CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Randomized Phase IIb Placebo-controlled Study of R-ICE Chemotherapy (Rituximab, Ifosfamide, Carboplatin, and Etoposide) with and without SGN-40 (anti-CD40 humanized monoclonal antibody) for Second-line Treatment of Patients with Diffuse Large B-Cell Lymphoma (DLBCL)
Brief Title:	A Randomized Phase IIb Placebo-Controlled Study of R-ICE Chemotherapy With and Without SGN-40 for Patients With DLBCL
Investigational Product:	SGN-40 (dacetuzumab)
Indication:	Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)
Phase:	Phase 2
Protocol Number:	SG040-0005 ClinicalTrials.gov ID: NCT00529503
Study Initiation Date:	First patient enrolled: 07-Dec-2007
Study Completion Date:	Last patient visit: 05-May-2011
Study Report Date:	28-Oct-2011
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Collaborator:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990, USA
Medical Monitor:	[redacted]
Good Clinical Practice:	This study was conducted in accordance with applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents will be retained in accordance with ICH GCP.

Sponsor

Seattle Genetics, Inc.
21823 30th Drive SE
Bothell, WA 98021, USA

Name of Finished Product

SGN-40 (dacetuzumab) for injection

Name of Active Ingredient

SGN-40 (dacetuzumab)

Study Title

A Randomized Phase IIb Placebo-controlled Study of R-ICE Chemotherapy (Rituximab, Ifosfamide, Carboplatin, and Etoposide) with and without SGN-40 (anti-CD40 humanized monoclonal antibody) for Second-line Treatment of Patients with Diffuse Large B-Cell Lymphoma (DLBCL)

Phase

Phase 2b

Study Center(s)

Patients were enrolled at 52 sites: 19 sites in the United States, 10 sites in Eastern Europe (Czech Republic, Hungary, and Poland), 19 sites in Western Europe (Belgium, France, Germany, Italy, and Spain), and 4 sites in Australia.

Publication(s) Based on the Study

Fayad A, Ansell SM, Advani R, Coiffier B, Bartlett NL, Stuart R, Forero-Torres A, Kuliczkowski K, and Drachman JG (2011). A phase 2b trial comparing dacetuzumab + R-ICE vs placebo + R-ICE in patients with relapsed diffuse large B-cell lymphoma. Ann Oncol 22: Abstract 145

Study Period

41 months

Date first patient enrolled: 07-Dec-2007

Date of last patient visit: 05-May-2011

Study Objectives

Primary:

To estimate the complete response (CR) rate of patients receiving R-ICE in combination with dacetuzumab versus R-ICE in combination with placebo in patients with DLBCL after receiving R-CHOP (rituximab, cyclophosphamide, doxorubin, vincristine, and prednisolone) or equivalent first-line therapy.

Secondary:

To assess the safety and tolerability of R-ICE in combination with dacetuzumab versus R-ICE in combination with placebo in patients with DLBCL after receiving R-CHOP or equivalent first-line therapy.

Tertiary:

- To estimate multiple measurements of clinical benefit for patients with DLBCL treated with combined therapy of R-ICE in combination with dacetuzumab versus R-ICE in combination with placebo:
  - Objective response rate (CR and partial response [PR])
  - Percentage of patients who subsequently undergo hematopoietic stem cell transplant (SCT)
  - Failure-free survival (FFS)
  - Overall survival (OS)
- To investigate patient-specific determinants of response to therapy:

- Expression levels of CD40 and other B cell surface markers (e.g., Bcl-6, CD10, CD20) on malignant cells
- Time since completion of first-line therapy
- International Prognostic Index (IPI) at randomization
- DLBCL subtype as determined by immunohistochemistry and/or gene expression profiling by cDNA microarray analysis

- To characterize the pharmacokinetic profile of dacetuzumab and rituximab when administered as part of the R-ICE regimen
- Response at 1 and 2 years following randomization

Methodology

This was a phase 2b, randomized, placebo-controlled, double-blind trial to compare the activity of R-ICE in combination with dacetuzumab vs. R-ICE in combination with placebo in patients with DLBCL. Randomization was to be 1:1 and study arms were to be stratified as follows:

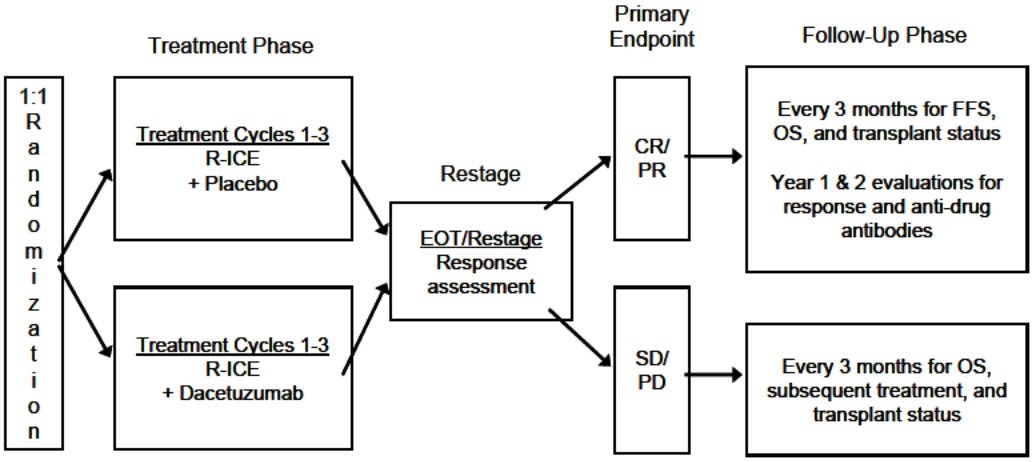
- Time since completion of first-line therapy
  - ≤12 months since completion of first-line therapy
  - >12 months since completion of first-line therapy
- Disease histology
  - de novo DLBCL and Follicular Grade 3b
  - transformed DLBCL

Antitumor activity assessments were to be performed by computed tomography (CT) and positron emission tomography (PET) scans of the neck, chest, abdomen, and pelvis within 28 days prior to randomization, 10 days after completing or discontinuing study treatment, and at 1 and 2 years following randomization. A best clinical response of CR, PR, stable disease (SD), or progressive disease (PD) per the Revised International Working Group Response Criteria for Malignant Lymphoma 2007 was to be determined by the investigator. An independent and blinded imaging core laboratory was to evaluate radiographic images in support of response assessment which was to be documented in a separate charter and reported separately. A planned futility analysis was to be conducted by an Independent Data Monitoring Committee (IDMC) after 112 patients (50% of planned patients) completed treatment and response assessment by the investigator.

Safety assessments included the incidence of adverse events, changes in laboratory values and vital signs, electrocardiogram (ECG), and physical examination findings. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used for grading adverse events. The IDMC reviewed blinded data at several pre-specified timepoints to oversee study conduct and patient safety.

Other study assessments were to include dacetuzumab and rituximab pharmacokinetic (PK) analysis, measurement of anti-drug antibodies, central pathology review of tumor specimens, lymphocyte subsets, DLBCL molecular subtype determination, and CD40 expression in lymphoma cells.

Study Schema



As shown in the figure above, patients were to receive R-ICE plus weekly investigational drug (dacetuzumab or placebo) for 3 cycles of 3 weeks each during the treatment phase. Ten days after completing or discontinuing study treatment, the patient was to be seen for an End of Treatment (EOT) visit and participation in the treatment phase of the study was to be complete. Patients were to receive therapy as follows:

Dosing and Administration of R-ICE and Dacetuzumab

	Cycle 1 (Wks 1–3)							Cycle 2 (Wks 4–6)					Cycle 3 (Wks 7–9)				
Cycle Day	**-2**	**-1**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**	**1**	**2**	**3**	**8**	**15**
Study Day	**-2**	**-1**	**1**	**2**	**3**	**8**	**15**	**22**	**23**	**24**	**29**	**36**	**43**	**44**	**45**	**50**	**57**
Rituximab ($375\ mg/m^2$)	X							X					X				
Investigational Drug (mg/kg)		2			4	8	8	8			8	8	8			8	8
Etoposide ($100\ mg/m^2$)			X	X	X			X	X	X			X	X	X		
Carboplatin (AUC=5 mg/mL*min)				X					X					X			
Ifosfamide [a] ($5\ g/m^2$)				X→					X→					X→			

a Ifosfamide was to be mixed with Mesna ($5\ g/m^2$) and administered as a 24-hour infusion.

Dose modifications of rituximab and dacetuzumab were not to be permitted. Delay of initiation of Cycle 2 or 3 due to clinically significant unresolved toxicity or cytopenia was to be allowed. Delays of more than 7 days relative to Day 1of the previous cycle were discouraged; delays of more than 21 days were not allowed. Dacetuzumab treatment was to be discontinued in the event R-ICE chemotherapy was discontinued.

Transfusions and growth factor support were allowed. Due to the myelosuppressive activity of ICE, it was expected that most patients would receive hematopoietic growth factors (granulocyte-colony stimulating factor, erythropoietin) and transfusions of blood products.

As standard of care, it was anticipated that stem cell mobilization may occur following the final chemotherapy, and for those who achieved at least a PR, hematopoietic SCT may occur for consolidation. Data were to be recorded to assess adequacy of hematopoietic stem cell collection and occurrence and engraftment of subsequent SCT.

During the follow-up phase, patients were to be contacted by telephone 30 days after the EOT visit for safety follow-up and every 3 months to determine if they have undergone SCT, clinical outcome after SCT, and OS until study closure. Follow-up was to cease 2 years after the last patient was randomized.

In addition to standard follow up, patients with ongoing CR or PR were to have study visits 1 and 2 years following randomization to determine failure-free survival (FFS) including evaluation of disease status by radiographic exam, physical exam, and bone marrow assessment (if positive at baseline), and to determine anti-drug antibody response.

Patients were to be followed for a maximum anticipated duration of 2 to 3 years after randomization (i.e., until study closure).

Number of Patients

Planned: 224

Analyzed: 151

Diagnosis and Primary Criteria for Inclusion

Patients were required to meet all of the inclusion and exclusion criteria listed below to be eligible to participate in this study.

Inclusion Criteria

1. Patient has pathologically confirmed diagnosis of diffuse large B-cell lymphoma (DLBCL), including both de novo and transformed DLBCL and follicular lymphoma, Grade 3b (FL3b).

    - Local pathology review is acceptable for determining eligibility.
    - Prior therapy for indolent lymphoma is not allowed.
    - For patients who have achieved a CR to first-line therapy, a repeat biopsy since relapse for confirmation of disease is required unless all of the following conditions are met:
        - Relapse has occurred within 1 year of completing first-line therapy.
        - In the investigator's opinion, the CT and PET imaging and clinical presentation are consistent with relapsed DLBCL or FL3b.
        - It is medically unsafe or infeasible to perform a biopsy due to the anatomic location of the tumor(s).
        - The site has confirmed that there is adequate tissue from the initial diagnostic biopsy for central review to confirm diagnosis and perform all immunohistochemical and pharmacogenomic studies.
2. Patient has received at least four cycles of first-line therapy with R-CHOP or equivalent first-line therapy including rituximab, cyclophosphamide, anthracycline or anthracenedione, and steroid with or without additional chemotherapy agent(s). For patients who achieve CR with first-line therapy, maintenance therapy prior to relapse is allowed.
3. Patient achieved a response of stable disease, partial response, or complete response following the last cycle of R-CHOP.
4. Patient currently has at least one site of measurable disease meeting both of the following criteria:

    - Bidimensional measurement with longest axis greater than or equal to 1.5 cm by radiographic imaging.
    - Positive FDG-PET scan at baseline.

    Local imaging review is acceptable for determining eligibility.
5. A fresh or archived tumor specimen is available for central review to confirm diagnosis.
6. Patient has completed first-line therapy at least four weeks prior to the date of randomization.
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.

8. Patient is at least 18 years old and no more than 75 years old.

9. Patient has the following required baseline laboratory data (eligibility can be based on local lab results):

   - Platelet count greater than or equal to 75,000/mm^3.
   - Absolute neutrophil count (ANC) greater than or equal to 1,000/mm3 (may be maintained by growth factors).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than or equal to 2.5 times upper limit of normal (ULN).
   - Total serum bilirubin level less than or equal to 1.5 times ULN.
   - Serum creatinine less than or equal to 1.5 times ULN.

10. If a female of childbearing potential, the patient has a negative serum or urine pregnancy test result (sensitivity at least 50 mIU/mL) within three days prior to the first dose of Investigational Drug or on Day -2, prior to first dose. (Females of non-childbearing potential are those who are postmenopausal greater than one year or who have had a bilateral tubal ligation or hysterectomy)

11. If female of childbearing potential or a male patient, patient agrees to use an effective contraceptive method from the time of informed consent, during the course of the study, and for 6 months following the last dose of Investigational Drug.

12. Patient is available for periodic blood sampling, study-related assessments, and management of toxicity at the treating institution.

13. Patient or their legally authorized representative understands and voluntarily signs the written informed consent prior to any study-specific procedures. A copy of the signed informed consent form will be retained by the treating institution.

Exclusion Criteria

Unless a signed medical exception has been documented and approved by the Medical Monitor prior to randomization, patients must be negative for all of the following exclusion criteria to be eligible for the study:

1. Patient has a history or clinical evidence of leptomeningeal or central nervous system (CNS) lymphoma.

2. Patient has received any therapy for relapsed or progressive disease except for local radiation, steroids, or single-agent rituximab (less than or equal to four infusions).

3. Patient has a documented history of a cerebral vascular event (stroke or transient ischemic attack) or myocardial infarction within six months of screening.

4. Patient has received a hematopoietic stem cell transplant.

5. Patient has been previously treated with an anti-CD40 mAb or any therapeutic radiolabeled antibody.

6. Patient has had major surgery within four weeks prior to randomization.

7. Patient has a known hypersensitivity or anaphylactic reaction to any component of the planned study treatment.

8. Patient has evidence of another invasive primary malignancy anytime in the 12 months prior to screening.

9. Patient has had any systemic viral, bacterial, or fungal infection requiring IV antibiotics within four weeks prior to planned date of randomization.

10. Patient has a known positive test for human immunodeficiency virus (HIV), hepatitis B (by surface antigen expression), or hepatitis C infection.

11. Patient is on systemic steroids exceeding 20 mg/day prednisone or equivalent during any of the seven days prior to randomization.

12. Patient is taking any other systemic immunosuppressive medication during the 14 days immediately prior to randomization (e.g., cyclosporine, azathioprine, mycophenylate mofetil).

13. Patient is pregnant or breastfeeding.

14. Patient has any serious underlying medical condition that would impair their ability to receive or tolerate the planned treatment or subsequent SCT.

15. Patient has been diagnosed with dementia or has altered mental status that would preclude the understanding and/or rendering of informed consent.

Test Product, Dose, Mode of Administration, Batch Number

SGN-40 (dacetuzumab); dose range 2 to 8 mg/kg (dose escalation in Cycle 1 to 8 mg/kg; then dosing on Days 1, 8, and 15 at 8 mg/kg in Cycles 2–3); intravenous; batch numbers SPE002-006, SRX001, SQT001, and SQT002

Combination Therapy

Rituximab (Rituxan®), Genentech USA, Inc. and Biogen Idec Inc.; 375 mg/m^2 (dosing on Day -2 in Cycle 1 and on Day 1 in Cycles 2–3); injection

Ifosfamide (Ifex®), Bristol Myers Squibb Company; 5 g/m^2 (dosing on Days 2–3 in Cycles 1–3; mixed with Mesna [5 g/m2]); 24-hr infusion

Carboplatin (Paraplatin®), Bristol Myers Squibb Company; AUC=5 mg/ml*min (dosing on Day 2 in Cycles 1–3); injection

Etoposide (Toposar®, VePesid®), Teva Pharmaceuticals; 100 mg/m^2; (dosing on Days 1–3 in Cycles 1–3; injection

Duration of Treatment

Patients were to receive 3 cycles of 3 weeks each for an expected treatment duration of 9 weeks unless unacceptable toxicity or disease progression occurred.

Criteria for Evaluation

Safety: The following safety parameters were assessed:

- Adverse events
- Laboratory parameters
- Anti-drug antibody immune response
- Adequate collection of hematopoietic progenitors
- Vital signs
- ECG

Pharmacokinetics/Pharmacodynamics: Dacetuzumab and rituximab blood levels

Efficacy: The following efficacy parameters were assessed:

- CR as assessed by CT and PET scans at completion of study therapy
- PR as assessed by CT and PET scans
- Occurrence of hematopoietic stem cell transplant (SCT)
- Failure-free survival

- Overall survival
- Response at 1 and 2 years following randomization

Correlative studies: determination of tumor histology, expression levels of CD40 and other B cell surface markers (e.g., Bcl-6, CD10, CD20) on malignant cells, and tumor phenotyping based on immunohistochemistry and/or gene expression profiling by cDNA microarray analysis

Statistical Methods

Determination of Sample Size

Sample size determination and the planned use of the study results were based on Fleming and Richardson (J Infect Dis. 2004;190:666-674) for the design and interpretation of phase 2b screening trials. Approximately 224 patients were to be randomized to ensure about 200 patients in total would be evaluable for efficacy. It was assumed for the purpose of sample size estimation that R-ICE plus placebo would be associated with a 45% CR rate and R-ICE plus dacetuzumab would be associated with a 60% CR rate. It was further estimated that approximately 90% of the patients randomized would be evaluable. Using the method of Fleming and Richardson, the sample size of a single phase 3 trial designed to support approval (i.e., without requiring an additional trial) was first calculated using a one-sided α=0.0005, 80% power and a test statistic based on CR rate difference with no continuity correction. To achieve these constraints, a total of 754 evaluable patients were required or 838 randomized. This implied that the number of randomized patients ranged from 838/4=210 to 838/3=280 for the present phase 2b screening trial following the procedure of Fleming and Richardson (i.e., phase 2b sample size is 1/3 to 1/4 the sample size of a single phase 3 trial). The sample size of 224 was consistent with their recommendation. Therefore, the number of evaluable patients was estimated to be 200. The sample size of 200 evaluable patients would yield a trial with a one-sided type 1 error of 15%. This sample size was also associated with approximately 87% power if the assumed treatment effect exists (i.e., 45% CR rate vs. 60% CR rate). There was 57% power to have a one-sided p-value less than or equal to 0.025 if the assumed treatment effect existed. These operating characteristics were calculated using the normal approximation to the binomial distribution without continuity correction.

Study Endpoints

Primary efficacy endpoint: CR at EOT using the independent review committee (IRC) integrated CT + PET + Oncology response assessment

Secondary efficacy endpoint: Failure-free survival (FFS) which was defined as time from randomization until treatment failure, which was defined as the earliest of the following events:

- Death from any cause
- Disease progression during treatment
- SD or PD at EOT

Tertiary efficacy endpoints:

- Clinical response (CR, PR, SD, PD and unknown) at EOT
- Overall survival (OS) defined as time from randomization to death from any cause
- Occurrence of hematopoietic SCT

Safety endpoints:

- Treatment-emergent adverse events (AEs) defined as events that first occurred or worsened after the first dose of study treatment (any agent)
- Serious adverse events (SAEs)
- Treatment-emergent AEs by maximum severity

- AEs leading to discontinuation of study treatment
- Death
- Laboratory parameters (chemistry, hematology, coagulation, urinalysis and lactate dehydrogenase [LDH])
- Total number of CD34+ cells/kg harvested

Planned Interim Analysis

One formal interim analysis for futility was planned. The futility analysis was based on data from approximately the first 50% of patients who completed the treatment phase. Inference was based on the actual number of patients observed at interim and was adjusted using a constrained boundaries approach (Burington and Emerson, Biometrics 2003;59:770-777). The primary efficacy endpoint (CR rate) based on the investigator assessment was used to assess futility. The Independent Data Monitoring Committee (IDMC) was guided by the boundaries specified in the DMC Charter to make a recommendation to the sponsor to continue the study as planned, stop the study for safety concerns, or stop the study for futility.

Analysis Sets

For efficacy analyses, all patients were grouped into either the placebo group or the dacetuzumab group according to their randomization assignments regardless of which drug they actually received.

The full analysis set was the primary efficacy analysis set and was defined as all patients who

- were randomized,
- received any dose of either dacetuzumab or placebo,
- had measurable disease as determined by the IRC, and
- had disease diagnosis as confirmed by the centralized pathology review of tumor specimens by an independent pathologist.

The modified intent-to-treat (mITT) set, defined as randomized patients who received any dose of study treatment (dacetuzumab or placebo), was used in the sensitivity analyses of efficacy.

The primary safety set consisted of all randomized patients who received at least one dose of either dacetuzumab or placebo. Patients receiving any dose of dacetuzumab were grouped into the dacetuzumab group. Patients who did not receive dacetuzumab but any dose of placebo were grouped into the placebo group.

Planned Statistical Analyses

The primary analysis of the primary efficacy endpoint was based on the full analysis set. The observed difference in the CR response rates between the treatment groups was calculated. Patients with missing clinical response were considered as not achieving CR. Confidence intervals for the CR response rates using two-sided 95% level and the rate difference using two-sided 70% and 95% levels, and p-value were also provided using normal approximations.

FFS and OS were analyzed using the Kaplan-Meier method based on the full analysis set and the mITT set. The medians, first and third quartiles of FFS and OS were provided if the quartiles could be estimated by the Kaplan-Meier method. Log-rank test was used to compare the two treatment groups.

Treatment-emergent AEs were summarized using Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 preferred terms and included severity and relationship to study treatment (dacetuzumab/placebo or R-ICE). Patient incidence rates of the AE endpoints were tabulated by system organ class and preferred term for each treatment group. All patients in the safety set were included in the safety analyses.

Toxicity grades of laboratory parameters were determined by the CTCAE criteria version 3.0. Cross-tabulation of baseline toxicity grade of ≥ 3 and post-baseline toxicity grade of ≥ 3 was provided for each treatment group. Laboratory values, change from baseline values and change from baseline in toxicity grade were summarized by

descriptive statistics for each treatment group. Shift tables from baseline toxicity grade to the worst post-baseline toxicity grade were also provided.

RESULTS SUMMARY

Disposition

Futility Analysis

A planned futility analysis was conducted after 112 patients (50% of planned patients) were enrolled and randomized (55 patients in the dacetuzumab + R-ICE arm, 57 patients in the placebo + R-ICE arm). (Dacetuzumab + R-ICE will be subsequently referred to as dacetuzumab, and placebo + R-ICE as placebo.) Because the CR rate at EOT (the primary endpoint) was not improved with dacetuzumab, the IDMC recommended that enrollment be stopped and treatment with dacetuzumab be discontinued for all patients. Among the 112 randomized patients, a total of 88 patients (79%) completed the treatment phase (43 patients [78%] dacetuzumab, 45 patients [79%] placebo). Twenty-four patients (21%) discontinued study treatment: 8 patients (7%) discontinued due to disease progression (4% dacetuzumab, 11% placebo), 7 (6%) due to adverse event (9% dacetuzumab, 4% placebo), 6 (5%) due to patient decision (5% dacetuzumab, 5% placebo), and 3 (3%) due to investigator decision (4% dacetuzumab, 2% placebo). By the time of the futility analysis, 39 additional patients had been randomized to the study and had begun treatment.

Final Analysis

A total of 151 patients were enrolled and randomized (75 patients in the dacetuzumab arm, 76 patients in the placebo arm). This international study enrolled patients at study sites as follows: 77 patients (51%) in the United States, 13 patients (9%) in Poland, 12 patients (8%) each in both the Czech Republic and Hungary, 11 patients (7%) in France, 9 patients (6%) in Spain, 6 patients (4%) in Belgium, 4 patients (3%) each in Australia and Germany, and 3 patients (2%) in Italy.

Among the 151 randomized patients, a total of 111 patients (74%) completed the treatment phase (57 patients [76%] dacetuzumab, 54 patients [71%] placebo). All randomized patients received the correct study treatment. Forty patients (26%) discontinued study treatment: 8 patients (5%) discontinued due to disease progression (3% dacetuzumab, 8% placebo), 8 (5%) due to adverse event (8% dacetuzumab, 3% placebo), 7 (5%) due to patient decision (5% dacetuzumab, 4% placebo), and 4 (3%) due to investigator decision (3% each dacetuzumab and placebo). Thirteen patients (9%) discontinued treatment due to a sponsor decision to terminate study treatment based on the futility analysis.

Patients were followed after study treatment discontinuation (or completion) for a median of 27.3 months. At the time of study termination, 54 patients (36%) had died due to disease progression, 13 (9%) had died due to other causes, 8 (5%) withdrew consent, and 1 (1%) discontinued due to an investigator decision. Seventy-five patients (50%) were in follow-up when the study was terminated by the sponsor.

Key Demographics and Baseline Characteristics

The median age of the 151 patients in the study was 59 years (range, 22 to 74); 135 patients (89%) were less than 70 years of age. Eighty-five patients (56%) were male and 133 (88%) were white. As per the inclusion criteria, all patients had an ECOG status less than or equal to 2, though most patients had an ECOG status of 0 or 1 (ECOG status 0, 71 patients [47%]; ECOG status 1, 70 patients [46%]; ECOG status 2, 10 patients [7%]).

Based on local pathology review, disease diagnoses for the 151 enrolled patients were as follows: de novo DLBCL for 131 patients (87%), transformed DLBCL for 13 patients (9%), and FL3b for 7 patients (5%). The median time since initial diagnosis was 10.8 months (range, 2 to 124). However, 50 patients were not included in the full analysis set (primary efficacy analysis set) either due to insufficient measurable disease by the independent radiographic review or inability to confirm the disease diagnosis based on central pathology review. The disease diagnosis for the remaining 101 patients in this analysis set was de novo DLBCL for 93 patients (92%), transformed DLBCL for 5 patients (5%), and FL3b for 3 patients (3%). The median time since initial diagnosis for this set of patients was 9.6 months (range, 2 to 124).

All patients had received first-line therapy of R-CHOP or equivalent with a median of 6 treatment cycles (range, 4 to 9). The median time since completion of first-line therapy was 7 months. Few patients (8%) had received maintenance rituximab since completing first-line therapy. Best response to first-line therapy was CR for 83

patients (55%), PR for 56 patients (37%), and SD for 11 patients (7%). One patient was enrolled who had progressed during first-line therapy; this was recorded as a major protocol violation. There were a total of 19 protocol violations where eligibility criteria were not met; no other major protocol violations were reported.

Treatment arms were well balanced with respect to age, gender, race, ECOG status, disease diagnosis, time since initial diagnosis, and prior therapy with the exception of best response to first-line therapy. Slightly more patients in the placebo arm had a best response of CR to first-line therapy (n=45, 59%) as compared to the dacetuzumab arm (n=38, 51%) and more patients randomized to the dacetuzumab arm had a best response of PR to first-line therapy (n=31, 41%) than patients in the placebo arm (n=25, 33%).

Patients enrolled were equally randomized between the 2 treatment arms by time since completion of first-line therapy (≤12 months: 67% dacetuzumab, 66% placebo; and >12 months: 33% dacetuzumab, 34% placebo) and by disease histology (FL3b or de novo DLBCL: 92% each dacetuzumab and placebo; and transformed DLBCL: 8% each dacetuzumab and placebo).

Pharmacokinetic/Pharmacodynamics

Accumulation of serum dacetuzumab was observed following multiple doses (weekly administration for 3 cycles of 3 weeks each) and dacetuzumab appeared to reach steady state after 2 cycles (or 6 weeks) by visual inspection. The mean end of infusion concentration was in the range of 259–282 µg/mL and predose trough concentrations were 105–123 µg/mL at steady state.

Accumulation of serum rituximab was observed following multiple doses (administered every 3 weeks for 3 cycles) and steady state was not achieved by the end of treatment by visual inspection. The mean concentration-time profiles of rituximab were similar when administered with or without dacetuzumab. The mean predose concentrations before the third dose were 60 and 63 µg/mL, and the mean end of infusion concentrations after the third dose were 228 and 250 µg/mL, when dosed with placebo or dacetuzumab, respectively.

Efficacy Results

Futility Analysis

A planned futility analysis, conducted after 50% of planned patients (n=112) were treated, revealed a similar CR rate between arms based on the investigator assessment. In the dacetuzumab arm, 20 patients (36% [(95% CI, 24% to 49%]) had a CR at EOT, and in the placebo arm, 24 patients (42% [95% CI, 29% to 55%]) had a CR at EOT. The rate difference was -6% with a 95% CI of -24% to +12%. Because the CR rate was not improved with dacetuzumab, further enrollment and treatment were stopped per study design.

The pre-specified primary efficacy endpoint was CR at EOT using the independent review committee (IRC) integrated CT + PET + Oncology response assessment. However, since the study was stopped for futility, the centralized oncology response assessment was not completed. Therefore, only radiographic response assessments by central review were available.

For the futility analysis set, the objective response rates (ORR: CR + PR) as assessed by the investigator at the end of treatment were similar between arms. The ORR for patients in the dacetuzumab arm was 64% (95% CI, 51% to 76%), and 68% (95% CI: 56% to 81%) in the placebo arm.

Clinical Response at End of Treatment – Futility Analysis Set

	R-ICE + Dacetuzumab (N=55) n (%)		R-ICE + Placebo (N=57) n (%)	
Response	Investigator	CT + PET	Investigator	CT + PET
Complete response (CR)	20 (36)	17 (31)	24 (42)	26 (46)
Partial response (PR)	15 (27)	13 (24)	15 (26)	12 (21)
Stable disease (SD)	8 (15)	16 (29)	4 (7)	10 (18)
Progressive disease (PD)	8 (15)	2 (4)	13 (23)	4 (7)
Unknown	4 (7)	7 (13)	1 (2)	5 (9)

Final Analysis

The primary analysis of the primary efficacy endpoint based on the full analysis set (n=101) also showed no difference in the CR rate between groups, 33% (95% CI, 20% to 46%) in the dacetuzumab arm and 36% (95% CI, 23% to 49%) in the placebo arm using the investigator assessment; the CR rates using the IRC assessment were 35% (95% CI, 22% to 48%) in the dacetuzumab arm and 40% (95% CI, 26% to 54%) in the placebo arm. For the full analysis set, the ORRs as assessed by the investigator at the end of treatment were 67% (95% CI, 54% to 80%) in the dacetuzumab arm and 64% (95% CI: 51% to 77%) in the placebo arm.

For the modified intent-to-treat (mITT) set of patients (n=151), there remained no difference in the CR rate between arms based on the investigator assessment. Twenty-seven patients in the dacetuzumab arm (36% [95% CI, 25% to 47%]) had a CR at EOT, and 28 patients (37% [95% CI, 26% to 48%]) had a CR at EOT in the placebo arm. Based on central review of radiographic assessments, the number of patients achieving a CR at EOT in the dacetuzumab arm was 22 (29% [95% CI, 19% to 40%]), and was 28 (37% [95% CI, 26% to 48%]) in the placebo arm.

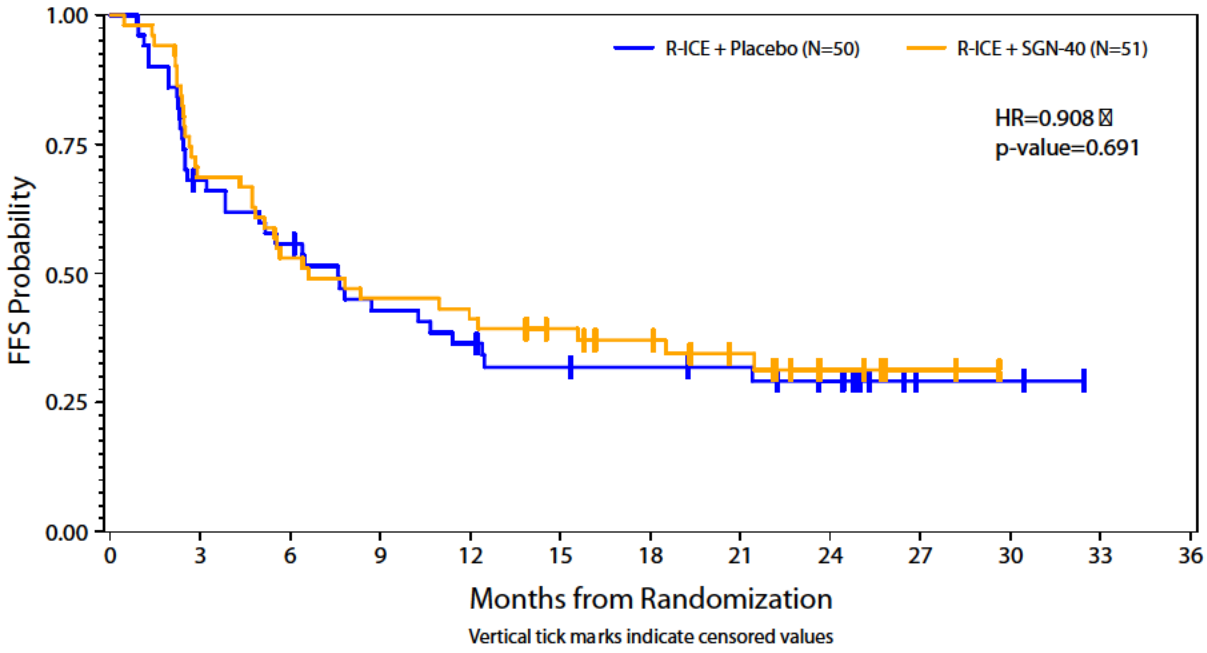
Clinical Response at End of Treatment – Full Analysis Set

	R-ICE + Dacetuzumab (N=51) n (%)		R-ICE + Placebo (N=50) n (%)	
Response	Investigator	CT + PET	Investigator	CT + PET
Complete response (CR)	17 (33)	18 (35)	18 (36)	20 (40)
Partial response (PR)	17 (33)	14 (27)	14 (28)	11 (22)
Stable disease (SD)	9 (18)	14 (27)	4 (8)	11 (22)
Progressive disease (PD)	6 (12)	2 (4)	13 (26)	6 (12)
Unknown	2 (4)	3 (6)	1 (2)	2 (4)

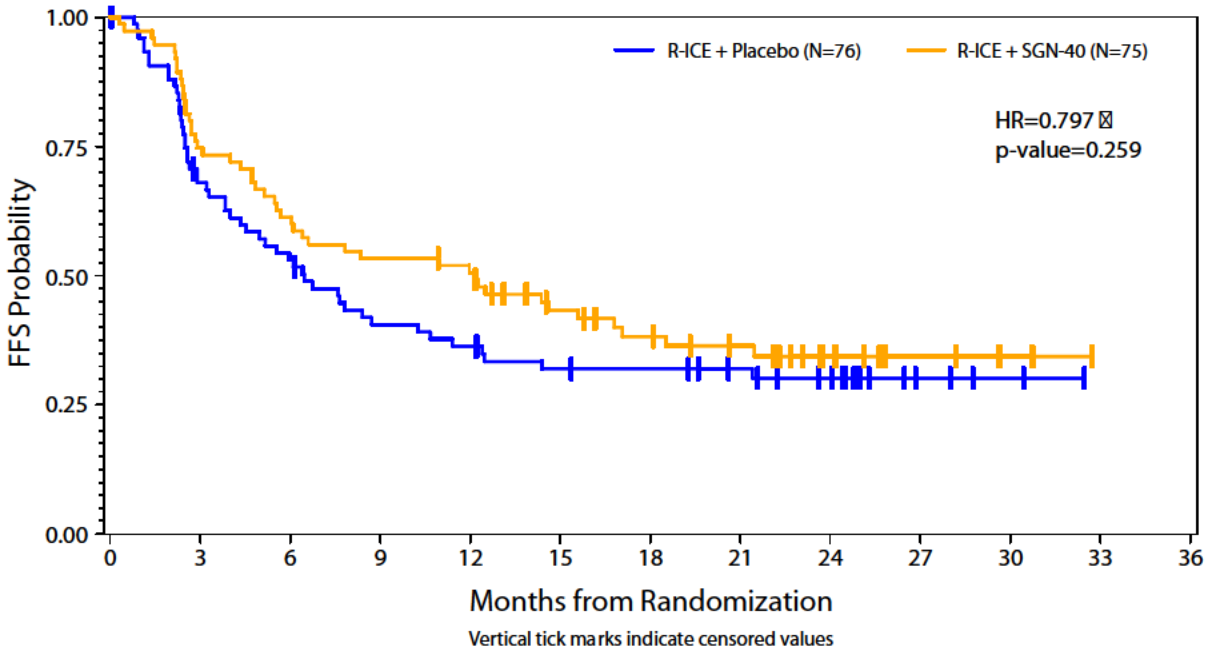
Among all patients enrolled in the study, 35 patients (47%) in the dacetuzumab arm and 40 patients (53%) in the placebo arm underwent autologous stem cell transplant (aSCT) after completion of study treatment. Collection of an adequate number of stem cells was similar in both arms (n=41, 80% dacetuzumab, n=43, 78% placebo) for the patients for whom stem cell mobilization (n=51 dacetuzumab, n=55 placebo) was attempted; reasons that patients did not receive transplant were balanced between arms.

An analysis of failure-free survival (FFS) using the investigator's response assessment for the full analysis set (n=101) yielded a hazard ratio (HR) close to 1 (HR=.908) and a p-value of 0.691. An analysis of the mITT set (n=151) revealed a hazard ratio of 0.797 and a p-value of 0.259. A subgroup analysis of FFS was conducted using the investigator's response assessment by post-treatment aSCT. The hazard ratios and p-values for these subgroups were comparable in the full analysis set; however in the mITT analysis set, the p-value for patients who had not received post-treatment aSCT was 0.036 (HR=.591) while the p-value for patients who underwent post-treatment aSCT was 0.399 (HR=0.750).

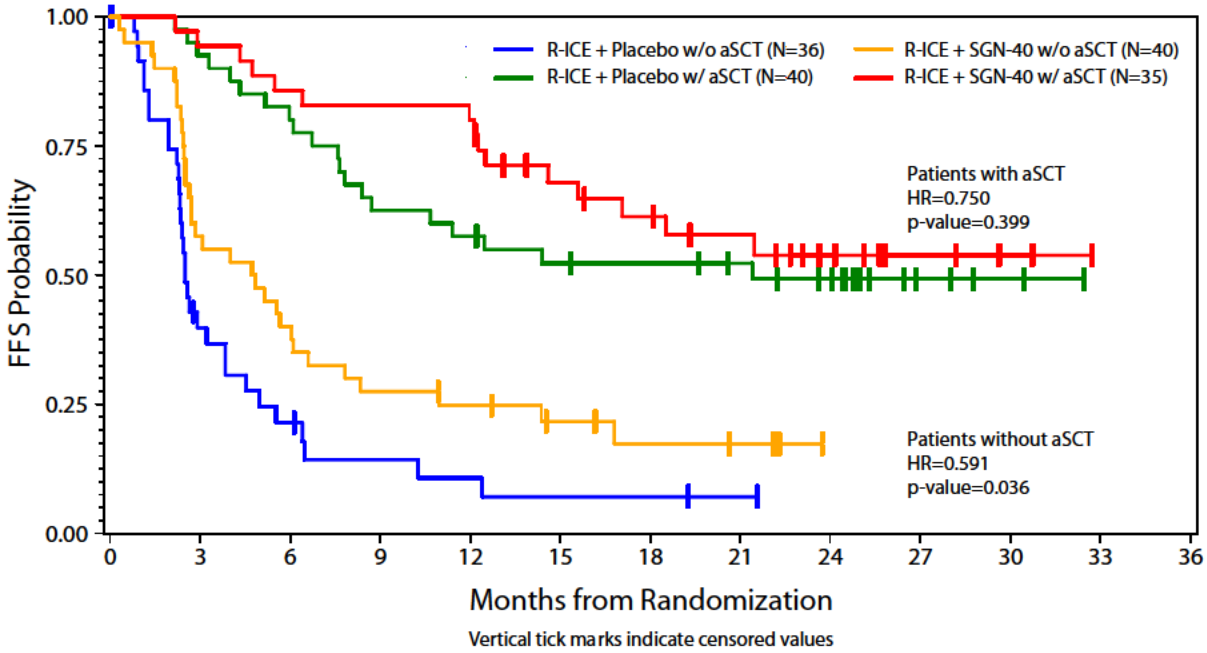
Kaplan-Meier Plot of FFS (per investigator assessment) – Full Analysis Set



Kaplan-Meier Plot of FFS (per investigator assessment) – mITT Analysis Set



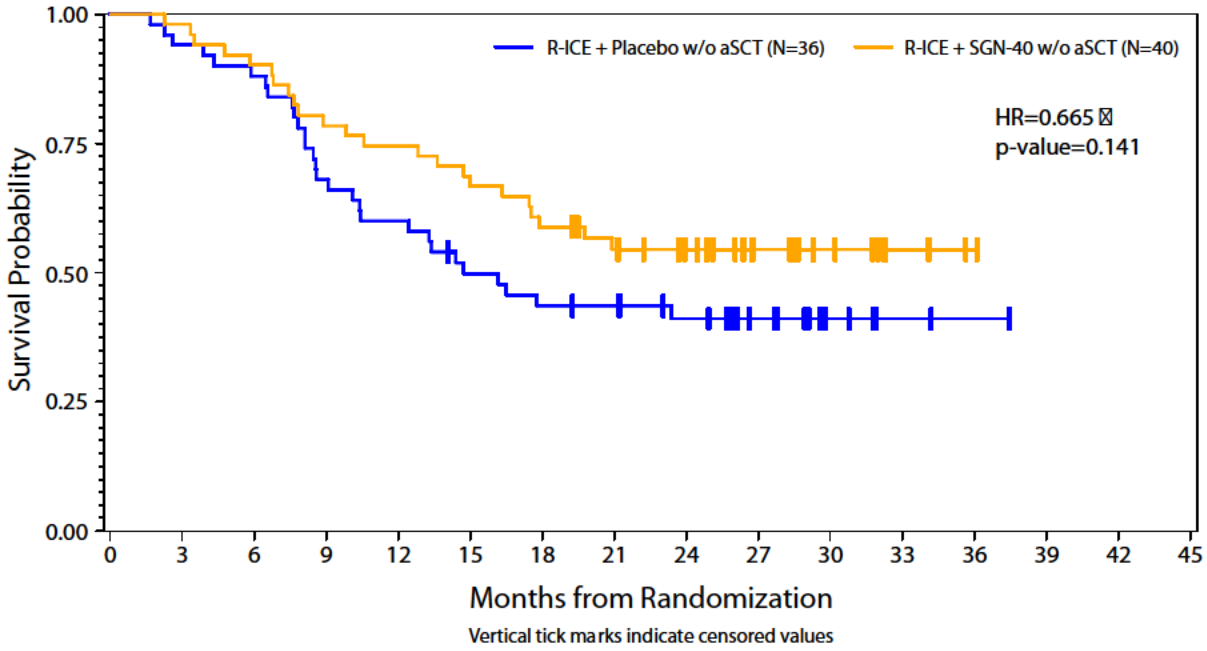
Kaplan-Meier Plot of FFS by Post-Treatment aSCT (per investigator assessment) – mITT Analysis Set



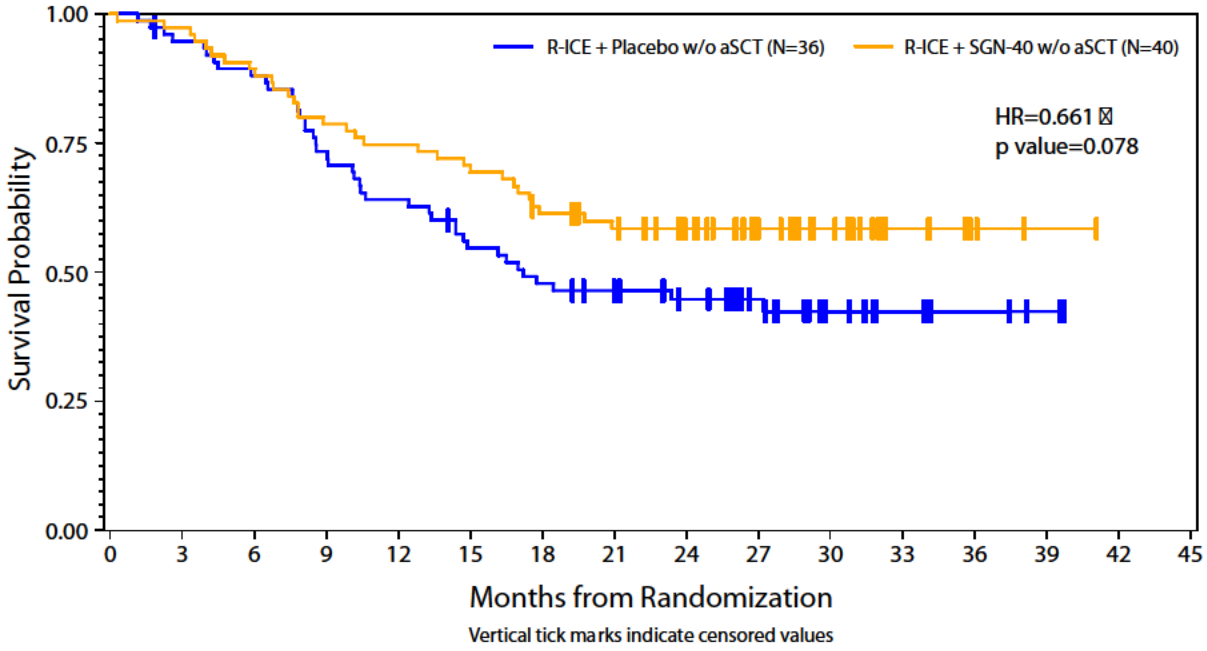
For the full analysis set, the estimated median OS for placebo patients was 14.7 months and the median OS for dacetuzumab patients had not been reached at the time of the analysis (HR=0.665, p-value=0.141). Using the mITT analysis set, the estimated median OS for placebo patients was 17.2 months and again, the median OS for dacetuzumab patients had not been reached at the time of the analysis (HR=0.661, p-value=0.078). A subgroup analysis was performed for OS by post-treatment aSCT. In the full analysis set, there was a non-significant trend toward improved survival among patients who received aSCT (HR=0.344, p-value=0.106); however in the mITT analysis set, the survival advantage with dacetuzumab for this subgroup was suggested (HR=0.195, p-value=0.004). However, these results were based on a small sample size for each of the subgroups. In addition, follow-up was halted at study termination and patients were censored at the date of last contact if the patient was alive at that time.

Fewer deaths occurred in patients who received dacetuzumab as compared to placebo (n=31, 41% vs. n=42, 55%, respectively) with a 40% reduction in death due to disease progression (n=20, 27% vs. n=34, 45%, respectively).

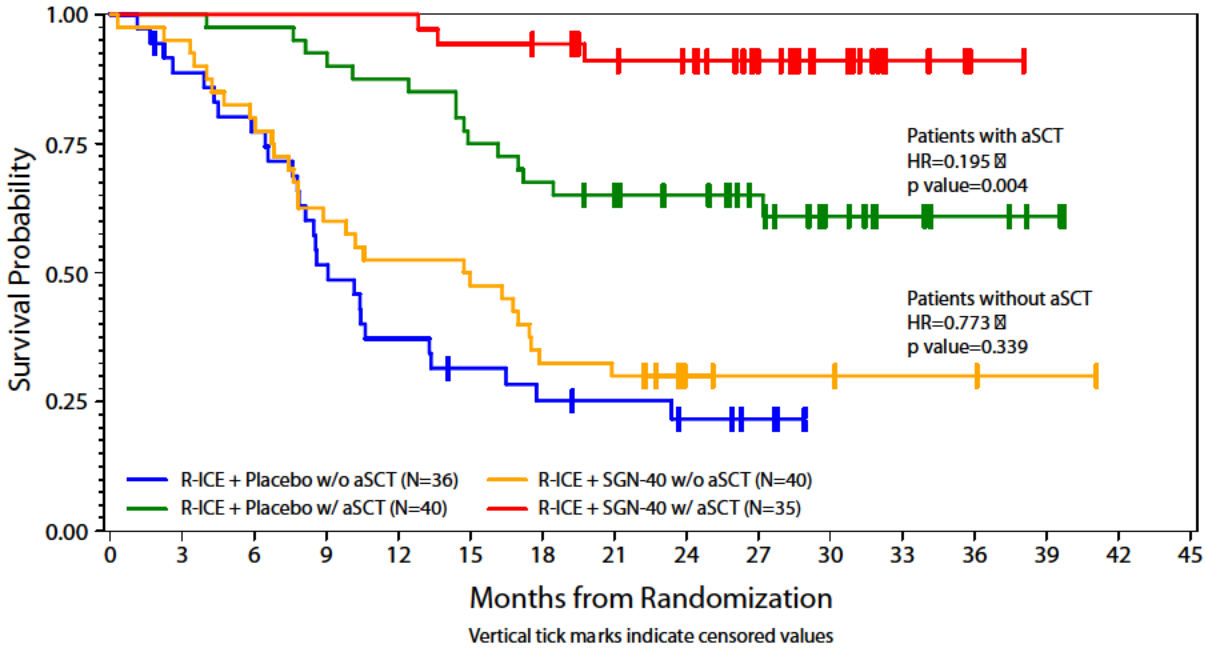
Kaplan-Meier Plot of OS – Full Analysis Set



Kaplan-Meier Plot of OS – mITT Analysis Set



Kaplan-Meier Plot of OS by Post-Treatment aSCT – mITT Analysis Set



Safety Results

All patients received at least one dose of study drug (dacetuzumab or placebo) and many patients completed planned therapy (n=111, 74%). The median compliance rate (actual dose over intended dose) for study treatment and for R-ICE dosing was 100% (range, 79% to 117%) for all drugs. The proportion of patients with dose eliminations of study treatment due to adverse event was higher in the dacetuzumab arm (16%) than in the placebo arm (7%). There were also more dose delays in the dacetuzumab arm.

Nearly all patients (96%) had at least 1 treatment-emergent adverse event (AE). Cytopenias occurred more frequently in the dacetuzumab arm including thrombocytopenia (68% dacetuzumab vs. 53% placebo), anemia (65% vs. 51%), neutropenia (35% vs. 26%), and febrile neutropenia (19% vs. 9%). Additional notable AEs that were observed in a higher proportion of patients in the dacetuzumab arm were headache (32% vs. 26%) and cough (16% vs. 3%).

Common Adverse Events[a]

Preferred Term	R-ICE + Dacetuzumab (N=75) n (%)	R-ICE + Placebo (N=76) n (%)
Thrombocytopenia	51 (68)	40 (53)
Anaemia	49 (65)	39 (51)
Nausea	40 (53)	42 (55)
Vomiting	31 (41)	26 (34)
Fatigue	29 (39)	31 (41)
Neutropenia	26 (35)	20 (26)
Headache	24 (32)	20 (26)
Constipation	23 (31)	25 (33)
Diarrhoea	19 (25)	15 (20)
Hypokalaemia	19 (25)	21 (28)
Pyrexia	16 (21)	12 (16)
Leukopenia	15 (20)	12 (16)
Febrile neutropenia	14 (19)	7 (9)
Cough	12 (16)	2 (3)
Alopecia	11 (15)	10 (13)
Insomnia	11 (15)	12 (16)

a Treatment-emergent adverse events of any relationship occurring in ≥15% of patients in either arm.

Overall, 80% of patients in the dacetuzumab arm and 75% of patients in the placebo arm had at least 1 AE Grade 3 or higher in severity. AEs ≥ Grade 3 that occurred in at least 10% of patients in either arm were thrombocytopenia, anemia, neutropenia, leukopenia, febrile neutropenia, and hypokalemia. Similar to the common adverse events, the incidence of cytopenias (≥ Grade 3) was higher in the dacetuzumab arm.

Grade 3 or Higher Adverse Events[a]

Preferred Term	R-ICE + Dacetuzumab (N=75) n (%)	R-ICE + Placebo (N=76) n (%)
Thrombocytopenia	47 (63)	35 (46)
Anaemia	37 (49)	21 (28)
Neutropenia	25 (33)	18 (24)
Leukopenia	14 (19)	12 (16)
Febrile neutropenia	12 (16)	7 (9)
Hypokalaemia	10 (13)	9 (12)

a Grade 3 or higher treatment-emergent adverse events of any relationship occurring in ≥10% of patients in either arm.

Serious adverse events (SAEs) occurred more frequently in the dacetuzumab arm (44% dacetuzumab, 30% placebo). SAEs occurring in more than 2 patients were febrile neutropenia (12% dacetuzumab, 7% placebo), neutropenia (7% dacetuzumab, 0% placebo), thrombocytopenia (7% dacetuzumab, 1% placebo), pancytopenia (4% dacetuzumab, 0% placebo), acute renal failure (4% dacetuzumab, 0% placebo), and pyrexia (3% dacetuzumab, 4% placebo). Again, cytopenias (SAEs) were more common in the dacetuzumab arm.

Death was reported for a total of 73 patients in the safety population; 4 patients died within 30 days of last study treatment. Disease progression was reported as the primary cause of death in more patients in the placebo arm (n=34) than in the dacetuzumab arm (n=20).

Deaths Within 30 Days of Last Study Treatment

Patient ID	Treatment Group	Days from Last Treatment to Death	Cause of Death
[redacted]	Placebo	5	Cardio-respiratory arrest
[redacted]	Dacetuzumab	4	Sepsis and febrile neutropenia
[redacted]	Placebo	21	Sepsis and cardiac arrest
[redacted]	Dacetuzumab	3	Asphyxia and aspiration

Six patients (8%) had an AE leading to treatment discontinuation in the dacetuzumab arm, compared with 2 patients (3%) in the placebo arm. Sepsis was reported as an adverse event leading to treatment discontinuation in 2 patients (1 patient per treatment arm). AEs leading to treatment discontinuation in the dacetuzumab arm were increased alanine aminotransferase, asphyxia, neutropenia, septic shock, and ventricular extrasystoles (1 patient each). One patient in the placebo arm discontinued treatment due to an AE of thrombocytopenia.

For hematologic laboratory abnormalities, the addition of dacetuzumab to R-ICE immunochemotherapy was associated with an increased incidence of thrombocytopenia, anemia, and neutropenia, compared to placebo plus R-ICE. In addition, there was an increase in febrile neutropenia in the dacetuzumab arm. However, the increased incidence of cytopenias and febrile neutropenia did not result in a clinically meaningful change in disposition. Similar numbers of patients in each arm were able to complete the intended treatment regimen and proceed to aSCT.

There did not appear to be any difference in the laboratory abnormality incidence or severity of electrolytes, BUN, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase between the study arms. Overall, the incidence of Grade 3 or higher non-hematological laboratory abnormalities was low in this study.

Results of anti-drug antibody assays were available for 121 patients and no immunogenicity against dacetuzumab was detected; however, the possibility that presence of dacetuzumab in the sample interfered with detection of the anti-drug antibody cannot be ruled out.

CONCLUSIONS

A planned futility analysis was conducted after 112 patients (50% of planned patients) completed treatment and response assessment by the investigator (55 patients in the dacetuzumab + R-ICE arm, 57 patients in the placebo + R-ICE arm). The CR rate at EOT (the primary endpoint) was not improved with dacetuzumab (36% dacetuzumab, 42% placebo), so the IDMC recommended that enrollment be stopped and treatment with dacetuzumab be discontinued for all patients. An additional 39 patients were randomized to the study after the data cutoff for the futility analysis, resulting in a total of 151 patients enrolled.

The primary analysis of the primary efficacy endpoint was based on the full analysis set (n=101). This analysis again showed no difference in the CR rate at EOT between treatment arms using the investigator's response assessment; 33% (95% CI, 20% to 46%) in the dacetuzumab arm achieved a CR and 36% (95% CI, 23% to 49%) achieved a CR in the placebo arm. The CR rates using the IRC assessment were 35% (95% CI, 22% to 48%) in the dacetuzumab arm and 40% (95% CI, 26% to 54%) in the placebo arm.

The treatment arms were balanced for demographic and prognostic factors. The majority of all patients enrolled had a disease diagnosis of de novo DLBCL (87%) based on local pathology review, and all patients had received first-line therapy with R-CHOP or equivalent first-line therapy. Patients were equally randomized between the 2 treatment arms by time since completion of first-line therapy (≤12 months and >12 months) and by disease histology (FL3b or de novo DLBCL, and transformed DLBCL).

In the 2 arms, a similar percentage of patients were able to complete planned treatment (76% dacetuzumab, 71% placebo), and the addition of dacetuzumab did not impact subsequent stem cell collection (dacetuzumab:

n=41/51 [successes/attempts], 80%; placebo: n=43/55, 78%). Overall, a similar percentage of patients in each arm underwent subsequent autologous stem cell transplantation (dacetuzumab: n=35/75, 47%; placebo: n=40/76, 53%).

An analysis of the secondary efficacy endpoint FFS did not reveal a prolonged time-to-event with dacetuzumab in the full analysis set (n=101; primary efficacy analysis set; HR=0.908, p-value=0.691) nor in the mITT analysis set (n=151; HR=0.797, p-value=0.259). However, in the mITT analysis set, there was a trend of delayed disease progression for patients who had not received post-treatment aSCT (HR=.591, p-value=0.036).

In the mITT analysis set, an analysis of OS demonstrated a trend toward improved survival in the dacetuzumab arm (HR=0.661, p-value=0.078). In a subgroup analysis, the combination of dacetuzumab + R-ICE suggested a survival advantage for patients who received an aSCT following treatment (HR=0.195, p-value=0.004). Despite no improvement in the CR rate, this trend toward improved OS may be explained by the potential immunomodulatory effect of dacetuzumab, a partially agonistic CD40 antibody.

Disease progression was reported as the primary cause of death in more patients in the placebo arm (n=34) than in the dacetuzumab arm (n=20).

Dacetuzumab was generally well tolerated in combination with R-ICE. With the exception of an increased incidence of cytopenias and febrile neutropenia in the dacetuzumab arm, there were no significant differences in patient safety between treatment arms.