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Three-year outcomes in recipients of mismatched unrelated bone marrow donor transplants using post-transplant cyclophosphamide: follow-up from a National Marrow Donor Program-sponsored prospective clinical trial

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CONFLICTS OF INTEREST

Dr. Perales reports honoraria from Adicet, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune and Omeros. He has received institutional research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Dr. Shah reports participation on advisory boards and/or consultancy for Kite Pharma, BMS, TG therapeutics, Miltenyi Biotec, Lilly Oncology, Epizyme, Incyte, Novartis, Seattle Genetics, and Umoja. He has research funding and honoraria from Miltenyi Biotec. In addition, Nirav Shah is on a scientific advisory board for Tundra Therapeutics.

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Abstract

The use of Post-Transplant Cyclophosphamide (PTCy) as Graft Versus Host Disease (GVHD) prophylaxis has resulted in reductions in GVHD and improved outcomes in allogeneic hematopoietic cell transplant (HCT) using HLA-mismatched related donors. We report the 3-year outcomes of the first multi-center prospective clinical trial using PTCy in the setting of mismatched unrelated donor (MMUD) bone marrow HCT. The study enrolled 80 patients (Either myeloablative (MAC) (N=40) or reduced intensity conditioning (RIC) (N=40)) with the primary endpoint of 1-year overall survival (OS). The median follow-up for this report is 34 months (range 12–46) in RIC and 36 months (range 18–49) in MAC. Three-year OS and non-relapse mortality (NRM) were 70% and 15%, and 62% and 10% in the RIC and MAC strata, respectively. No GVHD was reported after 1 year. Relapse incidence was 29% and 51% in RIC and MAC strata. OS did not differ based on HLA match grade (63% in the 7/8 strata and 71% in the 4–6/8 strata). These encouraging outcomes, sustained 3 years post-HCT, support the continued exploration of MMUD HCT using a PTCy platform. Important future areas to address include relapse reduction and furthering our understanding of optimal donor selection based on HLA and non-HLA factors.

INTRODUCTION

Post-transplant cyclophosphamide (PTCy) as graft versus host disease (GVHD) prophylaxis to facilitate hematopoietic cell transplantation (HCT) across HLA barriers has become widely accepted[1]. Pioneered in the haploidentical related donor (haplo) setting, this approach now has established efficacy. While the use of haplo donors expands access to

HCT for those without a matched donor available, there remain patients for whom a haplo donor is not available[2] or where this may not be the best donor choice (e.g., presence of donor specific antibodies, familial disease syndromes or age of the donor)[3,4]. To meet this need, we investigated the use of PTCy in mismatched unrelated donor (MMUD) HCT in a phase II multicenter prospective trial. The trial met its primary endpoint of overall survival >65% at 1 year (1 year OS was 76%; 90% CI: 67.3–83.3)[5]. Here we report 3-year follow-up data.

METHODS

Patient eligibility was previously described[5]. The study enrolled 80 patients with hematological malignancies, who had no suitable matched donor available, at 11 United States (US) centers from 12/2016 to 3/2019. There were two non-randomized conditioning intensity strata, either reduced intensity (RIC) or myeloablative conditioning (MAC). Following conditioning, patients received a fresh bone marrow (BM) graft on day 0, PTCy on days +3, +4, and sirolimus/mycophenolate mofetil starting on day +5. The study was approved by the National Marrow Donor Program (NMDP) central institutional review board (IRB) (n=2) or the transplant center (TC) IRB (n=9) (NCT02793544). All patients provided written informed consent.

Three-year follow-up data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Data within one-year post-HCT were reconciled with data collected in the clinical trial. Relapse, non-relapse mortality (NRM), and chronic GVHD (cGVHD) were estimated by cumulative incidence function with death without relapse, relapse, and death without cGVHD as competing risks, respectively. Patients without the event were censored at date of second transplant or last contact. OS, progression-free survival, and GVHD-free, relapse-free survival (GRFS) were estimated using the Kaplan-Meier method[6]. Survival probabilities were calculated from the date of HCT to the date of death or last contact.

RESULTS AND DISCUSSION

Patient, donor and HCT characteristics are shown in Table 1. Considering HLA-A, B, C and DRB1 at high resolution, the HLA match grade was 7/8 in 61% and 4–6/8 in 39% of transplants (43% in RIC, 36% in MAC). 48% of patients were from a racial/ethnic minority group.

Survival and toxicity

The median follow-up (data lock: September 2021) was 34 months (range 12–46) in RIC and 36 months (range 18–49) in MAC, with OS at 3 years of 70% in the RIC strata and 62% in the MAC strata (Figure 1a). Table 2 shows all outcomes at 3 years. The incidence of GVHD was low at one year (particularly in the RIC strata[5]), and notably no additional cases of GVHD of any type or grade were reported after 1 year, likely contributing to the NRM of less than 15% seen across all patients at 3 years (Figure 1b).

Relapse

The relapse rate in the RIC strata of 29% at 3 years (23% at 1 year) is similar to published reports of PTCy-based HCT[7]. Conversely, we report a high rate of relapse of 51% at 3 years (30% at 1 year) in the MAC strata. This stratum had a predominance of patients with acute myeloid leukemia (AML) and >90% of these had an intermediate or high disease risk index (DRI) at HCT, which may be one explanation for the higher incidence in this cohort. The median time to relapse in the MAC patients (N=19) was 7.57 months (range: 1.84–30.33), with those relapsing within 6 months of HCT having a short survival (N=9, 2.14 months (range: 0.69–10.72)). Of note, eight of the 10 patients who relapsed >6 months post-HCT, all with acute leukemia, remain alive at last follow-up (median follow-up post relapse is 11.68 months (range: 3.32–37.17) (Supplemental Table 1). Only one patient received additional cells (donor lymphocytes). Five of the eight patients had GVHD, the onset of which occurred prior to the relapse. These findings are provocative and warrant further investigation, including into the mechanism of relapse and potential differences between donor types[8]. Besides low numbers, an important limitation of the study is that pre-HCT measurable residual disease (MRD) data were not routinely collected. Another potential contributor to higher relapse is that only BM was allowed as a graft source in this study. While data are not yet available specific to the MMUD setting, we can extrapolate from a recent meta-analysis including several thousand patients receiving a haplo-HCT with PTCy, where a 16% reduction in relapse risk (HR 0.84; p =0.001) was reported with the use of peripheral blood stem cell (PBSC) grafts compared with BM grafts[9]. Although the meta-analysis also reported a higher rate of GVHD with PBSC compared to BM, the overall low rates of severe cGVHD and lack of late onset cases observed in our study, suggest that a slight increase in GVHD associated with PBSC may be justifiable to allow better disease control long term. In fact, the field has already moved decisively in this direction, with CIBMTR data showing that currently 90% of MMUD transplants using PTCy (as standard of care) are performed using PBSC (data not shown). NMDP/CIBMTR is currently testing the approach of using PBSC prospectively in a study (ACCESS, NCT04904588).

HLA match grade

An open question in the field is the importance of the degree of HLA mismatching in the PTCy setting. Emerging data in the haplo setting suggest that assessing qualitative rather than quantitative effects may be more relevant[10]. A study of 1434 recipients of haplo HCT showed that the total number of HLA mismatches was not significantly associated with outcomes (confirming previous studies)[11,12] rather that individual loci (mis)matches were associated with better outcomes. Specifically, mismatches in the GVHD direction at HLA-DRB1 were associated with decreased relapse (and better DFS when in conjunction with a match at DQB1), and HLA-B leader matching and HLA-DPB1 TCE-nonpermissive mismatching were each associated with improved overall survival[13]. Although our study was underpowered to detect a true difference related to match grade, as well as to assess mismatches at individual loci, we did not observe a difference in survival dependent on HLA match grade (63% in the 7/8 strata and 71% in the 4–6/8 strata, p=0.733) (Supplemental Figure 1). The incidence of cGVHD was, in fact, higher in the *better* matched patients (37% vs. 16%), as were the relapse rates (44% vs. 33%). We also analyzed the impact of HLA-DPB1 matching and found no significant differences in any outcome (data not shown).

In our study, match grade was equivalent between the strata, suggesting no specific selection bias by conditioning intensity (although donor selection bias by transplant center was noted, data not shown).

This report is limited by the small numbers included in the phase II clinical trial, the registry level data included in the long term follow up (vs. clinical trial intensity/frequency of data) and the exploratory and descriptive nature of some endpoints.

In conclusion, these encouraging longer term outcomes support the use of PTCy-based MMUD HCT to expand access to HCT. In fact, NMDP data already show a 25% global increase in MMUD transplants in 2021–2022 (S. Devine, personal communication), and emerging data suggested outcomes using MMUDs may be superior to haplo in some settings[14]. Future research should focus on relapse reduction and early relapse detection strategies, with biological correlates thoughtfully included in prospective clinical trials[15], as well as improving the precision of donor selection in the HLA mismatched setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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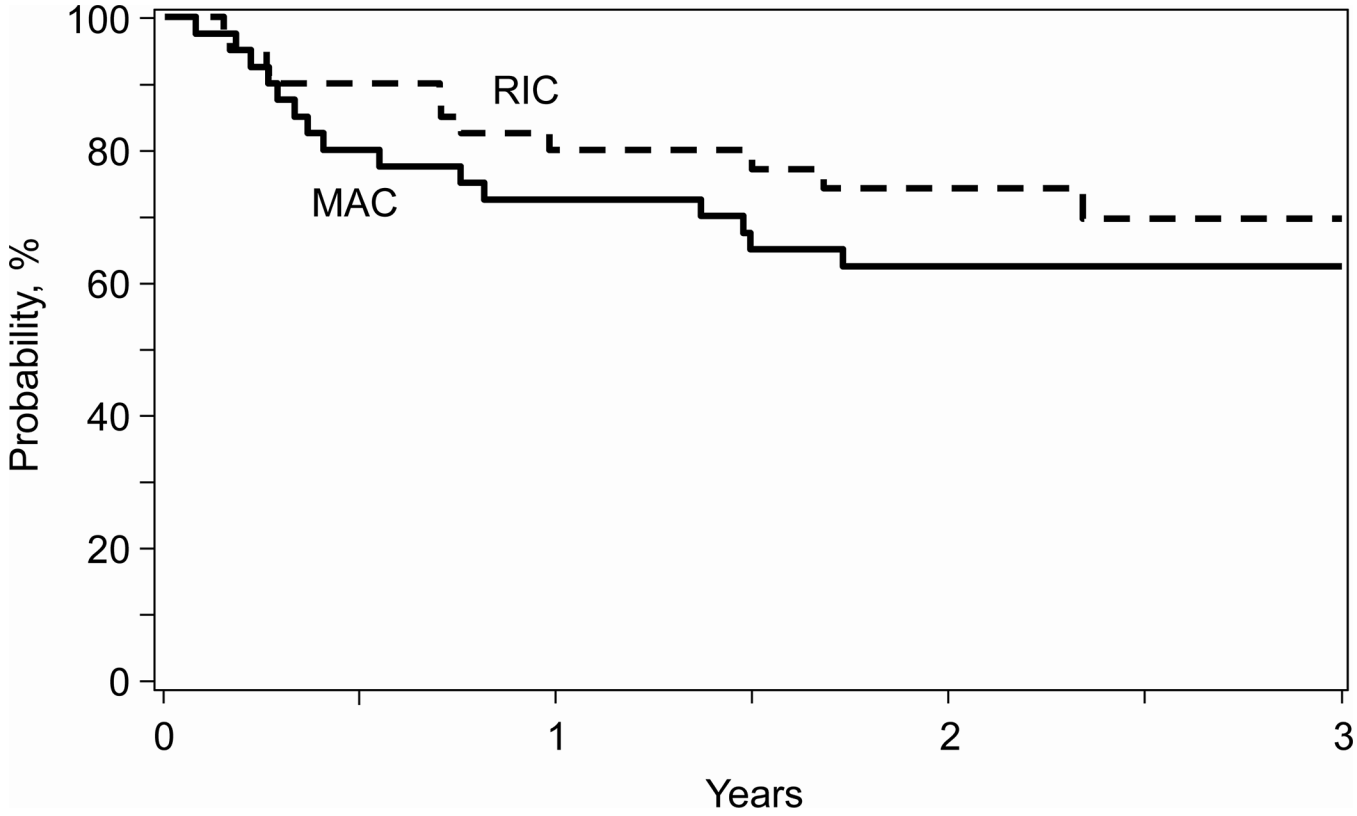
Highlights

1. PTCy prophylaxis is associated with encouraging 3-year outcomes in MMUD HCT
2. No new onset GVHD was reported beyond 1 year
3. Outcomes were not worse in vases with a higher degree of HLA mismatch



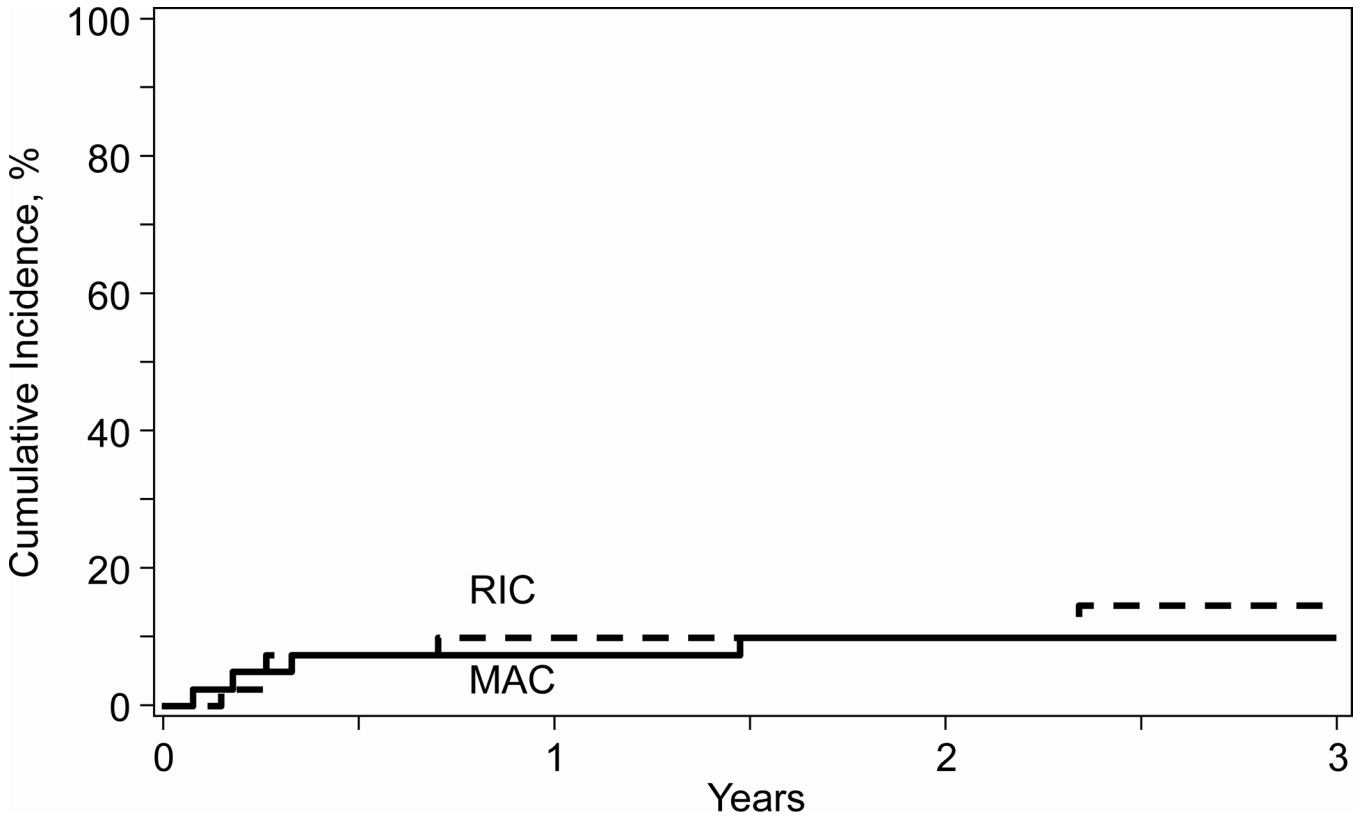


Figure 1:

a. 3-year overall survival by conditioning intensity, b. 3-year non-relapse mortality by conditioning intensity. RIC: reduced intensity conditioning, MAC: Myeloablative conditioning

Table 1:

Baseline characteristics for clinical trial patients by conditioning intensity

Characteristic	MAC	RIC	Total
No. of patients	40	40	80
No. of centers	9	8	11
HIV infection pre-HCT - no. (%)			
No	40	36 (90)	76 (95)
Yes	0	4 (10)	4 (5)
Age at HCT, years - no. (%)			
Median (min-max)	48.5 (18–66)	59.5 (23–70)	51.5 (18–70)
15–29	8 (20)	3 (7.5)	11 (13.8)
30–49	13 (32.5)	11 (27.5)	24 (30)
50–70	19 (47.5)	26 (65)	45 (56.3)
Sex - no. (%)			
Male	23 (58)	19 (48)	42 (53)
Female	17 (43)	21 (53)	38 (48)
Race - no. (%)			
American Indian or Alaska Native	1 (3)	0	1 (1)
Asian	1 (3)	1 (3)	2 (3)
Black or African American	9 (23)	6 (15)	15 (19)
White	29 (73)	31 (78)	60 (75)
Not reported/unknown	0	2 (5)	2 (3)
Ethnicity - no. (%)			
Hispanic or Latino	12 (30)	7 (18)	19 (24)
Not Hispanic or Latino	28 (70)	33 (83)	61 (76)
Race/ethnicity - no. (%)			
White/non-Hispanic	17 (43)	25 (63)	42 (53)
Others	23 (58)	15 (38)	38 (48)
Karnofsky score - no. (%)			
70	2 (5)	1 (3)	3 (4)
80	12 (30)	12 (30)	24 (30)
90	21 (53)	17 (43)	38 (48)
100	5 (13)	10 (25)	15 (19)
HCT-CI - no. (%)			
0	4 (10)	9 (23)	13 (16)
1	2 (5)	8 (20)	10 (13)
2	10 (25)	4 (10)	14 (18)
3+	24 (60)	19 (48)	43 (54)
Disease status at HCT - no. (%)			
AML	23 (57.5)	14 (35)	37 (46.3)
CR1	22	10	32
CR2+	1	2	3

Characteristic	MAC	RIC	Total
PIF	0	2	2
ALL	10 (25)	7 (17.5)	17 (21.3)
CR1	7	6	13
CR2+	3	1	4
CLL	0	3 (7.5)	3 (3.8)
CR	0	3	3
MDS	2 (5)	0	2 (2.5)
CR	1	0	1
HI	1	0	1
Other acute leukemia	4 (10)	0	4 (5)
CR1	3	0	3
CR2+	1	0	1
NHL	1 (2.5)	11 (27.5)	12 (15)
CR1	0	5	5
CR2+	1	3	4
Relapse	0	2	2
PIF	0	1	1
HL	0	5 (12.5)	5 (6.3)
CR1	0	2	2
Relapse	0	1	1
PIF	0	2	2
Refined disease risk index - no. (%)			
Low	3 (8)	6 (15)	9 (11)
Intermediate	29 (73)	21 (53)	50 (63)
High	3 (8)	7 (18)	10 (13)
Very high	0	3 (8)	3 (4)
N/A	5 (13)	3 (8)	8 (10)
CMV serostatus - no. (%)			
Negative	16 (40)	18 (45)	34 (43)
Positive	24 (60)	22 (55)	46 (58)
Time between diagnosis to HCT - no. (%)			
< 6 months	14 (35)	10 (25)	24 (30)
>= 6 months	26 (65)	30 (75)	56 (70)
Number of prior auto HCTs - no. (%)			
0	38 (95)	37 (93)	75 (94)
1	2 (5)	3 (8)	5 (6)
Infused total nucleated cells, $\times 10^8$/kg - median (min-max)	2.81 (0.6–520.8)	2.8 (0.76–5.8)	2.8 (0.76–520.8)
Infused CD34+ cells, $\times 10^6$/kg - median (min-max)	2.72 (0.89–5.24)	2.2 (0.39–6.23)	2.66 (0.39–6.23)
Conditioning regimen - no. (%)			
TBI/Cy/Flu	0	40	40 (50)
Bu/Cy	3 (8)	0	3 (4)

Characteristic	MAC	RIC	Total
Bu/Flu	31 (78)	0	31 (39)
TBI/Cy	6 (15)	0	6 (8)
HLA match - no. (%)			
7/8	26 (65)	23 (58)	49 (61)
6/8	8 (20)	11 (28)	19 (24)
5/8	5 (13)	2 (5)	7 (9)
4/8	1 (3)	4 (10)	5 (6)
Donor age, years - no. (%)			
Median (min-max)	27 (18–56)	29 (21–44)	29 (18–56)
18–29	24 (60)	23 (58)	47 (59)
30–39	9 (23)	11 (28)	20 (25)
40–49	4 (10)	6 (15)	10 (13)
50–59	3 (8)	0	3 (4)
Donor weight, kg - median (min-max)	77 (55–103)	77 (52–104)	77 (52–104)
Donor sex - no. (%)			
Male	20 (50)	24 (60)	44 (55)
Female	20 (50)	16 (40)	36 (45)
Donor/recipient sex - no. (%)			
M-M	12 (30)	12 (30)	24 (30)
M-F	8 (20)	12 (30)	20 (25)
F-M	11 (28)	7 (18)	18 (23)
F-F	9 (23)	9 (23)	18 (23)
Donor/recipient CMV serostatus - no. (%)			
+/+	16 (40)	13 (33)	29 (36)
+/−	8 (20)	7 (18)	15 (19)
−/+	8 (20)	9 (23)	17 (21)
−/−	8 (20)	11 (28)	19 (24)
Donor/recipient ABO match - no. (%)			
Matched	20 (50)	24 (60)	44 (55)
Minor mis-match	12 (30)	5 (13)	17 (21)
Major mis-match	8 (20)	8 (20)	16 (20)
Bi-directional	0	3 (8)	3 (4)

Table 2:

3-year univariate outcomes for clinical trial patients by conditioning intensity

	MAC (N = 40)		RIC (N = 40)	
Outcomes	**N**	**Prob (90% CI)**	**N**	**Prob (90% CI)**
Overall survival	40		40	
1-year	29	72.5 (60.3–83.2)%	29	79.9 (68.6–89.2)%
3-year	11	62.4 (49.5–74.5)%	11	69.6 (55.8–81.8)%
Non-relapse mortality	40		40	
1-year	24	7.5 (2.1–15.8)%	26	10 (3.6–19.2)%
3-year	9	10 (3.5–19.2)%	9	14.7 (5.7–26.9)%
Relapse	40		40	
1-year	24	35 (23-48)%	26	20 (10.6–31.5)%
3-year	9	50.5 (36.3–64.7)%	9	29.4 (17.7–42.7)%
Progression-free survival	40		40	
1-year	23	57.5 (44.5–70)%	25	70 (57.5–81.1)%
3-year	8	39. 5 (26.4–53.4)%	8	55.9 (41.6–69.8)%
Chronic GVHD	40		40	
1-year	15	37.5 (25.2–50.6)%	24	20 (10.6–31.5)%
3-year	6	37.5 (25.2–50.6)%	6	20 (10.6–31.5)%
Severe Chronic GVHD	40		40	
1-year	25	12.5 (5.2–22.4)%	29	5 (0.9–12.2)%
3-year	8	12.5 (5.2–22.4)%	12	5 (0.9–12.2)%
GVHD-/relapse-free survival (GRFs)	40		40	
1-year	10	25 (14.7–37)%	19	55 (42–67.6)%
3-year	3	16.9 (8.2–27.8)%	5	44.3 (30.6–58.5)%