2	-	-
Infection w/ gr3-4 neut, lung	1	-	-
Infection Gr0-2 neut, lung	1	-	-
Infection Gr0-2 neut, rectum	1	-	-
Infection Gr0-2 neut, urinary tract	1	-	-
Infection w/ unk ANC lung	1	-	-
Infection w/ gr3-4 neut, blood	1	-	-

Table 5a: Treatment-Related Toxicities

	Treatment A (n=44)		
	Grade		
	3	4	5
Toxicity	(n)	(n)	(n)
AST, SGOT	1	-	-
Bilirubin	1	-	-
Hyperglycemia	2	-	-
Hypophosphatemia	1	1	-
Hyponatremia	4	-	-
Metabolic/Laboratory-other	1	-	-
Neuropathy-sensory	1	-	-
Esophagus, pain	1	-	-
Head/headache	1	-	-
Dyspnea	-	2	-
Hypoxia	1	-	-
Vaginal mucositis	1	-	-
Thrombosis/thrombus/embolism	1	2	-
WORST DEGREE	10	23	1

Table 5b: Lethal Adverse Events (acquired through AdEERS)

Case #	Description
24029	Death NOS. Patient died while on study of unknown etiology possibly due to disease or treatment-related.
24037	Leukemia, secondary to oncology chemotherapy possibly due to CHOP therapy.

Table 6: Second Primary Cancer

Case #	Site
24001	Basal cell carcinoma
24001	Renal carcinoma
24022	Breast
24037	Gastrointestinal stromal tumor

Table 7: Responses by IPI Group

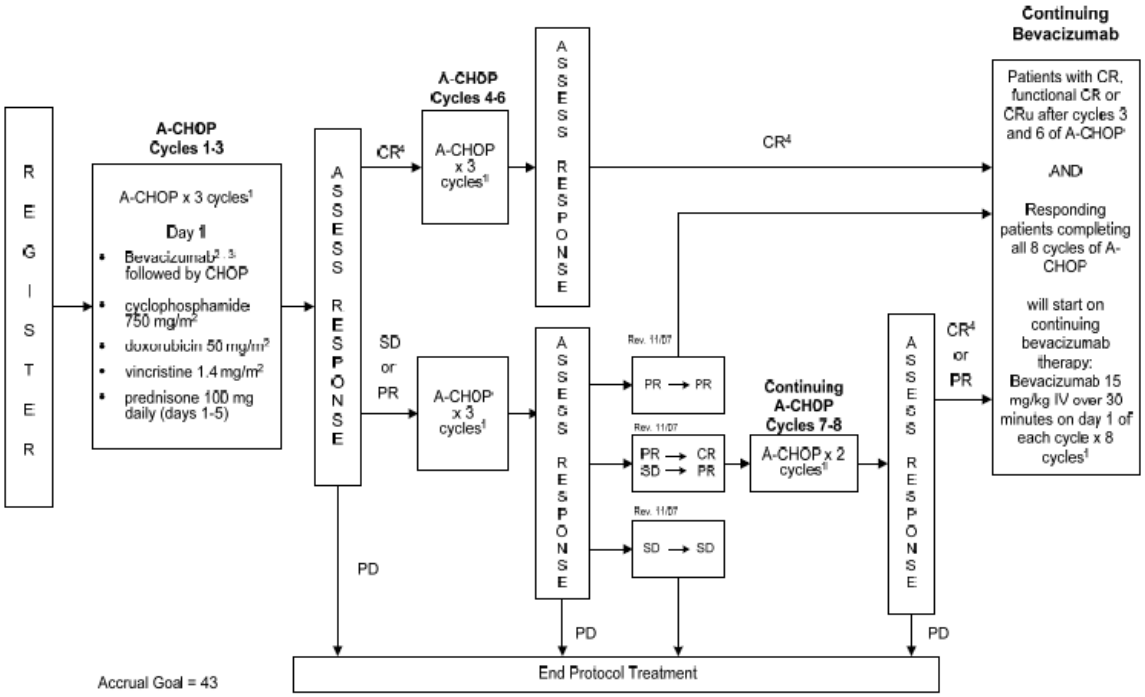
	IPI_group						ALL	
	Missing		High (n=14)		Low (n=24)			
	N	%	N	%	N	%	N	%
Response-best overall								
CR	0	0	4	10.26	11	28.21	15	38.46
CRu	0	0	1	2.56	3	7.69	4	10.26
PR	1	2.56	8	20.51	7	17.95	16	41.03
SD	0	0	0	0	1	2.56	1	2.56
PD	0	0	1	2.56	2	5.13	3	7.69
Response (3 cycle of ACHOP)								
CR	0	0	0	0	10	25.64	10	25.64
CRu	0	0	3	7.69	3	7.69	6	15.38
PD	0	0	1	2.56	2	5.13	3	7.69
PR	1	2.56	7	17.95	7	17.95	15	38.46
SD	0	0	3	7.69	2	5.13	5	12.82
Response (6 cycle of ACHOP)								
CR	0	0	2	5.13	9	23.08	11	28.21
CRu	0	0	0	0	3	7.69	3	7.69
Off-Study	1	2.56	2	5.13	5	12.82	8	20.51
PD	0	0	2	5.13	1	2.56	3	7.69
PR	0	0	7	17.95	6	15.38	13	33.33
SD	0	0	1	2.56	0	0	1	2.56
Response (8 cycle of ACHOP)								
CRu	0	0	0	0	1	2.56	1	2.56
N/A*	0	0	4	10.26	9	23.08	13	33.33
Off-Study	1	2.56	6	15.38	9	23.08	16	41.03
PD	0	0	0	0	2	5.13	2	5.13
PR	0	0	3	7.69	2	5.13	5	12.82
SD	0	0	1	2.56	0	0	1	2.56
Unevaluable**	0	0	0	0	1	2.56	1	2.56
Total	1	2.56	14	35.9	24	61.54	39	100

* Those were the patients that did not get 8 cycles; they went from 6 cycles straight to continuing Bevacizumab.

**24033, off study due to adverse events/side effects/complications.

10 Figures

Figure 1 – Study Schema



Note: Doses are based on actual body weight.

1. A cycle is defined as 21 days.
2. Bevacizumab is administered on day 1 of each cycle followed by CHOP.
3. Bevacizumab is given at 15 mg/kg over 90 minutes in cycle 1. If tolerated it can be given over 60 minutes in cycle 2 and 30 minutes in cycle 3 and subsequent cycles.
4. CR = CR, CRu or functional CR as defined in section 6.

Figure 2: Progression-Free Survival (A), Overall Survival (B), Progression-Free Survival by Histology Groups (C) and Overall Survival by Histology Groups