Overall Survival in Newly Diagnosed MM Patients With Del(17p): A Report From the Connect® MM Registry

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BACKGROUND

- The chromosomal abnormality del(17p) is detected in 10% to 15% of patients with multiple myeloma and is associated with early relapse and short survival[1-6]
- Prognosis is likely to result from the effects of multiple abnormalities
  - del(6q) and del(1p32) were found to correlate with poor progression-free survival (PFS) and overall survival (OS), respectively[7]
  - Other abnormalities such as trisomy 15 and monosomy 14 may have protective effects on PFS[7]
  - Hyperdiploidy may not counter adverse cytogenetics as previously believed[8]
- Limited data exist outside of clinical trials, and there is no uniform or optimal treatment (Tx) approach, including the appropriate role of autologous stem cell transplant (ASCT), for patients with del(17p)[9,10]
- Connect MM®, the first and largest prospective, observational, US-based, multicenter registry was designed to report the natural history, management, and outcomes of patients with newly diagnosed multiple myeloma (NDMM) in clinical practice[11]
- Connect MM® contains a relatively large cohort of del(17p) patients

OBJECTIVES

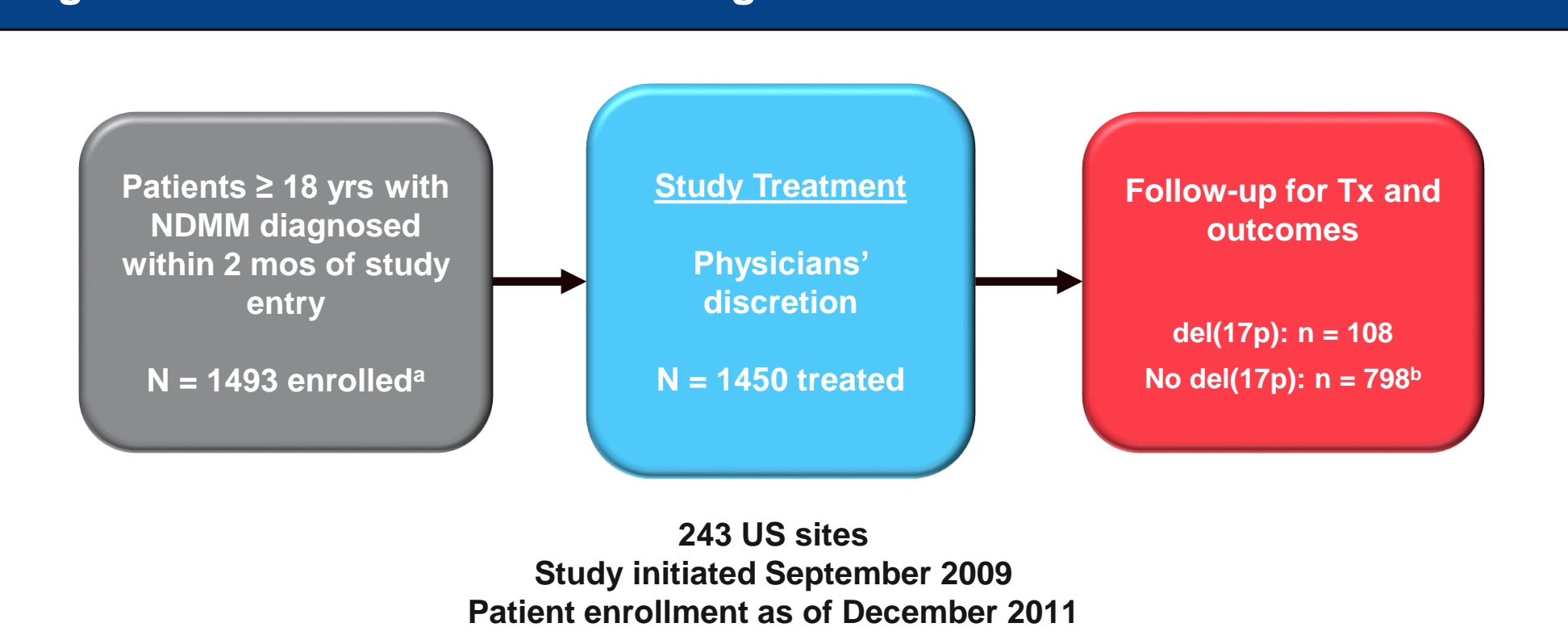- Analyze disease characteristics, overall response, PFS, and OS in patients with NDMM and del(17p) enrolled in the Connect MM registry
- Analyze the correlation between baseline characteristics and outcomes

METHODS

Study Design
- Observational noninterventional disease registry initiated in September 2009 (Figure 1)
  - Eligible NDMM patients were enrolled at 243 US sites (community, academic, and Veterans Affairs centers)
    - Patients had to have been diagnosed with MM within 60 days of enrollment
  - Data were collected at baseline and each subsequent quarter using an electronic case report form
- 1493 patients enrolled up to December 2011
  - Outcomes data through December 24, 2014 for 1450 treated patients were analyzed

Figure 1. CONNECT MM® Trial Design

Patients ≥ 18 yrs with NDMM diagnosed within 2 mos of study entry → Study Treatment: Physicians' discretion → Follow-up for Tx and outcomes

N = 1493 enrolled[a]
N = 1450 treated
del(17p): n = 108
No del(17p): n = 798[b]

243 US sites
Study initiated September 2009
Patient enrollment as of December 2011

Registered at ClinicalTrials.gov as NCT01081028
[a] The first cohort consists of 1493; the study is currently enrolling the second cohort of 1500.
[b] 544 patients did not have del(17p) data available.
NDMM, newly diagnosed multiple myeloma; pt, patient; Tx, treatment.

Assessments
- PFS and OS were described with survival curves for prespecified groups. Group comparisons were tested with log-rank tests
- OS was also analyzed for preselected baseline factors using Cox proportional hazards model
- Survival analysis was adjusted for sex, race, therapy received, and ASCT
  - Adjusted survival curves were produced to provide survival curves for each attribute level at the same overall mean values for the covariates
  - The adjusted curves were based on a Cox regression model containing the plotted attributes together with ISS stage and age as covariates
- "Novel agents" were considered to be bortezomib, carfilzomib, lenalidomide, and pomalidomide

RESULTS

Patient Characteristics
- Median follow-up was 33.5 mos (range, 0.03-55.9 mos)
- del(17p) status was analyzed in 906 patients (mainly by FISH) and found to be present in 108 (11.9%)
- In del(17p) patients (Table 1)
  - Median age was 69 yrs vs 66 yrs in non-del(17p) patients
  - 58% were male
  - 82% were white
  - 46% had International Staging System stage III disease

Table 1. Patient Characteristics

Characteristic	del(17p) (n = 108)	No del(17p) (n = 798)
Median age (range), yr	69 (27-89)	66 (24-93)
< 65 yrs, %	41	44
≥ 65 to < 75 yrs, %	29	32
≥ 75 yrs, %	31	24
Male, %	58	57
Race, %		
White	82	82
Black	11	14
Other	7	4
ISS Stage	(n = 78)	(n = 482)
I	24	28
II	29	38
III	46	34

Treatment and Response
- 34 (31%) patients with del(17p) and 310 (39%) without del(17p) received ASCT (Table 2)
- 25% of del(17p) patients and 29% of non-del(17p) patients received ≥ 2 novel agents in their first line of treatment, compared with 71% and 65% who received 1 novel agent, and 4% and 6% who did not receive first-line novel agents (Table 3)
- Overall response to treatment and duration of response were slightly lower for patients with del(17p) (Table 3)

Table 2. Treatment

Characteristic	del(17p) (n = 108)	No del(17p) (n = 798)
SCT, %	31	39
SCT in first course, %	17	24
SCT intent, %	40	49
Triplet Tx, %	55	57
Novel agents in first course, first regimen, %[a]		
0	4	6
1	71	65
2	25	29

[a] Novel agents include bortezomib, carfilzomib, lenalidomide, and pomalidomide.
SCT, stem cell transplant; Tx, treatment.

Table 3. Response to First Line of Therapy

	del(17p) (n = 68)	No del(17p) (n = 526)
Overall response rate (≥ partial response), %	62	66
Median duration of response,[a] mos	8	9

[a] For patients with ≥ partial response.

RESULTS (cont)

Progression-free Survival
- 1-yr, 2-yrs, and 3-yrs PFS were shortened for patients with del(17p) compared with patients without del(17p)
- A similar pattern was observed in almost all subgroups examined (Table 4)
- Patients with or without del(17p) treated with 1 novel agent in the first line of treatment had slightly but not significantly shorter PFS than those with 2 novel agents (Figure 2)
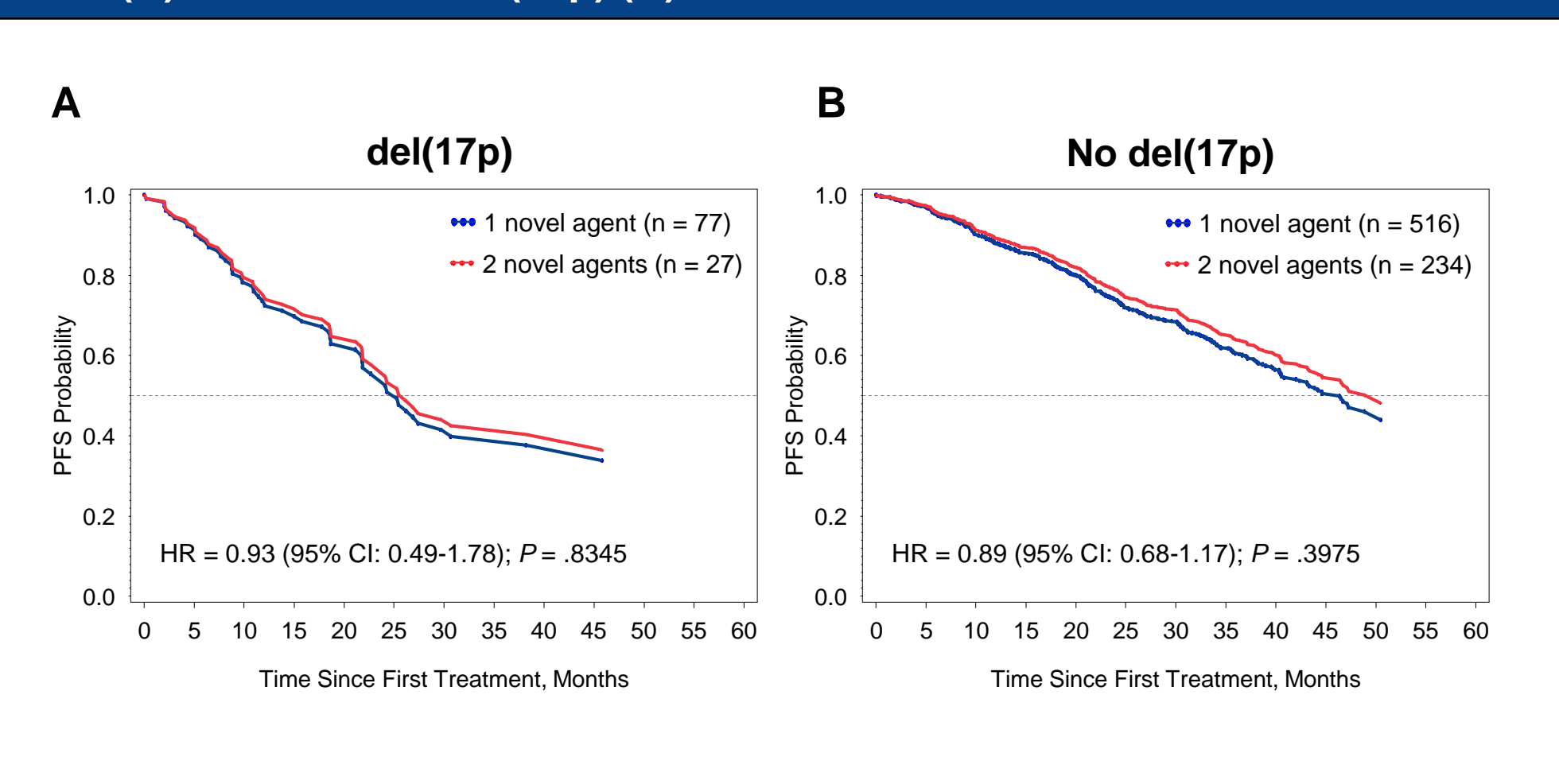
Table 4. Kaplan-Meier Estimated PFS Probability by Subgroup

Patients	N del(17p)	N No del(17p)	1-y PFS (95% CI) del(17p)	1-y PFS (95% CI) No del(17p)	2-y PFS (95% CI) del(17p)	2-y PFS (95% CI) No del(17p)	3-y PFS (95% CI) del(17p)	3-y PFS (95% CI) No del(17p)
All patients	108	793	71.9 (62.8-80.9)	87.3 (84.9-89.7)	50.2 (39.3-61.2)	73.0 (69.7-76.3)	38.7 (27.8-49.7)	61.1 (57.3-64.9)
Age								
< 65 yrs	44	352	70.7 (56.6-84.7)	91.3 (88.3-94.3)	40.3 (23.9-56.7)	79.5 (75.0-83.9)	27.9 (12.7-43.1)	66.9 (61.6-72.2)
≥ 65 to < 75 yrs	31	256	61.1 (43.1-79.1)	89.1 (85.1-93.1)	41.8 (21.7-61.9)	72.3 (66.4-78.1)	41.8 (21.7-61.9)	61.7 (55.1-68.3)
≥ 75 yrs	33	185	85.3 (71.9-98.7)	76.4 (69.8-83.0)	75.7 (58.5-93.0)	60.3 (52.4-68.3)	54.1 (32.3-75.9)	47.3 (38.6-56.1)
Sex								
Male	63	454	70.4 (58.5-82.3)	88.0 (84.9-91.2)	48.4 (34.4-62.4)	75.0 (70.7-79.3)	34.6 (20.9-48.3)	63.2 (58.2-68.1)
Female	45	339	74.1 (60.2-88.1)	86.4 (82.6-90.2)	52.8 (35.2-70.3)	70.3 (65.1-75.5)	45.2 (27.3-63.1)	58.4 (52.5-64.2)
Race								
White	89	647	74.0 (64.2-83.9)	87.1 (84.4-89.8)	50.1 (38.1-62.2)	73.4 (69.8-77.1)	36.8 (24.9-48.6)	61.1 (56.9-65.2)
Black	12	111	58.3 (30.4-86.2)	87.5 (81.1-93.9)	46.7 (16.4-76.9)	67.3 (58.0-76.7)	46.7 (16.4-76.9)	55.5 (46.0-67.0)
Other	7	35	68.6 (32.1-100)	90.9 (81.1-100)	68.6 (32.1-100)	83.8 (70.7-96.9)	68.6 (32.1-100)	76.2 (60.6-91.8)
ASCT								
Yes	34	309	82.0 (69.0-95.1)	92.8 (88.9-95.7)	67.0 (49.9-84.1)	80.0 (75.5-84.6)	51.2 (32.4-70.0)	65.6 (60.0-71.1)
No	74	484	66.3 (54.4-78.2)	83.4 (79.9-86.9)	40.8 (27.2-54.3)	67.3 (63.2-71.4)	31.7 (18.6-44.8)	58.0 (52.9-63.1)
Triplet Tx								
Yes	59	451	74.2 (62.0-86.4)	88.6 (85.6-91.6)	52.3 (36.0-68.6)	74.9 (70.9-78.9)	43.7 (26.6-60.7)	59.6 (54.7-64.5)
No	49	342	66.8 (52.6-81.0)	85.8 (81.6-89.5)	44.7 (29.0-60.2)	72.4 (67.2-77.6)	39.1 (23.7-54.5)	64.0 (58.1-69.8)
Novel agents[a]								
0	4	47	75.0 (32.6-100)	74.5 (60.7-88.3)	50.0 (1.0-99.0)	55.2 (39.2-71.2)	—	49.4 (33.2-65.6)
1	77	513	73.8 (63.2-84.3)	86.2 (83.1-89.3)	51.7 (38.4-64.9)	71.5 (67.3-75.7)	35.8 (22.9-48.6)	60.6 (55.8-65.3)
2	27	233	66.0 (46.8-85.2)	91.9 (88.4-95.3)	46.0 (24.8-67.2)	79.1 (73.7-84.5)	40.9 (19.8-61.9)	64.3 (57.6-71.0)

[a] Novel agents include bortezomib, carfilzomib, lenalidomide, and pomalidomide.
ASCT, autologous stem cell transplant; PFS, progression-free survival; Tx, treatment.

Figure 2. Adjusted PFS by Novel Agents in First Regimen for Patients With (A) and Without del(17p) (B)

A del(17p): 1 novel agent (n = 77); 2 novel agents (n = 27)
HR = 0.93 (95% CI: 0.49-1.78); P = .8345

B No del(17p): 1 novel agent (n = 516); 2 novel agents (n = 234)
HR = 0.89 (95% CI: 0.68-1.17); P = .3975

Adjusted for ISS stage and age.
HR, hazard ratio; ISS, International Staging System; PFS, progression-free survival.

Survival
- OS probabilities for all del(17p) patients were 1 yr: 78.7 (95% CI: 70.8-86.6); 2 yrs: 60.5 (95% CI: 50.8-70.2); and 3 yrs: 54.7 (95% CI: 44.7-64.8) (Table 5)
- Patients with del(17p) had lower survival when compared with those without del(17p) (hazard ratio [HR] = 1.80 [95% CI: 1.31-2.47]; P = .0003; Figure 3)
- Patients with del(17p) who received ASCT had a similar survival to patients without del(17p) who did not receive ASCT (HR = 0.95 [95% CI: 0.77-1.18]; P = .6674; Figure 4)
  - Patients with del(17p) who did not receive ASCT had a lower survival than patients without del(17p) who did not receive ASCT (HR = 0.80 [95% CI: 0.67-0.96]; P = .0145; Figure 4)
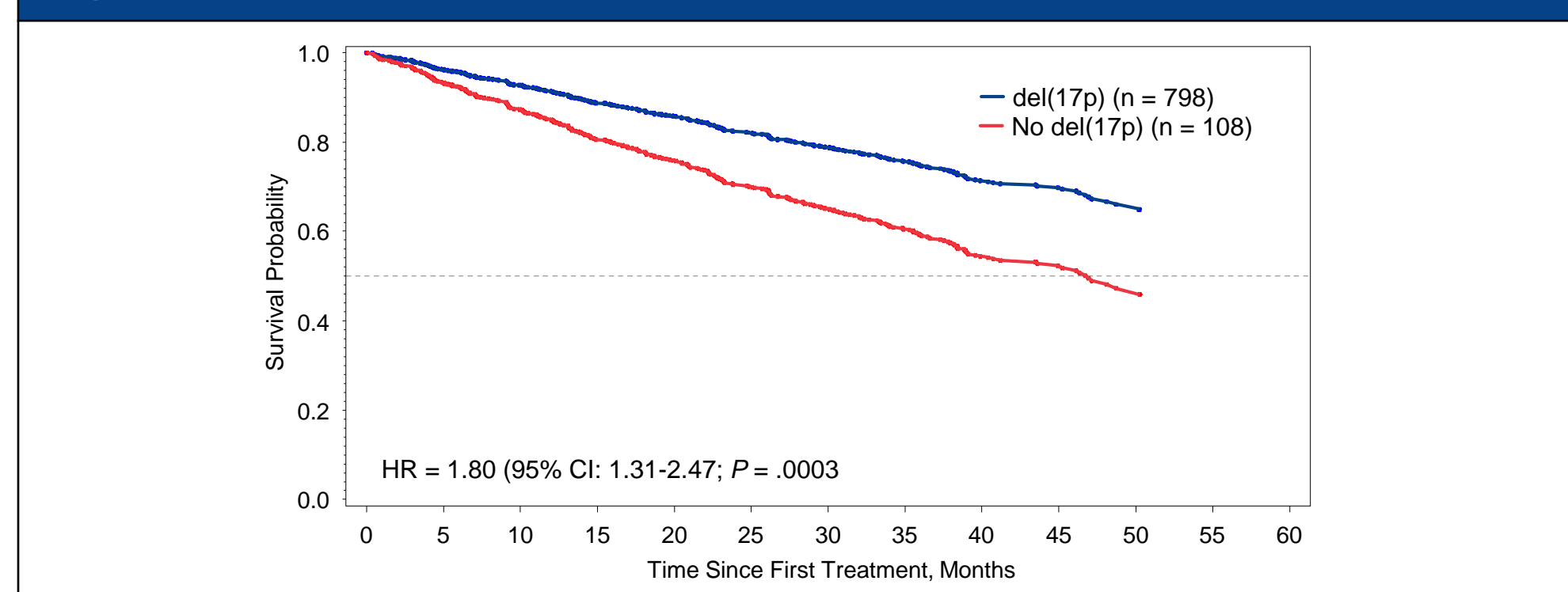
Univariate and Multivariate Analysis
- Among patients with del(17p), univariate and multivariate analysis found that hypercalcemia (serum calcium ≥ 11.5 mg/dL) was associated with a 2.67-fold higher rate of death in del(17p) patients (P = 0.025; Table 6)

RESULTS (cont)

Table 5. Kaplan-Meier Estimated OS Probability by Subgroup

Patients	N del(17p)	N No del(17p)	1-yr OS (95% CI) del(17p)	1-yr OS (95% CI) No del(17p)	2-yrs OS (95% CI) del(17p)	2-yrs OS (95% CI) No del(17p)	3-yrs OS (95% CI) del(17p)	3-yrs OS (95% CI) No del(17p)
All patients	108	798	78.7 (70.8-86.6)	90.5 (88.4-92.5)	60.5 (50.8-70.2)	81.5 (78.8-84.3)	54.7 (44.7-64.8)	72.7 (69.4-75.9)
Age								
< 65 yrs	44	352	80.5 (68.3-92.7)	95.1 (92.8-97.4)	66.6 (51.6-81.6)	88.0 (84.5-91.5)	57.7 (41.7-73.7)	80.6 (76.3-85.0)
≥ 65 to < 75 yrs	31	258	80.2 (66.0-94.4)	89.8 (86.1-93.5)	57.9 (39.4-76.3)	82.1 (77.3-86.8)	57.9 (39.4-76.3)	73.7 (68.2-79.3)
≥ 75 yrs	33	188	74.5 (59.2-89.8)	82.6 (77.0-88.2)	54.9 (37.3-72.5)	68.2 (61.0-75.5)	49.0 (30.5-65.8)	55.4 (47.6-63.2)
Sex								
Male	63	456	83.1 (73.5-92.7)	90.8 (88.1-93.5)	64.8 (52.2-77.3)	81.3 (77.6-85.0)	58.7 (46.7-71.8)	72.6 (68.3-76.9)
Female	45	342	71.5 (56.9-86.0)	90.1 (86.9-93.3)	54.5 (39.1-69.8)	81.8 (77.6-86.0)	49.0 (33.5-64.6)	72.7 (67.7-77.8)
Race								
White	89	652	76.4 (67.4-85.5)	90.7 (88.1-92.7)	59.0 (48.1-69.9)	80.8 (77.7-83.9)	52.4 (41.5-63.3)	72.2 (68.6-75.8)
Black	12	111	83.3 (62.2-100)	89.8 (84.0-95.5)	83.3 (62.2-100)	82.9 (75.7-90.1)	83.3 (62.2-100)	70.0 (60.0-79.1)
Other	7	35	100	94.0 (86.0-100)	30.0 (0.0-76.8)	90.7 (80.6-100)	30.0 (0.0-76.8)	90.7 (80.6-100)
ASCT								
Yes	34	310	90.6 (80.5-100)	98.7 (97.4-100)	73.4 (57.5-89.3)	92.4 (89.5-95.4)	66.0 (48.8-83.3)	87.1 (83.3-91.0)
No	74	488	72.9 (62.5-83.3)	85.1 (81.8-89.1)	54.3 (42.4-66.3)	74.2 (70.1-78.2)	49.3 (37.2-61.4)	62.7 (58.1-67.3)
Triplet Tx								
Yes	59	462	78.2 (67.2-89.1)	93.9 (91.6-96.2)	59.4 (45.8-73.0)	86.0 (82.7-89.2)	52.0 (36.1-64.4)	79.7 (75.8-83.5)
No	49	346	79.3 (67.8-90.7)	85.9 (82.1-89.6)	61.7 (47.8-75.7)	75.5 (70.8-80.2)	59.4 (45.2-73.5)	62.9 (57.4-68.4)
Novel agents[a]								
0	4	48	75.0 (32.6-100)	83.8 (72.9-94.8)	50.0 (1.0-99.0)	81.4 (69.7-93.1)	50.0 (1.0-99.0)	68.5 (54.2-82.8)
1	77	516	80.8 (69.5-88.0)	88.5 (85.7-91.3)	61.1 (49.7-72.5)	78.0 (74.4-81.7)	57.8 (46.2-69.4)	68.9 (64.6-73.1)
2	27	234	79.2 (62.9-95.4)	96.1 (93.6-98.6)	61.0 (40.9-81.0)	89.2 (85.1-93.3)	46.9 (26.1-67.7)	81.7 (76.5-87.0)

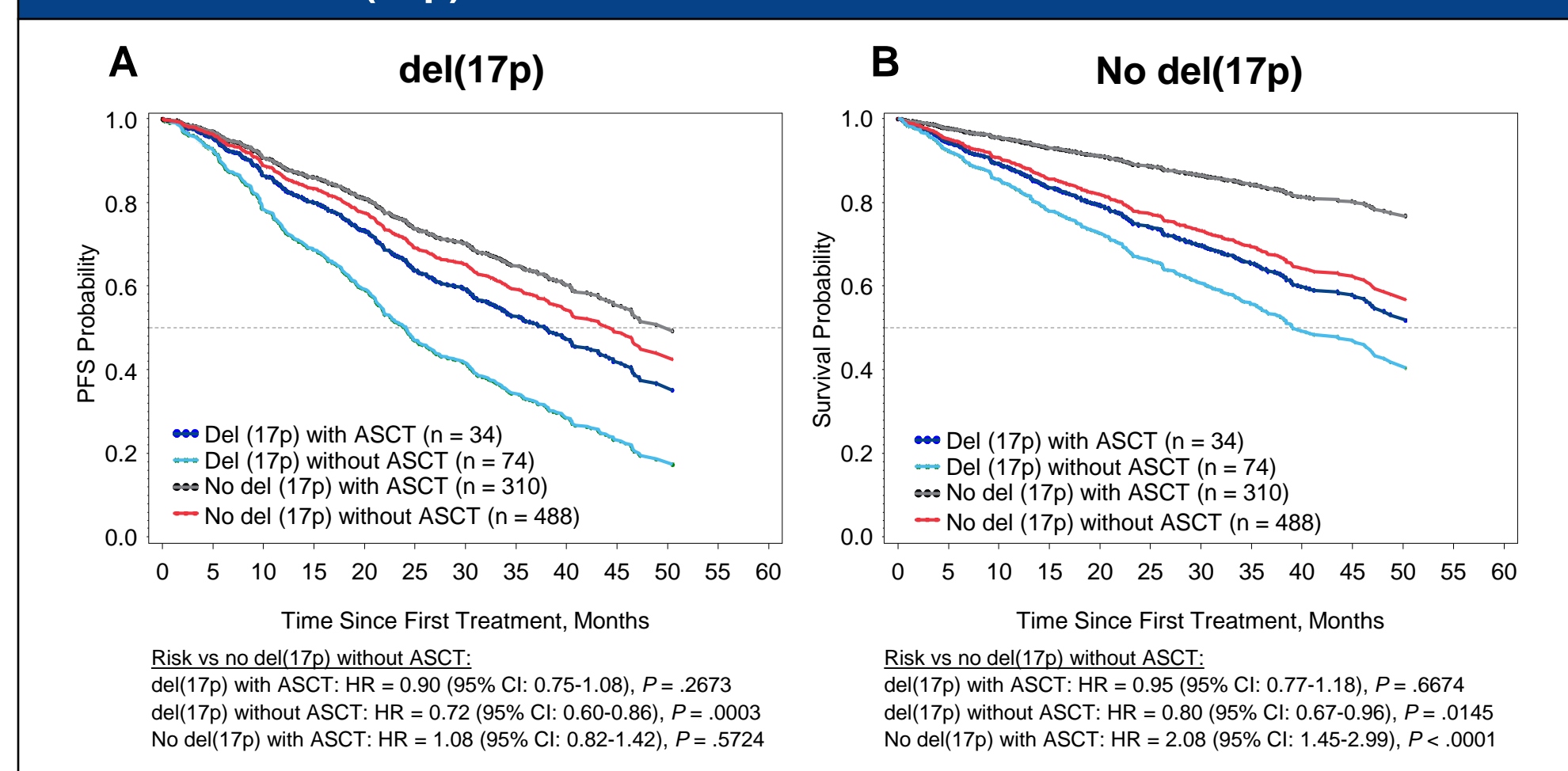[a] Novel agents include bortezomib, carfilzomib, lenalidomide, and pomalidomide.
ASCT, autologous stem cell transplant; OS, overall survival; Tx, treatment.

Figure 3. OS by del(17p) Status

del(17p) (n = 798)
No del(17p) (n = 108)

HR = 1.80 (95% CI: 1.31-2.47; P = .0003)

Adjusted for ISS stage and age.
HR, hazard ratio; ISS, International Staging System; OS, overall survival.

Figure 4. Adjusted PFS (A) and OS (B) for Patients Receiving ASCT With and Without del(17p)

A del(17p)
Del (17p) with ASCT (n = 34)
Del (17p) without ASCT (n = 74)
No del (17p) with ASCT (n = 310)
No del (17p) without ASCT (n = 488)

B No del(17p)
Del (17p) with ASCT (n = 34)
Del (17p) without ASCT (n = 74)
No del (17p) with ASCT (n = 310)
No del (17p) without ASCT (n = 488)

Risk vs no del(17p) without ASCT:
del(17p) with ASCT: HR = 0.90 (95% CI: 0.75-1.08), P = .2673
del(17p) without ASCT: HR = 0.72 (95% CI: 0.60-0.86), P = .0003
No del(17p) with ASCT: HR = 0.80 (95% CI: 0.67-0.96), P = .0145

Risk vs no del(17p) without ASCT:
del(17p) with ASCT: HR = 0.95 (95% CI: 0.77-1.18), P = .6674
del(17p) without ASCT: HR = 1.08 (95% CI: 0.82-1.42), P = .5724

Adjusted for ISS stage and age.
ASCT, autologous stem cell transplant; HR, hazard ratio; ISS, International Staging System; OS, overall survival; PFS, progression-free survival.

RESULTS (cont)

Table 6. Baseline Factors Impacting OS in Patients With del(17p)

Variable	Univariate analysis HR (95% CI)	Univariate analysis P Value	Multivariate analysis HR (95% CI)	Multivariate analysis P Value
Age (10-yr increments)	1.25 (0.95-1.64)	0.115		
Alkylator in first regimen	1.46 (0.73-2.87)	0.286		
Body mass index	0.97 (0.92-1.03)	0.321		
Novel agent in first regimen	0.99 (0.52-1.87)	0.968		
Sex (female vs male)	1.53 (0.87-2.69)	0.144		
Stem cell transplant	0.45 (0.23-0.89)	0.021		
History of MGUS	0.95 (0.37-2.41)	0.909		
History of smoldering myeloma	0.59 (0.18-1.89)	0.371		
IMWG cytogenetic high risk	1.10 (0.65-1.86)	0.729		
ISS disease stage	1.56 (1.03-2.37)	0.037	1.30 (0.83-2.03)	.244
Eastern Cooperative Oncology Group performance status	1.14 (0.89-2.02)	0.044		
History of diabetes	0.75 (0.35-1.61)	0.465		
History of hypertension requiring treatment	1.21 (0.68-2.13)	0.522		
History of peripheral neuropathy	0.36 (0.05-2.64)	0.316		
History of venous thromboembolism	1.85 (0.45-7.67)	0.397		
Multiple lytic lesions (> 3 lesions)	1.24 (0.67-2.30)	0.494		
Compression fracture	1.13 (0.59-2.15)	0.716		
Clonal bone marrow plasma cell count > 10%	0.61 (0.15-2.51)	0.489		
Myeloma bone involvement	0.96 (0.48-1.93)	0.907		
Hypercalcemia (serum calcium ≥ 11.5 mg/dL)	3.43 (1.52-7.75)	0.003	2.67 (1.134-6.33)	.025
Renal insufficiency (serum creatinine > 2 mg/dL)	1.74 (0.88-3.42)	0.109	1.20 (0.59-2.57)	.636
Anemia (Hb < 10 g/dL or > 2 below LLN)	0.95 (0.53-1.71)	0.868		
Presence of M-component	0.54 (0.14-2.02)	0.363		
Beta-2 microglobulin ≥ 5.5 mg/L	1.60 (0.92-2.95)	0.092		
Creatinine clearance (10-point increments)	0.94 (0.87-1.02)	0.157		
Monoclonal protein ≥ 10%	1.44 (0.80-2.61)	0.226		

Hb, hemoglobin; HR, hazard ratio; IMWG, International Myeloma Working Group; ISS, International Staging System; LLN, lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance.

CONCLUSIONS

- Patients in the CONNECT MM® registry with del(17p) were slightly older and more had ISS stage III disease vs those without del(17p)
- Overall response rate and duration of response were slightly reduced in patients with del(17p) vs those without del(17p)
- del(17p) was associated with lower PFS and OS
  - Median OS was consistent with 3.1 yrs for patients with del(17p) at the time of diagnosis found by a Mayo Clinic study[12]
- ASCT and treatment with 2 novel therapies showed trends toward benefits in patients with del(17p)
  - Greater patient numbers are likely needed to demonstrate significance
- Treatment with 2 novel therapies is associated with slightly improved PFS in patients with or without del(17p)
- Hypercalcemia correlates with a lower probability of survival for patients with del(17p)

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