SUPPLEMENTARY APPENDIX

Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study

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Supplementary Appendix

Supplementary methods

Inclusion/exclusion criteria

Inclusion criteria

1. Signed written informed consent form.
2. Age ≥18 and ≤80 years at time of study inclusion.
3. Histologically confirmed, previously untreated CD20-positive diffuse large B-cell lymphoma (DLBCL) according to the World Health Organization (WHO) classification system.
4. Patients with an International Prognostic Index (IPI) score of 1–5 or IPI score of 0 with bulky disease, defined as one lesion ≥7.5 cm.
5. At least one bi-dimensionally measurable lesion defined as ≥1.5 cm in its largest dimension on computed tomography (CT) scan, positron emission tomography-CT (PET-CT) scan or magnetic resonance imaging (MRI).
6. Adequate hematologic function, defined as follows:
    a. Hemoglobin ≥9 g/dL (Note: no transfusions allowed within 2 weeks prior to the start of study drug administration).
    b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L.
    c. Platelet count ≥75 x 10^9/L.
    d. Note: abnormalities outside the above listed are allowed if related to involvement of bone marrow by the underlying disease.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
8. Agreement to use adequate contraception during the study treatment period and for at least 12 months after the last dose of study drug:

a. For women of childbearing potential: agreement to use two adequate methods of contraception, including at least one method with a failure rate of <1% per year (e.g., hormonal implants, combined oral contraceptives, vasectomized partner). Women of childbearing potential are defined as either pre-menopausal or women who are <2 years after the onset of menopause and are not surgically sterile.
b. For men (unless vasectomized): agreement to use a barrier method of contraception.

Exclusion criteria

1. Primary or secondary central nervous system lymphoma, histologic evidence of transformation to Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, primary cutaneous DLCBCL, or primary DLBCL of the testis.
2. Transformed lymphoma or follicular lymphoma IIIB.
3. Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation.
4. History of other malignancy, except:
    a. Patients with curatively treated basal or squamous cell carcinoma or melanoma of the skin or *in situ* carcinoma of the cervix are eligible;
    b. A malignancy that has been treated but not with curative intent will be excluded, unless the malignancy has been in remission without treatment for ≥5 years prior to enrolment.
5. Inadequate renal function, defined as creatinine >1.5 times the upper limit of normal (ULN) (unless creatinine clearance [CrCl] normal), or calculated CrCl <30 mL/min (using the Crockcroft–Gault formula).
6. Inadequate hepatic function, defined as any of the following abnormal laboratory values:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x the ULN
    b. Alkaline phosphatase >2.5 x the ULN

c. Total bilirubin ≥1.5 x the ULN (patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3.0 x the ULN).

7. Known human immunodeficiency virus (HIV) infection or HIV seropositive status.
8. Active and/or severe bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with intravenous (IV) antibiotics or hospitalization (related to the completion of the course of antibiotics except if for tumor fever) within 4 weeks prior to the start of the study drug administration.
9. Active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection (must be ruled out during screening). Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAB] and negative or positive hepatitis B surface antigen [HBsAg] with undetectable HBV deoxyribonucleic acid [DNA]) may be included but these patients must be followed closely. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) testing for HCV ribonucleic acid (RNA) is negative.
10. Other serious underlying medical conditions, which, in the investigator's judgment, could impair the ability of the patient to participate in the study (e.g., significant cardiovascular disease, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease).
11. Recent major surgery (within 4 weeks prior to the start of the study drug administration) other than for diagnostic purposes.
12. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products.
13. Contraindication to any of the individual components of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), including prior receipt of anthracyclines.
14. Prior treatment with cytotoxic drugs or rituximab for another condition (e.g., rheumatoid arthritis) or prior use of an anti-CD20 antibody.

15. Treatment with a monoclonal antibody within 3 months prior to the start of study drug administration.
16. Ongoing corticosteroid use at a dose of >30 mg/day of prednisone or equivalent. The dose of corticosteroid treatment ≤30 mg/day of prednisone or equivalent must be stable for at least 4 weeks prior to the start of study drug administration. A pre-phase of high-dose prednisolone (e.g. 100 mg/day for 3 to 5 days) is acceptable for patients with aggressive non-Hodgkin lymphoma (NHL).
17. Chemotherapy or other investigational therapy within 4 weeks prior to the start of study drug administration.
18. Inability to provide informed consent.
19. History of poor compliance during previous lines of therapy.
20. Life expectancy of less than 6 months.
21. Pregnancy or lactation. A negative serum pregnancy test is required for women of childbearing potential within 7 days prior to the start of study drug administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the start of study drug administration. Women of childbearing potential are defined as either pre-menopausal or women who are <2 years after the onset of menopause and are not surgically sterile.

Details of ethical approval

The study was conducted in line with International Conference on Harmonisation E6 guidelines for Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by independent ethics committees at each center.

Study treatments

Each 1,400 mg dose of rituximab subcutaneous (SC) was given as 11.7 mL of a 120 mg/mL solution by slow manual injection over 5 to 6 minutes. Rituximab IV was given by infusion through a

dedicated line at an initial rate of 50 mg/hour, which could be increased at 30-minute intervals to a maximum rate of 400 mg/hour. Commercially available standard CHOP chemotherapy was used.

Assessments

Tumor assessments were based on CT or MRI scans of the neck, chest, abdomen, and/or pelvis. Tumor response was assessed by the investigator according to International Working Group response criteria for NHL[1] after cycle 4 (interim staging) and at 30±3 days after day 1 of the last treatment cycle (final response evaluation). The 1999 response criteria were considered appropriate as not all centers had access to a PET scanner. Patients completed the validated Rituximab Administration Satisfaction Questionnaire (RASQ)[2] and Cancer Treatment Satisfaction Questionnaire (CTSQ)[3] at cycles 3 and 7.

Time savings were measured, including for rituximab administration time (time from start to end of rituximab SC injection/IV infusion), chair/bed time (time a patient occupied an infusion chair/bed for a single R-CHOP treatment cycle), and hospital time (time a patient was in hospital for one R-CHOP cycle).

Patients underwent an end-of-treatment safety assessment 30±3 days after day 1 of their last induction cycle. All adverse events (AEs) and serious adverse events (SAEs) were recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v 4.0). After study closure any deaths, SAEs, or AEs of special interest were recorded.

Analysis populations

The intent-to-treat population included all randomized patients who had completed a baseline assessment and at least one-on treatment efficacy assessment. Safety analyses were conducted on the safety population included all patients who received at least one dose of study drug.

Statistical analysis – primary efficacy analysis

The primary efficacy analysis (investigator-assessed CR/CRu) was performed in the ITT population after all patients had completed induction. CR/CRu rates were analyzed by frequency tables including 95% 2-sided Clopper-Pearson confidence intervals (CIs). PFS was analyzed by the Kaplan–Meier method. At the time of the primary analysis, sub-analysis according to patient stratification factors, secondary outcomes, and RASQ and CTSQ outcomes were also evaluated.

Safety assessments included AEs, SAEs, grade ≥3 AEs, and ARRs according to NCI CTCAE 4.0, along with laboratory tests, and vital signs measurements.

References

1. Cheson BD, Horning SJ, Coiffier 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(4):1244.
2. Rule S, Briones J, Smith R, et al. Preference for Rituximab Subcutaneous (SC) and Intravenous (IV) Among Patients With CD20+ Non-Hodgkin's Lymphoma (NHL) Completing the RASQ Measure In Randomized Phase III Studies Prefmab and Mabcute. Value Health. 2014;17(7):A537.
3. Trask PC, Tellefsen C, Espindle D, Getter C, Hsu MA. Psychometric validation of the cancer therapy satisfaction questionnaire. Value Health. 2008;11(4):669-679.

Supplementary results

Exploratory safety analysis

Analysis of AEs in body surface area (BSA) subgroups showed an apparent higher incidence of grade ≥3 AEs and serious AEs (SAEs) in patients with low BSA (≤1.7 m^2) in the SC versus the IV arm, with a trend towards a higher incidence of grade ≥3 AEs and SAEs with decreasing BSA in the SC arm (Table S2). This increased incidence appeared to be driven by male patients. However, when analyzed further, there was no significant difference in the rates of grade ≥3 AEs or SAEs between treatment arms in male patients with low BSA and the observed difference was driven by the low sample size in the IV group. The imbalance in AEs between the SC and IV arms in the low BSA subgroup also appeared to be driven by neutropenia (grade ≥3 neutropenia was 30% in the SC arm versus 20% in the IV arm and febrile neutropenia was 16% in the SC arm versus 2% in the IV arm), as both a grade ≥3 AE and SAE. An exploratory analysis revealed that there was no significant interaction effect (P>0.05 for all comparisons) for AEs of grade ≥3 or SAEs with any of the covariates BSA, age group, or gender; therefore treatment effect on grade ≥3 AEs and SAEs (i.e., rituximab SC vs IV) is not modified by any of these parameters.

Treatment satisfaction

Overall, 428 patients were included in the RASQ analysis population with 423 (SC, 282; IV, 141) completing the RASQ at cycle 7. The mean RASQ scores were higher across all domains for rituximab SC versus IV (Table S3), with a mean satisfaction score of 90 (SC) versus 77 (IV; Figure 3, main text). More patients in the rituximab SC group versus the IV group thought that the length of time taken to get the SC injection/IV infusion was just right, (SC, 79%; IV, 58%). When patients in the SC group were asked, if given the option, which treatment they would prefer: 91% stated a preference to receive SC over IV.

A total of 421 patients were included in the CTSQ analysis population with 419 (SC, 278; IV, 141) completing the CTSQ at cycle 7. The mean satisfaction score was 86 (SC) versus 84 (IV; Figure 3, main text), and mean CTSQ scores for other domains were similar between the treatment arms (Table S4). RASQ and CTSQ results for cycle 3 were similar to those for cycle 7.

Time savings

From cycle 2 onwards, median administration time was 0.1 h (for each cycle) in the SC group, and ranged between 2.6 h (cycle 8) and 3 h (cycle 2) in the IV group. In cycle 2, 83% of patients in the SC arm had a chair/bed time ≤4 h, whereas 62% in the IV arm had a chair/bed time ≥4 h. For every cycle from cycle 2 onwards, a higher proportion of patients spent <2 h in a chair/bed receiving rituximab SC than IV (range: SC, 27%-56% vs IV, <1%-5%). In cycle 2, 65% of SC patients required ≤6 h of hospital time overall; whereas 52% receiving rituximab IV required ≥6 h.

Table S1. Most common treatment-emergent AEs in cycle 2 or later in the safety population.

Patients	Rituximab SC plus CHOP (n=369)	Rituximab IV plus CHOP (n=188)	P-Value by Fisher's Exact Test
AEs of any grade in ≥10% of patients			
Overall events	337 (91.3)	170 (90.4)	0.7548
Neutropenia	96 (26.0)	45 (23.9)	0.6083
Febrile neutropenia	46 (12.5)	13 (6.9)	0.0575
White blood cell count decreased	46 (12.5)	19 (10.1)	0.4859
Anemia	79 (21.4)	37 (19.7)	0.6605
Neutrophil count decreased	72 (19.5)	40 (21.3)	0.6552
Fatigue	55 (14.9)	22 (11.7)	0.3636
Nausea	51 (13.8)	30 (16.0)	0.5260
Alopecia	49 (13.3)	23 (12.2)	0.7902
Lymphocyte count decreased	48 (13.0)	17 (9.0)	0.2089
Peripheral neuropathy	42 (11.4)	18 (9.6)	0.5655
Cough	37 (10.0)	13 (6.9)	0.2731
Pyrexia	36 (9.8)	20 (10.6)	0.7666
Grade ≥3 AEs in ≥2% of patients			
Overall events	215 (58.3)	102 (54.3)	0.3675
Neutropenia	80 (21.7)	34 (18.1)	0.3744
Febrile neutropenia	46 (12.5)	13 (6.9)	0.0575
Anemia	16 (4.3)	7 (3.7)	0.8240
Leukopenia	7 (1.9)	5 (2.7)	0.5501
Pneumonia	20 (5.4)	4 (2.1)	0.0795
Neutrophil count decreased	47 (12.7)	25 (13.3)	0.8940
White blood cell count decreased	27 (7.3)	10 (5.3)	0.4723
Lymphocyte count decreased	20 (5.4)	9 (4.8)	0.8420
Platelet count decreased	11 (3.0)	3 (1.6)	0.4021
SAEs seen in ≥2% of patients			
Overall events	141 (38.2)	62 (33.0)	0.2639
Febrile neutropenia	43 (11.7)	12 (6.4)	0.0515
Neutropenia	13 (3.5)	9 (4.8)	0.4943

Pneumonia	25 (6.8)	6 (3.2)	0.1162
ARRs seen in ≥2% of patients			
Overall events	77 (20.9)	40 (21.3)	0.9128
Injection-site reactions*	21 (5.7)	0 (0)	0.0002
Fatigue	7 (1.9)	4 (2.1)	1
Nausea	8 (2.2)	4 (2.1)	1
Neutrophil count decreased	5 (1.4)	8 (4.3)	0.0400
Lymphocyte count decreased	15 (4.1)	4 (2.1)	0.3249

Data are n (%).

AE: adverse event; ARR: administration-related reaction; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; IV: intravenous; SAE: serious adverse event; SC: subcutaneous.

*Erythema, pain, bruising, discoloration, hematoma, hypertrophy, induration, inflammation, and swelling.

Table S2: Analysis of grade ≥3 AEs and SAEs on or after cycle 2 by subgroup.

Patients	Rituximab SC plus CHOP	Rituximab IV plus CHOP
Grade ≥3 AEs		
Age <60 years		
Low BSA*	20/35 (57%)	9/21 (43%)
Medium BSA†	25/49 (51%)	9/19 (47%)
High BSA‡	24/58 (41%)	12/36 (33%)
Age ≥60 years		
Low BSA*	50/77 (65%)	16/33 (49%)
Medium BSA†	40/70 (57%)	25/43 (58%)
High BSA‡	36/80 (45%)	22/36 (61%)
Male		
Low BSA*	18/26 (69%)	3/8 (38%)
Medium BSA†	36/62 (58%)	17/33 (52%)
High BSA‡	49/116 (42%)	25/56 (45%)
Female		
Low BSA*	52/86 (61%)	22/46 (48%)
Medium BSA†	29/57 (51%)	17/29 (59%)
High BSA‡	11/22 (50%)	9/16 (56%)
SAEs		
Age <60 years		
Low BSA*	8/35 (23%)	4/21 (19%)
Medium BSA†	19/49 (39%)	5/19 (26%)
High BSA‡	9/58 (16%)	8/36 (22%)
Age ≥60 years		
Low BSA*	35/77 (46%)	10/33 (30%)
Medium BSA†	32/70 (46%)	16/43 (37%)
High BSA‡	23/80 (29%)	15/36 (42%)
Male		
Low BSA*	16/26 (62%)	3/8 (38%)
Medium BSA†	29/62 (47%)	11/33 (33%)
High BSA‡	25/116 (22%)	19/56 (34%)
Female		
Low BSA*	27/86 (31%)	11/46 (24%)

Medium BSA[†]	22/57 (39%)	10/29 (35%)
High BSA[‡]	7/22 (32%)	4/16 (25%)

Data are n (%).

AE: adverse event; BSA: body surface area; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; IV: intravenous; SAE: serious adverse event; SC: subcutaneous.

*BSA ≤1.7 m^2. [†]BSA >1.7–≤1.9 m^2. [‡]BSA >1.9 m^2.

Table S3*:* Mean (SD) RASQ scores at cycles 3 and 7 (ITT RASQ population).

Domain	Visit	Rituximab SC	Rituximab IV
Physical impact	Cycle 3	87.11 (12.889)	84.46 (15.145)
	Cycle 7	86.24 (14.012)	81.49 (16.848)
Psychological impact	Cycle 3	84.23 (14.219)	77.25 (17.355)
	Cycle 7	85.65 (13.920)	78.65 (18.233)
Impact on activities of daily living	Cycle 3	82.96 (16.802)	60.37 (19.960)
	Cycle 7	83.77 (16.117)	57.38 (19.230)
Convenience	Cycle 3	82.31 (13.533)	62.38 (19.813)
	Cycle 7	82.32 (13.428)	60.14 (17.473)
Satisfaction	Cycle 3	87.59 (12.854)	78.28 (16.946)
	Cycle 7	89.58 (12.051)	77.39 (18.232)

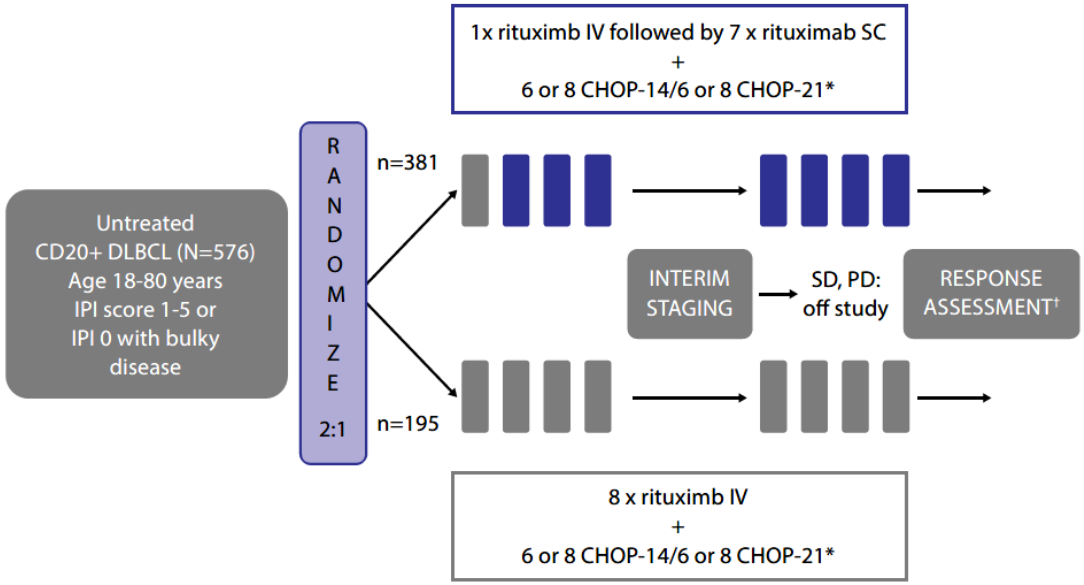
ITT: intent-to-treat; IV: intravenous; RASQ: Rituximab Administration Satisfaction Questionnaire; SC: subcutaneous; SD: standard deviation.

Table S4*:* Mean (SD) CTSQ scores at cycles 3 and 7 (ITT CTSQ population).

Domain	Visit	Rituximab SC	Rituximab IV
Expectations of therapy	Cycle 3	79.74 (17.760)	82.13 (18.058)
	Cycle 7	79.35 (17.422)	82.94 (16.536)
Feelings about side effects	Cycle 3	63.38 (18.650)	62.73 (21.241)
	Cycle 7	60.69 (21.594)	57.62 (23.339)
Satisfaction with therapy	Cycle 3	86.02 (11.066)	83.25 (12.571)
	Cycle 7	85.92 (11.428)	83.60 (13.451)

CTSQ: Cancer Treatment Satisfaction Questionnaire; ITT: intent-to-treat; IV: intravenous; SC: subcutaneous; SD: standard deviation.

Figure S1. MabEase Study Design.



All patients received CHOP chemotherapy (cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone/prednisolone 100 mg) every 14 (CHOP-14) or 21 days (CHOP-21). The CHOP regimen was chosen by the treating physician according to local practice. The length of each treatment cycle and the number of cycles received depended on the chemotherapy backbone. Patients received six cycles of CHOP when a complete response was reached after four cycles, or otherwise eight cycles, as a CHOP-14 or CHOP-21 cycle. No dose reductions were permitted for rituximab SC or IV. Dose modifications to chemotherapy because of toxicity (delay, reduction, or discontinuation) were permitted (as per protocol) and recorded. Of 576 randomized patients, 572 received treatment (rituximab SC n=378; rituximab IV n=194).

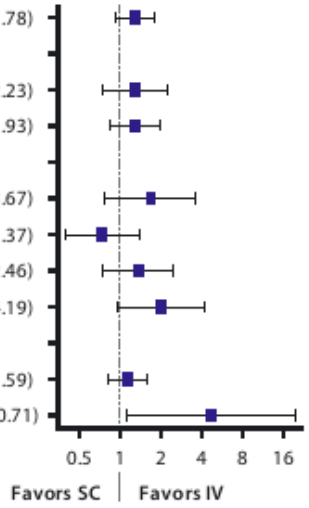
CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL: diffuse large B-cell lymphoma; IPI: International Prognostic Index; PD: progressive disease; SC: subcutaneous; SD: stable disease.

*Selected by investigators. †Cheson et al, 1999 criteria.

Figure S2. Subgroup Analysis of Progression-Free Survival.

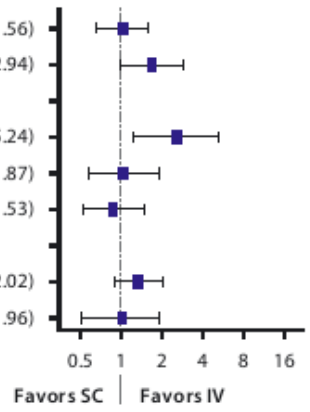
A

Subgroup factors	Total n	Rituximab SC (N=381) n	Events	Rituximab IV (N=195) n	Events	HR†	95% CI
Overall	576	381	114	195	46	1.26	(0.90-1.78)
Age at screening							
<60 years	223	147	41	76	17	1.27	(0.72-2.23)
≥60 years	353	234	73	119	29	1.26	(0.82-1.93)
IPI risk category							
Low	179	118	26	61	8	1.66	(0.75-3.67)
Low-intermediate	171	114	24	57	15	0.72	(0.38-1.37)
High-intermediate	141	94	38	47	14	1.33	(0.72-2.46)
High	85	55	26	30	9	1.96	(0.91-4.19)
Chemotherapy regimen during induction							
CHOP-21	518	345	100	173	44	1.11	(0.78-1.59)
CHOP-14	58	36	14	22	2	4.70	(1.07-20.71)



B

Subgroup factors	Total n	Rituximab SC (N=381) n	Events	Rituximab IV (N=195) n	Events	HR†	95% CI
Gender							
Male	309	209	62	100	29	1.01	(0.65-1.56)
Female	267	172	52	95	17	1.70	(0.98-2.94)
BSA at screening							
Low (≤1.70 m^2)	171	115	43	56	9	2.55	(1.24-5.24)
Medium (>1.70-≤1.90 m^2)	188	123	31	65	16	1.02	(0.56-1.87)
High (>1.90 m^2)	217	143	40	74	21	0.90	(0.53-1.53)
Race							
White	454	298	84	156	33	1.35	(0.90-2.02)
Non-White	122	83	30	39	13	1.02	(0.53-1.96)



BSA: body surface area; CI: confidence interval; HR: hazard ratio; IPI: International Prognostic Index; IV: intravenous; SC: subcutaneous.

*All randomized patients. †HR from unstratified Cox model.