# Phase II Trial of Brentuximab Vedotin in Relapsed/Refractory Germ Cell Tumors

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# Abstract

Background

CD-30 is highly expressed in some patients with non-seminomatous germ-cell tumors. Brentuximab vedotin is an antibody-drug conjugate directed to CD-30. We report a phase 2 trial of brentuximab vedotin in patients with chemo-refractory GCT.

Patients and Methods

This is a single arm, two cohort phase 2 trial investigating brentuximab vedotin 1.8 mg/kg IV every 3 weeks until disease progression or intolerable toxicities in patients with relapsed GCT who have no curative options. Patients with mGCT who progressed after first line cisplatin-based chemotherapy and after at least 1 salvage regimen (high-dose or standard-dose chemotherapy) were eligible. CD30 expression was assessed and two cohorts defined: CD30 positive and CD30 negative/unknown.

Results

18 patients were enrolled. Median age 34.7 (range, 23-56). All patients had non-seminoma. Median AFP 4.9 (range, 1-219,345) and hCG 282 (range, 0.6-172,064). Five patients had late relapse (>2years). Median number of previous chemotherapy regimens was 3 (range, 2-7). Ten patients received prior high-dose chemotherapy. Seven patients had positive CD30 staining. There were two grade 3 treatment-related adverse events. No partial or complete responses were observed. 6 patients achieved radiographic stable disease (range, 9-14.9 weeks), 5 had elevated AFP or hCG at trial entry and all 5 had transient >50% decline in baseline AFP/hCG: 4 had CD30 -ve and 2 had CD30 +ve staining; 10 patients had progression of disease as their best response; 2 were not evaluable for response.

Conclusion

Brentuximab vedotin does not appear to have clinically meaningful single-agent activity in patients with refractory GCT.

Trial Registration Number: NCT02689219

Date of registration: February 12, 2016


# Key Message

In this phase II trial, brentuximab vedotin was well tolerated but did not appear to have single agent activity in refractory germ cell tumors. CD-30 staining was positive in 7 patients. Six patients had stable disease while the rest had progressive disease as best response.

# Introduction

Testicular cancer is the most common solid malignancy in men under age 40 [1]. The introduction of platinum-based combination chemotherapy transformed the outcomes of patients with metastatic disease from almost uniformly fatal to a disease curable in 80% of patients [2, 3]. Patients who relapse after first-line chemotherapy are treated with salvage surgery, standard-dose chemotherapy, or high-dose chemotherapy plus peripheral-blood stem-cell transplant [4-7]. Salvage therapy will cure about 50% of relapsed patients. There remains a substantial proportion of patients who progress after salvage therapy and are incurable with current known treatment options. Introducing novel classes of anti-cancer therapy to improve remission and cure rates remains an active area of investigation in patients with relapsed refractory germ-cell tumors (GCT).

Brentuximab vedotin is an antibody-drug conjugate (ADC) which binds to CD30 on the cell surface. This initiates the internalization of the ADC-CD30 complex which then traffics to the lysosomal compartment. Within the cell, a single defined active species, the antimitotic agent monomethyl auristatin E (MMAE), is released via proteolytic cleavage. Binding of MMAE to tubulin results in the disruption of the intracellular microtubule network and hence the apoptotic death of the CD30-expressing cell. Contributions to the mechanism of action by other antibody-associated functions have not been excluded [8]. Brentuximab vedotin has demonstrated robust clinical activity in CD30 expressing tumors such as classical Hodgkin's lymphoma, anaplastic large cell lymphoma, mycosis fungoides, and peripheral T-cell lymphoma [9, 10].

CD30 is expressed on the surface of 93%-98% of testicular embryonal carcinoma, with positive staining present in >50% of tumor cells [11-14]. Moreover, there have been reports of weak expression of CD30 in yolk sac tumors and primary mediastinal germ cell tumors [14, 15]. Retrospective data indicates that CD30 expression was retained in patients with non-seminomatous germ cell tumors (NSGCT) even after multiple lines of therapy, making this a potential reliable therapeutic target [16]. Based on these promising data, a trial evaluating the clinical activity of brentuximab vedotin in CD30-expressing non-lymphomatous malignancies was conducted (NCT01461538). Seven patients with CD30 expressing testicular cancer were enrolled on this trial: 5 with germ-cell tumors (GCT), 1 patient with Leydig cell tumor, and 1 patient with Sertoli cell tumor. Two of 7 patients enrolled achieved an objective response; both with NSGCT [17]. One patient achieved a complete response that was durable for almost 4 years after treatment discontinuation. Another study evaluating brentuximab vedotin as salvage therapy in relapsed GCT indicated that treatment was well tolerated in this patient population. Among 9 patients enrolled in the first stage of this phase II trial, the objective response rate (ORR) was 22.2% with 1 complete response and 1 partial response [18].

A study evaluating the activity of brentuximab vedotin in B-cell non-Hodgkin lymphoma, showed no correlation between clinical response and CD30 expression [19]. Although the precise mechanism underlying this phenomenon remains unknown, some evidence indicates a bystander effect, whereby free anti-microtubule agent MMAE is released from dying cells in concentrations sufficient to be cytotoxic in neighboring tumor cells [20].

Based on these encouraging early clinical data indicating possible efficacy, we conducted a multicenter phase II open-label trial to evaluate the activity of brentuximab vedotin in relapsed/refractory GCT.

# Patients And Methods

### Patients

Eligible patients had histologically confirmed metastatic non-seminomatous GCT with the exception of pure teratoma who progressed after first-line cisplatin-based chemotherapy and after at least one salvage regimen. Patients with late relapse, defined as progression >2 years from initial therapy, and primary mediastinal NSGCT were eligible. Relapsed patients who were not candidates for salvage chemotherapy were also eligible for this trial. Patients with pure seminoma were excluded. Patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 and/or elevation of tumors markers [alpha-fetoprotein (AFP) and/or b-human chorionic gonadotropin (b-hCG)]. Patients with rising tumor markers and no radiographic progressive disease were eligible if two consecutive rising tumor marker values at least 1 week apart were documented. All patients were required to provide archived tumor tissue from a biopsy or the original primary tumor for CD30 expression evaluation and other exploratory analyses. Patients were eligible regardless of CD30 staining result based on central immunohistochemistry. Full eligibility criteria are listed in the trial protocol (supplementary material, online only).

### Treatment Program

Planned treatment consisted of brentuximab vedotin 1.8 mg/kg administered intravenously over 30 minutes once every 21 days. Patients who experienced grade ≥ 2 peripheral neuropathy had the dose reduced to 1.2 mg/kg IV every 3 weeks. Treatment was continued until documented disease progression, development of unacceptable toxicity, withdrawal of consent, or decision by investigator to discontinue treatment.

### Study Design, Endpoints, and Statistical Analysis

This was a multicenter, open-label phase II trial of single agent brentuximab vedotin with 2 cohorts. Cohort 1 enrolled patients with CD30 positive tumors. Cohort 2 enrolled patients with CD30 negative or unknown tumors. The primary endpoint was to determine the objective response rate (ORR) using RECIST v1.1. Secondary endpoints were progression-free survival (PFS), overall survival (OS), toxicity measured by CTCAE v4.0, and correlation of CD30 staining intensity and localization to ORR and PFS. CD30 expression was assessed using immunohistochemistry with anti-CD30 BerH2 at the Indiana University Simon Comprehensive Cancer Center Clinical Trials Office Laboratory. A Simon's two-stage optimal design was utilized within each cohort with type I error rate of 4.7% and power of 80% [21]. The null hypothesis was an ORR≤5% and the alternate hypothesis was ORR≥20%. For each cohort, the planned sample size was n=29 response-evaluable patients. Within each cohort, if no objective responses were observed in the first 10 patients, enrollment in that cohort would be terminated. The study schema is

depicted in Figure 1. CD30 staining was characterized by intensity (0 to 3+) and by localization (cell wall vs. cytoplasmic) using descriptive statistics. CD30 status was considered positive if staining intensity was ≥1+. The analysis plan called for correlating CD30 status with ORR using logistic regression and with PFS using proportional hazards regression. As both cohorts were closed early, these regression analyses were not completed. Toxicity was reported combining the two cohorts. The protocol was approved by the institutional review boards of all participating institutions.

# Results

### Patient and Disease Characteristics

Seven CD30 positive and eleven CD30 negative patients with relapsed/refractory GCT (N=18) were enrolled between May 2016 and September 2018 at 3 academic institutions. One patient had unknown CD30 expression and was categorized and allocated to the CD30 negative group. Patient and disease characteristics are listed in Table 1. Median age was 35 (range 23-57 years). One female patient with ovarian GCT was enrolled (CD30 –ve). All patients had non-seminoma histology. Tumor markers where elevated in 16 out of 18 patients: AFP only in 5, hCG only in 10, both AFP and hCG in 1. Metastatic sites included retroperitoneal lymph nodes in 7 patients, pulmonary metastasis in 14 patients, liver metastasis in 8 patients, brain metastasis in one, and bone metastasis in 3. The median number of previous lines of chemotherapy was 3 (range 2-7). Ten patients (55.6%) had undergone prior high-dose chemotherapy and autologous stem-cell transplant. Twelve patients (66.7%) received prior ifosfamide or paclitaxel-containing salvage chemotherapy regimens. Five patients (27.8%) had late relapse defined as disease progression/recurrence more than 2 years after first line cisplatin-based combination chemotherapy.

### Treatment Administration

All 18 patients enrolled in this study across both cohorts received at least one dose of brentuximab vedotin 1.8 mg/kg per study protocol. The median number of doses was 2 (range 2-4) in the CD30 positive cohort and 3 (range 1-6) in the CD30 negative cohort. One patient in the CD30 negative cohort received only 1 dose of brentuximab vedotin and died due to disease progression. Dose reductions were required for 2 CD30 negative patients due to adverse events.

### Efficacy

No partial or complete responses were observed. Six out of 18 enrolled patients had stable disease. Five of the 6 patients with stable disease had elevated AFP or hCG at trial entry; all 5 patients had >50% decline in AFP or hCG which was transient and followed with rising markers at time of progression. Two of these 6 patients were in the CD30 positive cohort (stable disease for 9 and 11.7 weeks respectively), and 4 were in the CD30 –ve cohort (stable disease for 9, 9, 12, and 14.9 weeks respectively). Of the remaining 12 patients, 10 had progressive disease as their best response. One patient in the CD30 positive and 1 in the CD30 negative cohort were not evaluable for efficacy due to death from complications of disease prior to any disease evaluation. Tumor responses evaluated via RECIST 1.1 in

CD30 –ve and CD30 positive cohorts are depicted in Figure 2. Note that the best response in 6 patients was determined solely based on rising tumor markers satisfying protocol criteria for disease progression. PFS and OS Kaplan–Meier curves are depicted in Figure 3 and 4 respectively (supplementary material, online only). Median PFS in the CD30 positive cohort was 1.2 months (95% CI: 0.9-2.1 months) and in the CD30 negative cohort was 1.4 months (95% CI: 0-2.1 months). Median OS in the CD30 positive cohort was 2.5 months (95% CI: 1.1-12.9 months) and in the CD30 negative cohort was 5.9 months (95% CI: 1.6-8.2 months).

Given no confirmed objective responses were observed among 10 response-evaluable patients in the CD30 negative cohort (one additional patient was unevaluable for response), the protocol-stipulated stopping criteria (<1/10 with response) were met and this cohort was closed for lack of efficacy rather than proceeding to the second Simon stage. The CD30 positive cohort was terminated before the interim analysis given slow accrual and lack of any signal of efficacy among the 6 response-evaluable patients. At last follow-up, 12 patients had died due to disease progression. There were no deaths due to toxicity.

### Biomarker Analysis

Out of the 7 CD30 positive patients, 1 had cytoplasmic staining (3+ intensity), 5 had cell wall staining (three had 3+ intensity and two had 2+ intensity), and 1 had an unknown staining localization. The two patients with stable disease both had CD30 cell wall staining (2+ and 3+ respectively).

### Toxicity

Brentuximab vedotin was generally tolerated in this patient population with 2 patients experiencing treatment-related grade 3 adverse events one with anemia and another with neutropenic fever. No grade 4 or 5 treatment-related adverse events were reported. Table 2 lists the most common adverse events reported.

## Discussion

There remains a substantial proportion of patients with metastatic GCT who relapse after initial chemotherapy and require some form of salvage surgery or chemotherapy [3]. Salvage chemotherapy can cure up to 50% of patients with relapsed disease when used in the appropriate clinical context [5, 6]. Salvage surgery is an effective option only in patients with loco-regional relapse [7]. Patients who progress after salvage chemotherapy have limited treatment options with generally short expected survival. The quest for novel and innovative therapeutic options in patients with refractory GCT is ongoing.

Results from early phase clinical trials evaluating molecularly targeted therapy in the treatment of relapsed/refractory GCT have been disappointing. Studies investigating imatinib, sunitinib, pazopanib, thalidomide, and trastuzumab indicated that these agents are largely inactive in this patient population

[22-26]. Initial trials investigating single agent immune checkpoint inhibition with pembrolizumab in patients with refractory GCT have been disappointing as well with no objective responses reported [27].

In this phase II trial, we evaluated the activity of brentuximab vedotin in this patient population with relapsed/refractory GCT. Brentuximab vedotin was well tolerated with two grade ≥3 treatment-related adverse events. No objective responses were observed among the 18 patients enrolled. Six patients achieved stable disease with 5 patients achieving a transient >50% decline in tumor markers. Two patients in the CD30 positive cohort had stable disease for 9 and 11 weeks, respectively. One of these patients normalized tumor markers during treatment and later progressed. Four patients in the CD30 negative cohort had radiographic stable disease for 14.9, 12, 9, and 9 weeks respectively. All other patients had progressive disease as their best response.

This phase II trial was initiated based on promising results from earlier studies indicating possible activity of brentuximab vedotin in refractory GCT. The first study had 2 objective responses out of 9 patients enrolled and the second had 2 objective responses out of 7 patients enrolled [17, 18]. However, in this larger phase II trial we did not observe a signal of activity in 18 patients enrolled and therefore both cohorts (CD30 positive and negative) were closed to accrual.

Although this phase II trial investigated a novel approach for salvage therapy in refractory GCT, there are limitations to report. This study had a small sample size of patients with refractory GCT. CD30 staining was performed on archival tumor tissue which may not represent the current CD30 expression status at the time of treatment with brentuximab vedotin on trial. Moreover, this study was not a biomarker selected study as all patients were eligible irrespective of CD30 expression. The CD30 positive cohort was closed prior to formal interim analysis due to lack of efficacy.

In conclusion, brentuximab vedotin was safe and well tolerated but did not demonstrate clinical benefit in this cohort of patients with refractory GCT. Future investigation should evaluate mechanisms of resistance and potential novel and innovative therapeutic approaches in patients with incurable GCT.

# Declarations

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**Conflict of interest statement/Competing interests:** There are no conflicts of interest to disclose.

**Availability of data and material:** All data and materials support published claims and comply with field standards.

**Code availability:** Not applicable

**Author Contributions:***Study concept and design:* Adra, Feldman, Einhorn, Albany. *Financial and administrative support:* Adra. *Provision of study materials or patients:* Adra. *Collection and assembly of data:* All authors. *Data analysis and interpretation:* All authors. *Drafting and writing: Ashkar, Adra. Review and final approval of manuscript:* All authors.

**Ethics approval:** This study was approved by the Indiana University IRB.

**Consent to participate:** Informed consent was obtained from all individual participants in this study.

**Consent for publication:** The authors affirm that human research participants provided informed consent for publication.

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# Tables

### Table 1. Patient and Disease Characteristics

| Characteristic | CD30-Negative | CD30-Positive | Overall |
|---|---|---|---|
| Total patients | 11 | 7 | 18 |
| Median age (range) | 37.3 (25.0-56.6) | 29.7 (23.3-45.3) | 34.7 (23.3-56.6) |
| Gender | | | |
| · Male | 10 (90.9%) | 7 (100%) | 17 (94.4%) |
| · Female | 1 (9.1%) | 0 | 1 (5.6%) |
| Location of primary tumor | | | |
| · Testis | 9 | 7 | 16 |
| · Mediastinum | 1 | 0 | 1 |
| · Ovarian | 1 | 0 | 1 |
| Metastatic site(s) | | | |
| · Retroperitoneum | 5 (46%) | 2 (29%) | 7 (39%) |
| · Pulmonary | 9 (82%) | 5 (71%) | 14 (78%) |
| · NPVM | | | |
| -Liver metastasis | 6 (55%) | 2 (29%) | 8 (44%) |
| -Brain metastasis* | 1 (9%) | 0 | 1 (6 %) |
| -Bone metastasis* | 3 (27%) | 0 | 3 (17%) |
| · Peritoneal nodule | 1 (9%) | 0 | 1 (6%) |
| No. of previous chemotherapy regimens | | | |
| · 2 | 3 (27%) | 1 (14%) | 4 (22%) |
| · 3 | 5 (46%) | 1 (14%) | 6 (33%) |
| · 4 | 1 (9%) | 3 (43%) | 4 (22%) |
| · 5 | 1 (9%) | 0 | 1 (6%) |
| · 6 | 1 (9%) | 1 (14%) | 2 (11%) |
| · 7 | 0 | 1 (14%) | 1 (6%) |
| Late Relapse (> 2 years) | 4 (36%) | 1 (14%) | 5 (28%) |
| Elevated Tumor Markers | | | |
| · AFP only | 5 (46%) | 0 | 5 (28%) |

| | | | |
|---|---|---|---|
| · hCG only | 6 (55%) | 4 (57%) | 10 (56%) |
| · AFP and hCG | 0 | 1 (14%) | 1 (6%) |
| Median Serum AFP ng/mL (range) | 5.7 (1.9-219345) | 3.3 (0.8-1894.7) | 4.9 (0.8-219345) |
| Median Serum hCG mIu/mL (range) | 13.5 (0.6-62524.6) | 3014 (0.8-172063.7) | 281.9 (0.6-172063.7) |
| ECOG performance status | | | |
| · 0 | 5 (46%) | 5 (71%) | 10 (56%) |
| · 1 | 6 (55%) | 2 (29%) | 8 (44%) |
| CD30 Staining Location | | | |
| · Cell Wall | N/A | 5 (71.4%) | N/A |
| · Cytoplasm | N/A | 1 (14.3%) | N/A |
| · Unknown | N/A | 1 (14.3%) | N/A |

Abbreviations: NPVM, non-pulmonary visceral metastasis; AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; IU, international unit; ECOG, Eastern Cooperative Oncology Group;

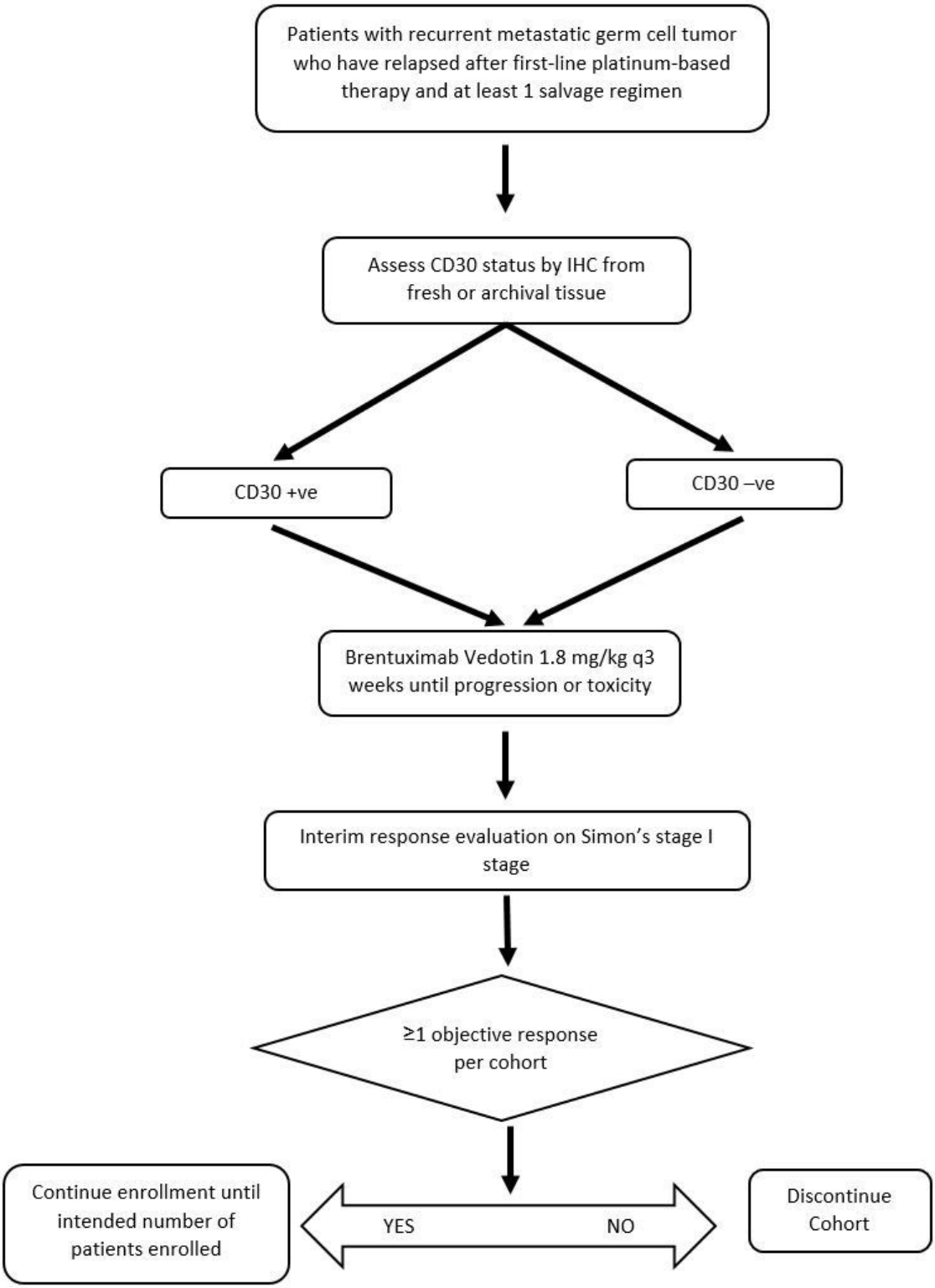
*Brain/bone imaging was not mandatory

Percentages are displayed in parenthesis (%) unless specified otherwise

**Table 2: Adverse Events in Patients Receiving Brentuximab Vedotin**

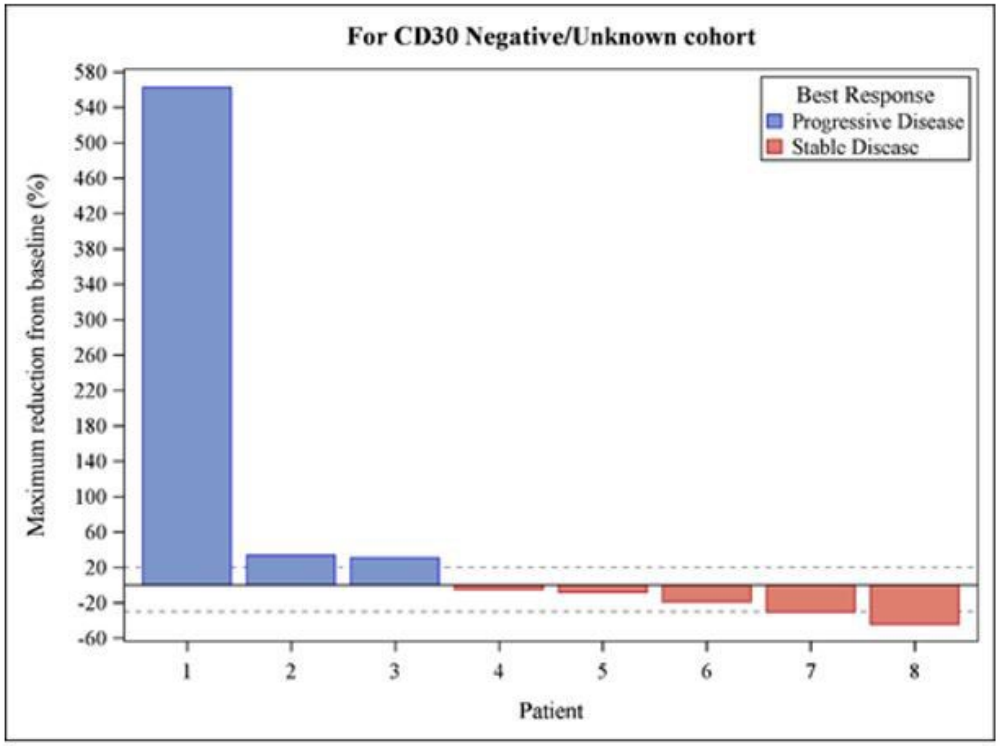
| | Patients (N=18) | |
|---|---|---|
| **Any adverse event** | **18 (100%)** | |
| **Treatment-related adverse events** | **14 (78%)** | |
| **Grade ≥ 3 treatment related adverse events** | **2 (11%)** | |
| **Treatment-related serious adverse events** | **1 (5.6%)** | |
| **Treatment-related adverse events resulting in treatment discontinuation** | **0** | |
| **Treatment-related adverse events leading to death** | **0** | |
| **Common treatment-related adverse events** | **Any Grade** | **Grade ≥ 3** |
| Anemia | 1 (6%) | 1 (6%) |
| Neutropenic fever | 2 (11%) | 1 (6%) |
| Anorexia | 3 (17%) | 0 |
| Fatigue | 4 (22%) | 0 |
| Peripheral sensory neuropathy | 4 (22%) | 0 |
| Pruritus | 6 (33%) | 0 |
| Maculopapular rash | 3 (17%) | 0 |
| Infusion related reaction | 2 (11%) | 0 |
| Nausea | 4 (22%) | 0 |
| Vomiting | 2 (11%) | 0 |

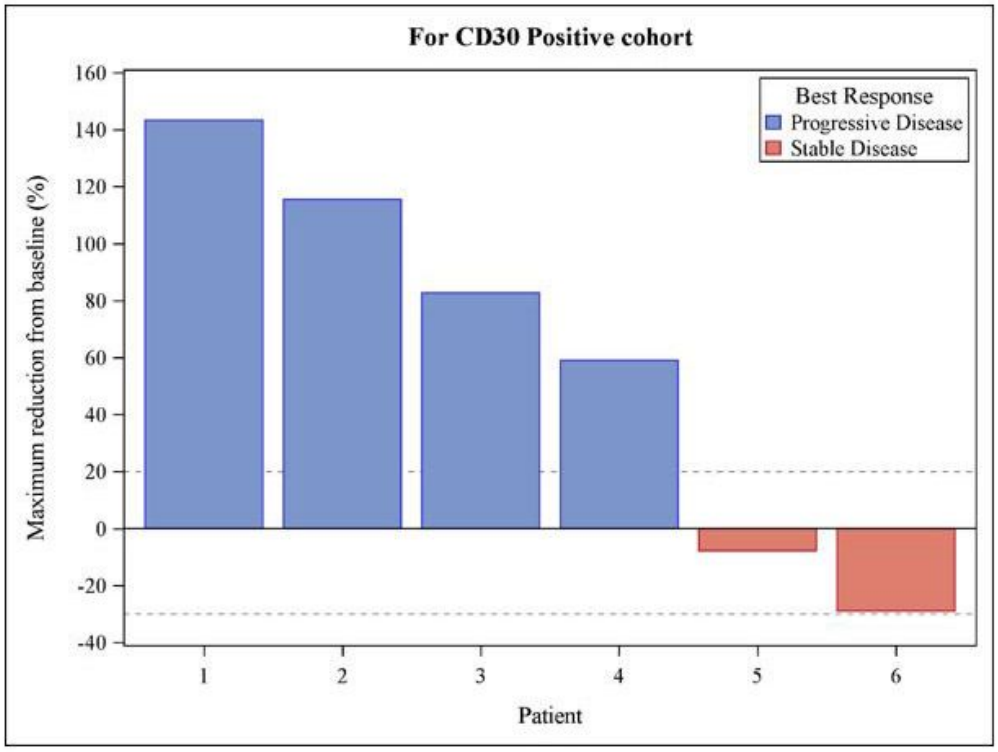
# Figures




## Figure 1

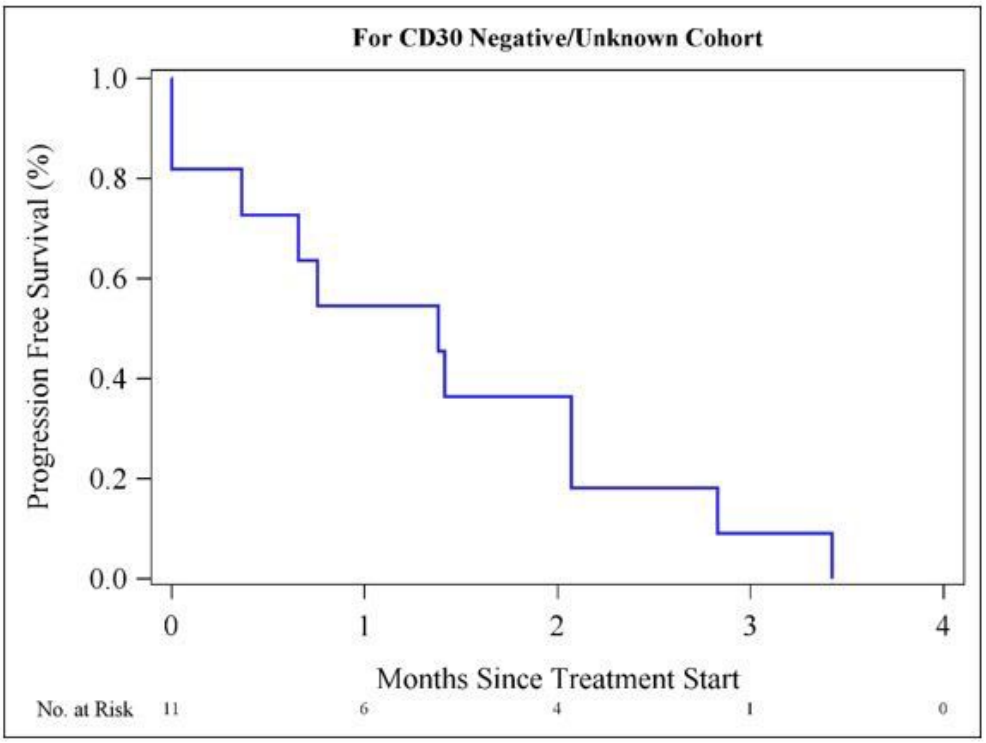
Study Schema

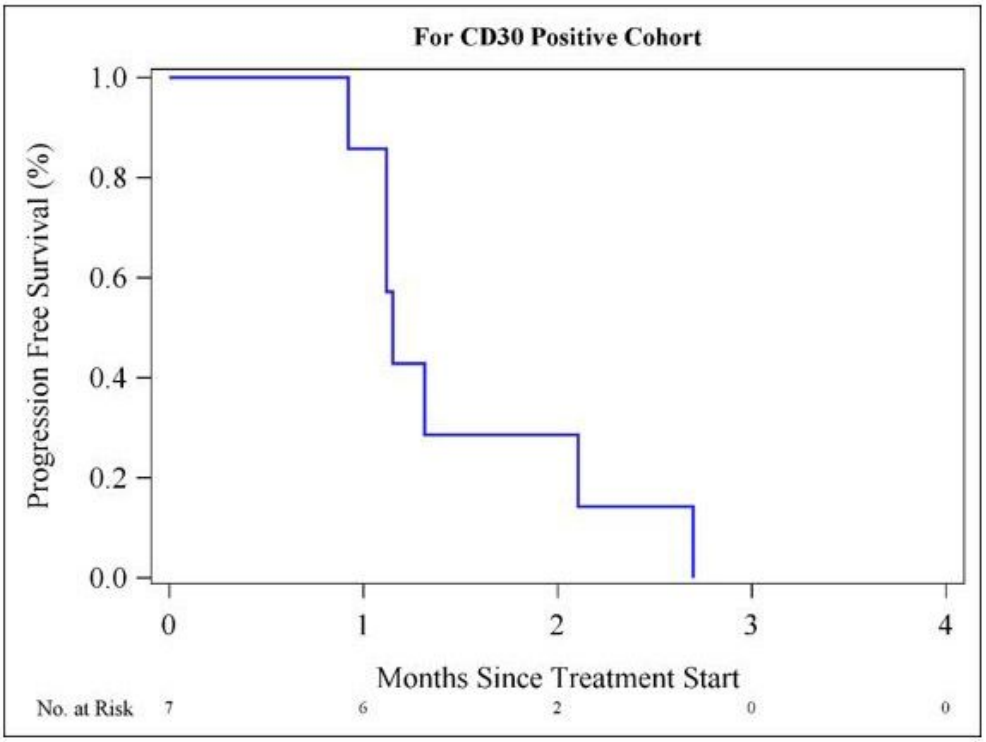



## Figure 2

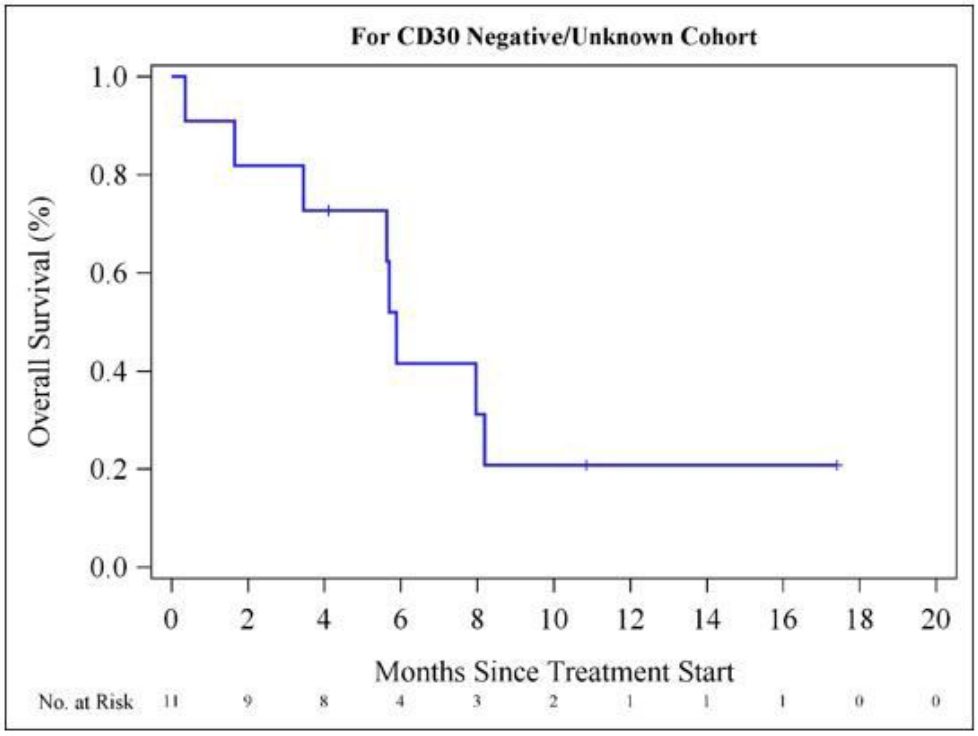
(a): Best overall response by RECIST v1.1 measurements in CD30 negative cohort. (b): Best overall response by RECIST v1.1 measurements in CD30 positive cohort.

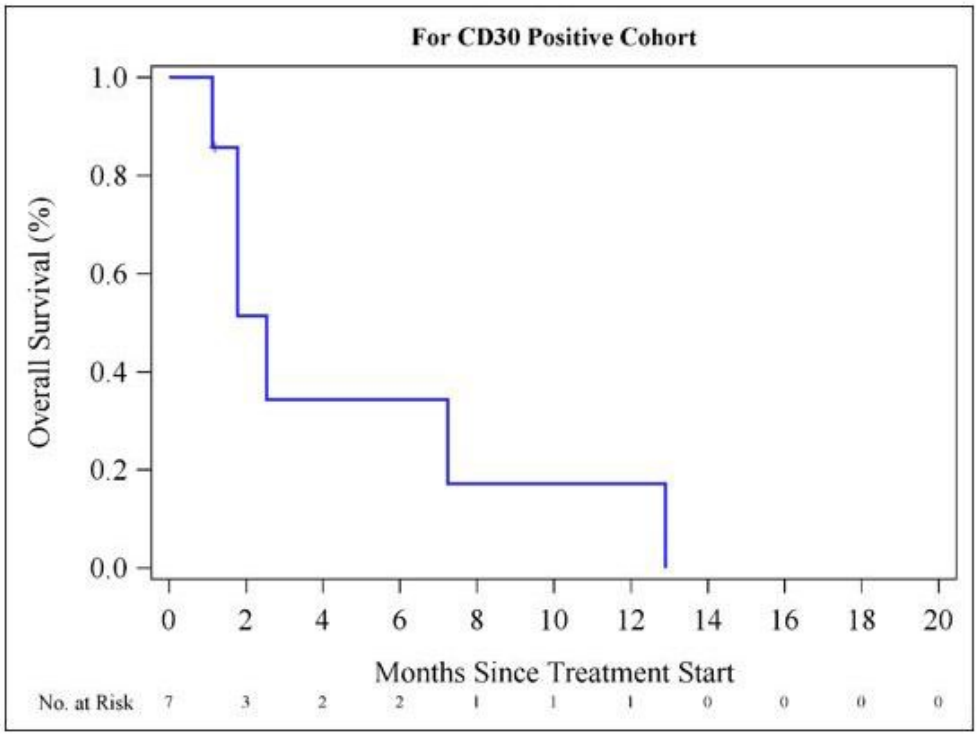



## Figure 3

(a): Progression-free survival in CD30 negative cohort. (b): Progression-free survival in CD30 positive cohort.




## Figure 4

(a): Overall survival in CD30 negative cohort. (b): Overall survival in CD30 positive cohort.