

SECONDARY MALIGNANCY IN ELDERLY MYELOMA PATIENTS

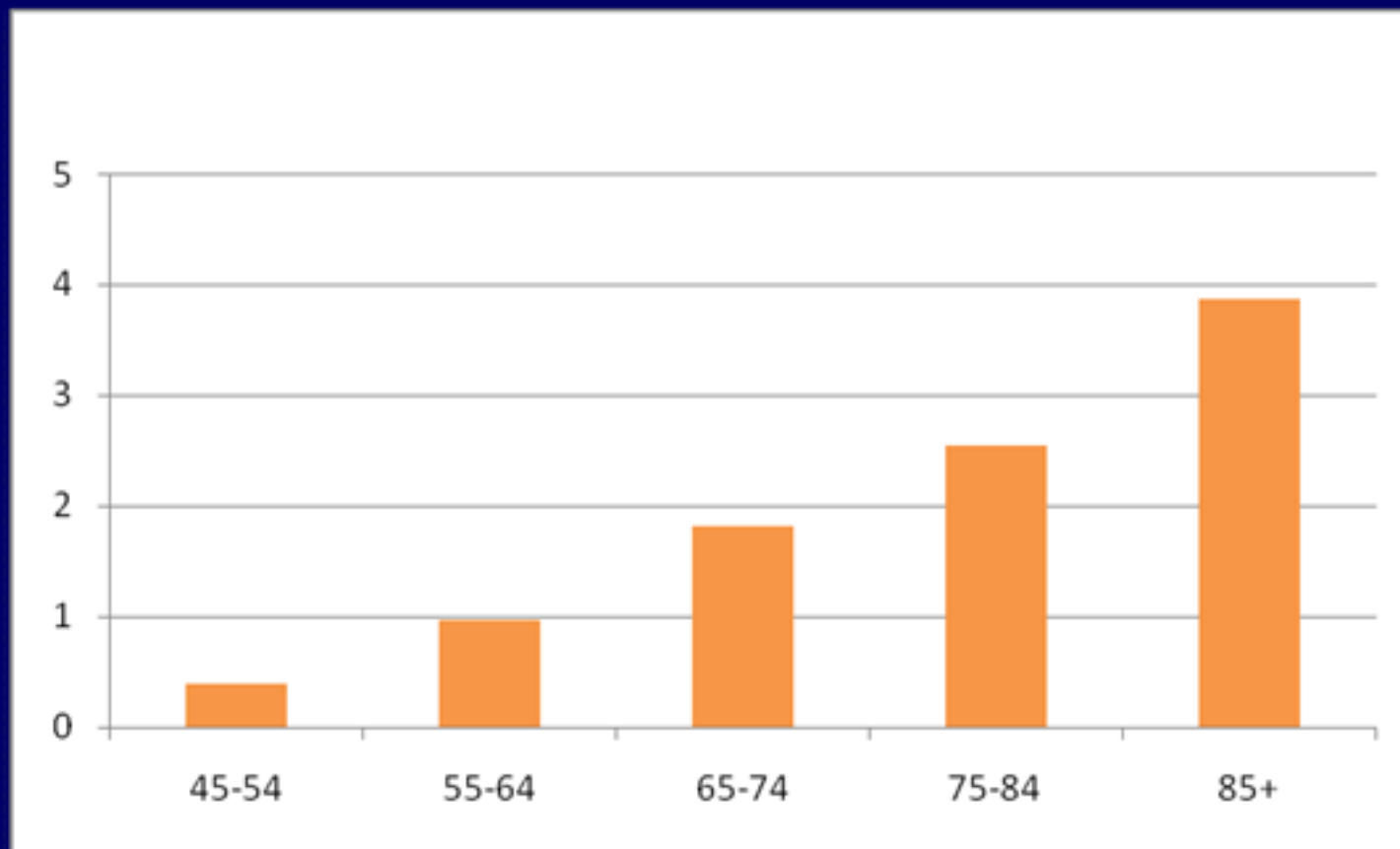
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On behalf of the



Incidence of second primary malignancies in normal population

INCIDENCE - Age specific rates (per 100 per year)



years of age

Piedmont Cancer Registry, Italy, City of Turin, 2005-2007

Background

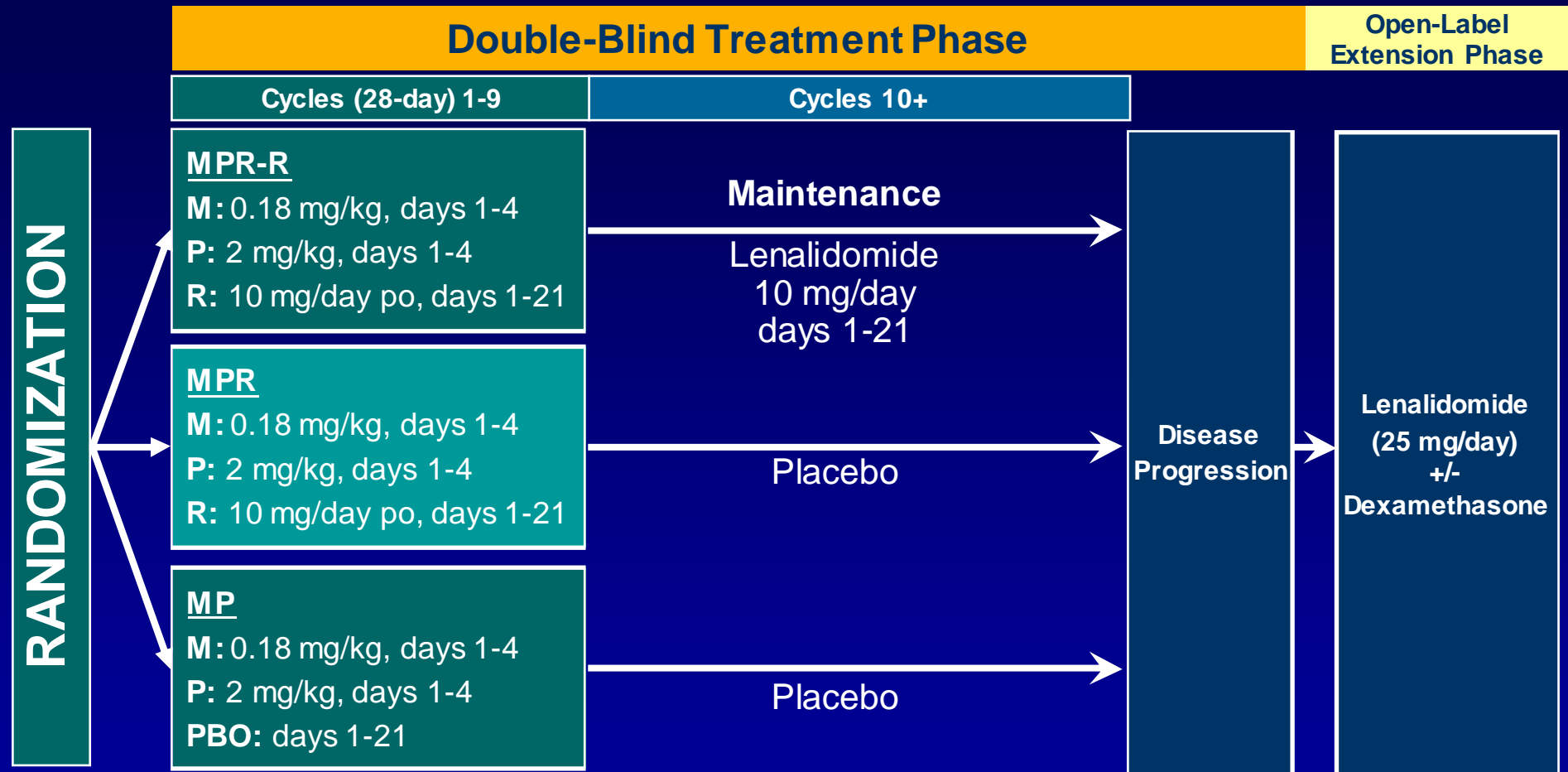
Retrospective Analysis		SPMs/Total	% SPMs
NCI SEER 1973-2000		1219/23838	5.1%
ASCT ¹ 1982-2000		29/800	3.6%
Australian Cancer Registry 1982-2001 ²		134/2174	6.1%

Trials	Therapy	Patients in Remission	SPMs/Total	% SPMs
IFM (4 yrs from dg) ³	Lenalidomide	60%	17/299	5.5%
	Placebo	33%	3/292	1.0%
CALCGB ⁴	Lenalidomide	NA	15/231	6.5%
	Placebo		6/229	2.6%
MM015 (2 yrs from dg) ⁵	MPR/MPR-R	24%/54%	11/535	3.1%
	Placebo	18.8%	2/154	1.3%

1. Forrest et al. 2003; 2. Youlden et al. 2011; 3. Attal M et al, ASH 2010; 4. McCarthy et al, ASH 2010; 5. Palumbo A et al, ASH 2010
 SPM, secondary primary malignancy; ASCT, autologous stem cell transplantation; NA, not available

MM-015: Study Design

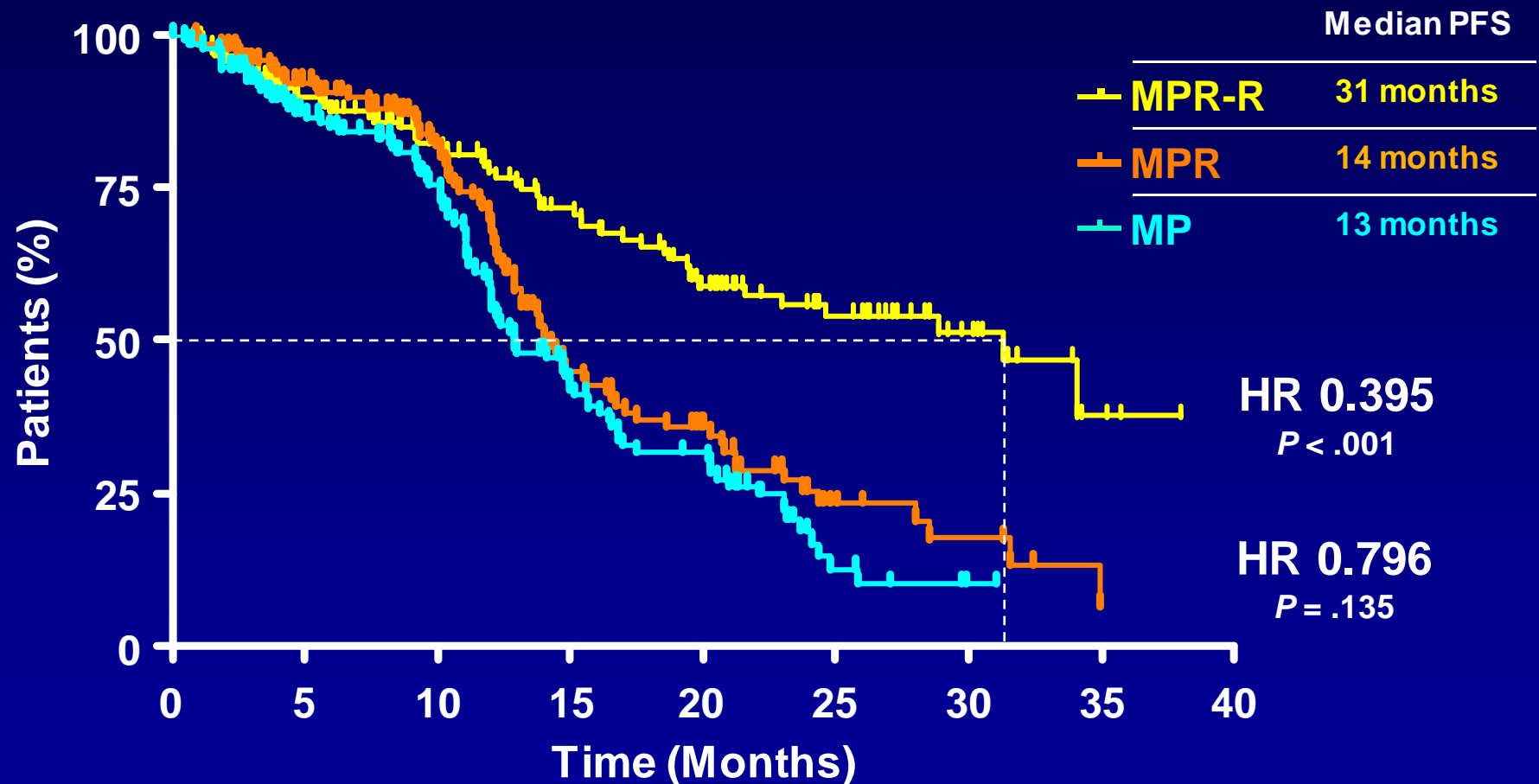
N = 459, 82 centers in Europe, Australia, and Israel



- Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)
- Primary comparison: MPR-R vs MP

ISS, International Staging System; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; NDMM, newly diagnosed multiple myeloma; PBO, placebo.

Progression-Free Survival All Patients 60% Reduced Risk of Progression



Median follow-up 25 months

MM-015: SPM

Data Cut-Off February 28, 2011

SPM, n (%)	MPR-R (n = 150)	MPR (n = 152)	MP (n = 153)
Total Invasive SPMs	12 (8.0)	9 (5.9)	4 (2.6)
Hematologic Malignancies	7 (4.7)	5 (3.3)	1 (0.7)
AML	4 (2.7)	2 (1.3)	0
MDS to AML	1 (0.7)	1 (0.7)	0
MDS	0	2 (1.3)	
T-ALL	1 (0.7)	0	0
CMML	1 (0.7)	0	0
B-cell malignancy	0	0	0
Solid tumors	5 (3.3)	4 (2.6)	3 (2.0)
Non-melanoma skin cancer	1 (0.7)	4 (2.6)	5 (3.3)

- Median follow-up: 30 months

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; T-ALL, T-cell acute lymphoblastic leukemia.

MM-015: SPM Incidence Rates

	MPR-R (n = 150)	MPR (n = 152)	MP (n = 153)
Total Invasive SPM	12	9	4
Person years	346	344	359
Incidence Rate*	3.5	2.6	1.1
95% CI	(1.97 - 6.11)	(1.36 - 5.03)	(0.42 - 2.97)
Hematologic SPMs, n	7	5	1
Person years	349	344	360
Incidence Rate*	2.0	1.5	0.3
95% CI	(0.96 - 4.21)	(0.60 - 3.49)	(0.04 - 1.97)
Solid tumor SPMs, n	5	4	3
Person years	348	346	360
Incidence Rate*	1.4	1.2	0.8
95% CI	(0.60 - 3.45)	(0.43 - 3.08)	(0.27 - 2.59)

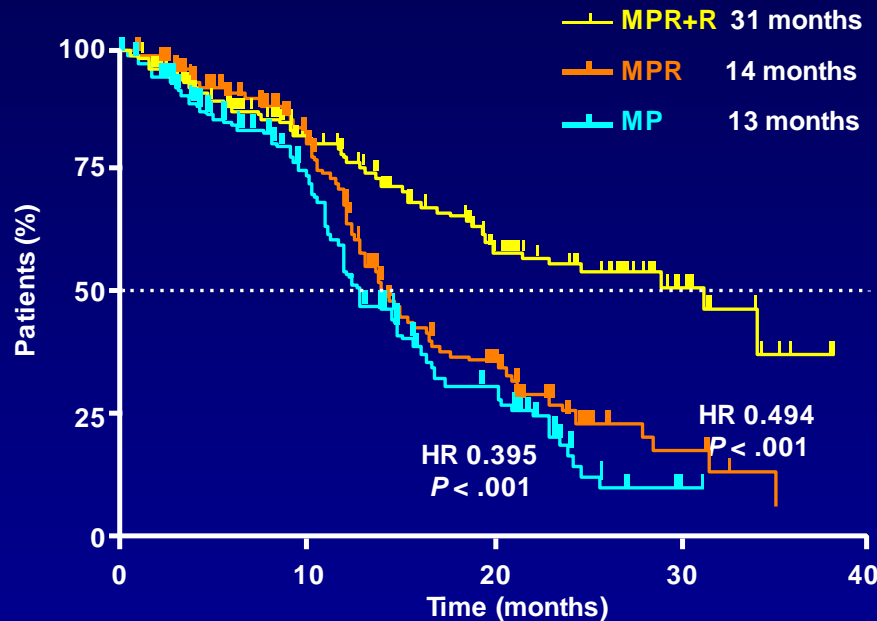
*Incidence Rate per 100 person years

MM-015: Sensitivity Analysis

Effect of SPM on PFS

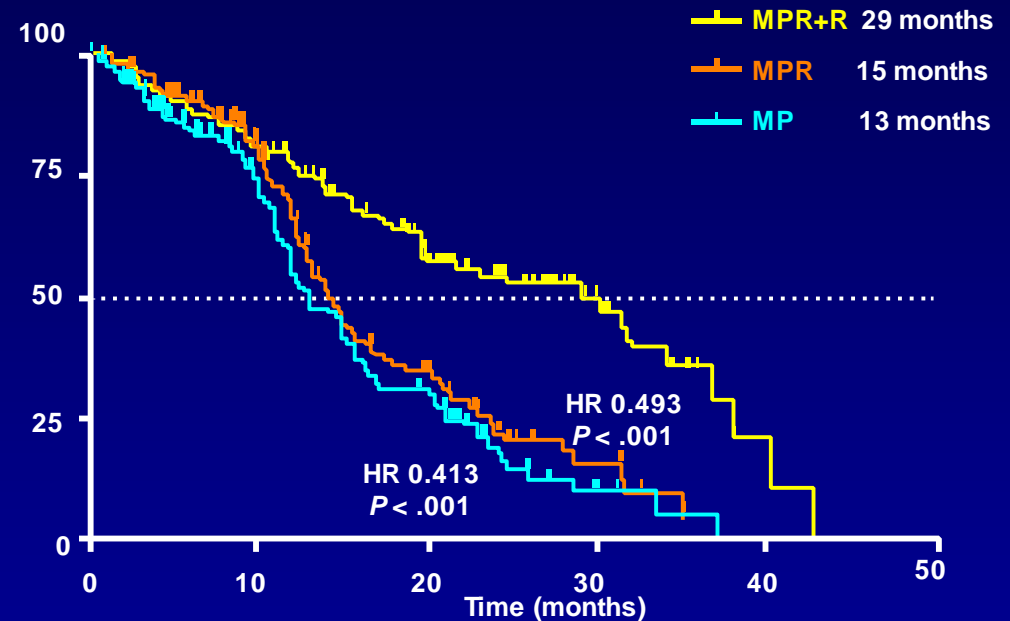
PFS

(Disease progression or death as event)



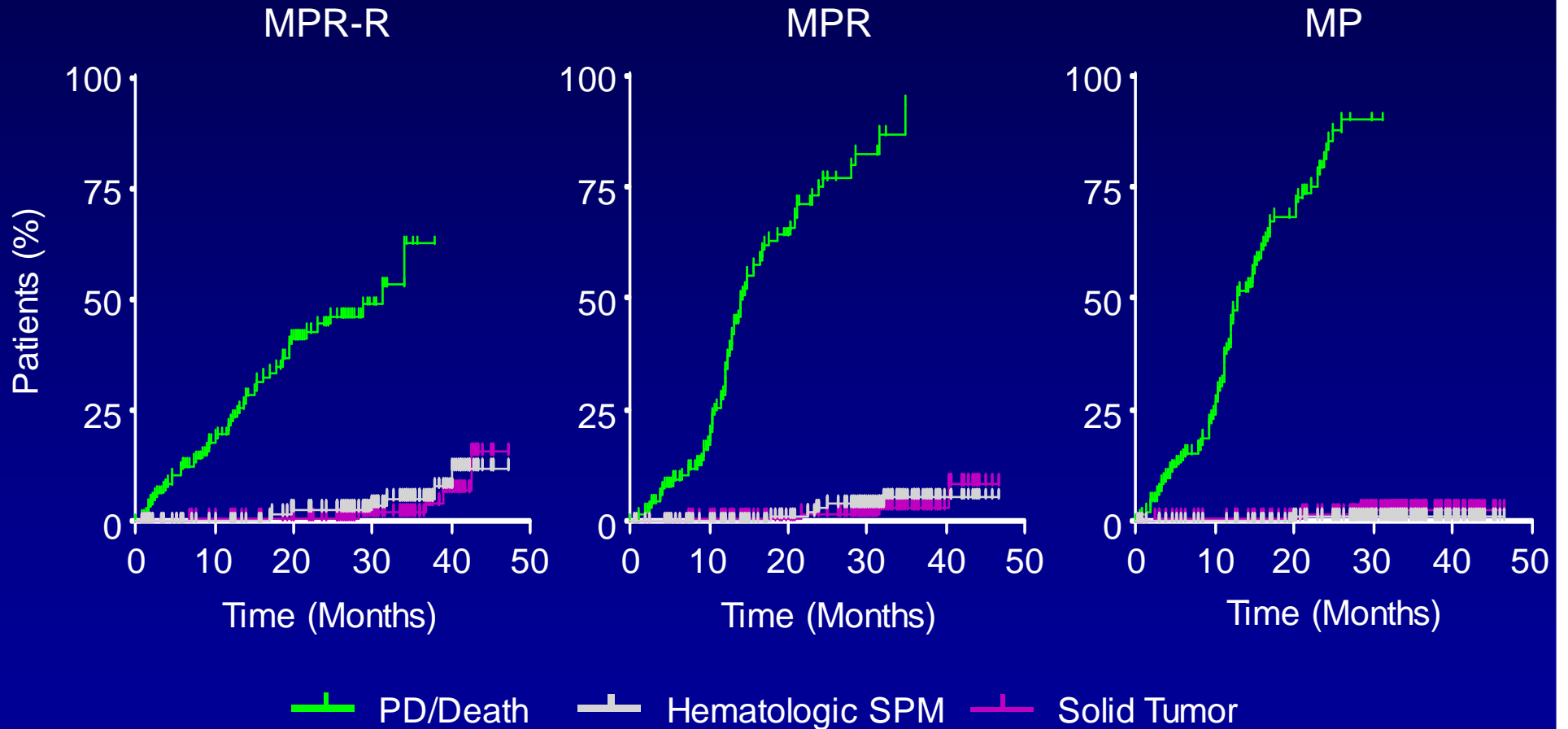
EFS

(Disease progression, death, or SPM as event)



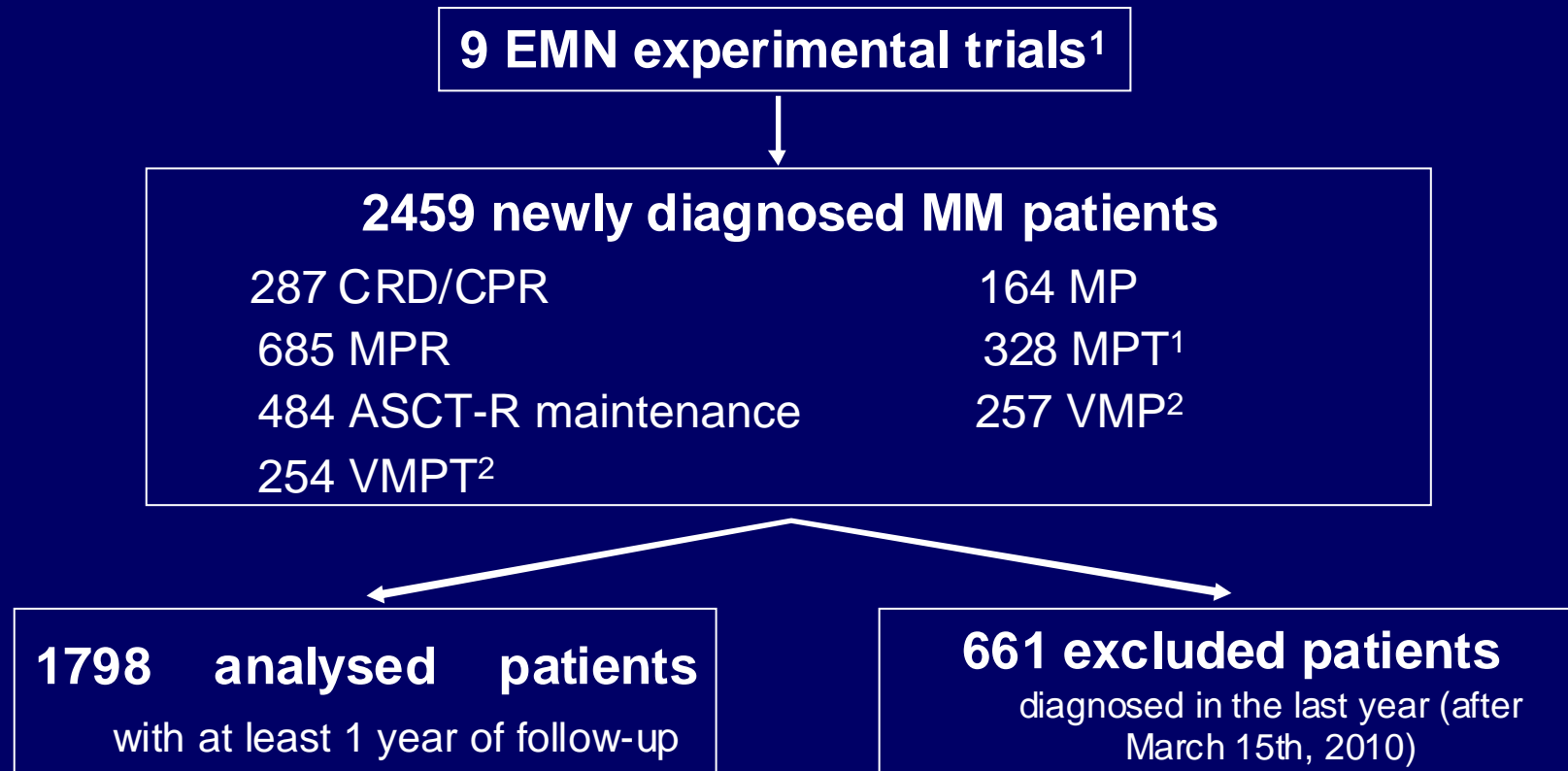
- Risk of death or disease progression at 2 years:
 - MPR-R: 45%; MP, 81%
- Risk of SPM at 2 years:
 - MPR-R: 3%; MP, 2%

Risk for SPM vs PD/Death (Safety Population)



MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; PD, progressive disease.

Retrospective study design



Times of observation were censored on March 15th, 2011

1. Palumbo A. *Blood*. 2008 Oct 15; 2. Palumbo A. *J Clin Oncol*. 2010 Dec 1; Gay F *Eur J Haematol*. 2010 Sep; Clinical trial.gov.

CRD, cyclophosphamide, lenalidomide, dexamethasone; CPR, cyclophosphamide, prednisone, lenalidomide; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; ASCT-R, autologous stem cell transplantation followed by lenalidomide maintenance; MPT, melphalan, prednisone, thalidomide; VMP, bortezomib, melphalan, prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide.

Patient characteristics

All analysed patients
(N=1798)

Age - median	69
< 65 years	32%
65-74 years	49%
≥ 75 years	19%
Male sex	51%
MM treatment	
Alkylating agents plus lenalidomide	30%
ASCT followed by lenalidomide	20%
No lenalidomide	50%
MP	9%
MPT	12%
VMP	14%
VMPT	14%

Alkylating agents, melphalan or cyclophosphamide; ASCT, autologous stem cell transplantation; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; VMP, bortezomib, melphalan, prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide.

Type of second primary malignancies

	All Patients (N=1798)	Alkylating plus Lenalidomide (N=534)	ASCT followed by lenalidomide (N=366)	No Lenalidomide (N=898)
SPMs	30 (1.66%)	6 (1.1%)	7 (1.9%)	17 (1.89%)
Hematologic SPMs	8 (0.44%)	1 (0.18%)	0	7 (0.77%)
ALL	1	1	0	0
AML	7	0	0	7
Solid SPMs	22 (1.22%)	5 (0.93%)	7 (1.91%)	10 (1.11%)
GI tract	7	0	3	4
Lung	6	1	2	3
Breast	4	1	1	2
Skin	2	1	1	0
Gynecologic	3	2	0	1

SPM, secondary primary malignancy; Alkylating agents, melphalan or cyclophosphamide; ASCT, autologous stem cell transplantation; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GI, gastrointestinal.

Incidence of second primary malignancies per 100 per year

Protocol	Median Follow-up (months)	Incidence (%)
All patients	27.7	0.72
Alkylating plus lenalidomide	20.4	0.66
ASCT followed by lenalidomide	26.4	0.87
No lenalidomide	33.8	0.67
MP	34.4	0.21
MPT	39.0	1.38
VMP	34.8	0.54
VMPT	34.4	0.28

Alkylating agents, melphalan or cyclophosphamide; ASCT, autologous stem cell transplantation; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; VMP, bortezomib, melphalan, prednisone; VMPT, bortezomib, melphalan, prednisone, thalidomide.

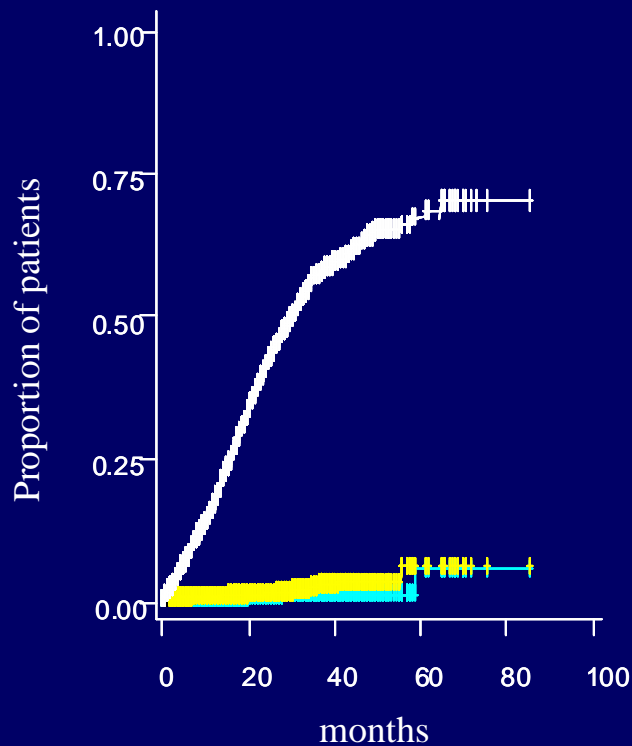
Type of second primary malignancies

Therapy	Type of SPMs	Sex	Age	Time (mo)	PFS (mo)
Alkylating+Len	Breast	F	72	56	74
	Prostate	M	66	9	68
	Prostate	M	67	35	68
	ALL	M	68	60	65
	Lung	M	73	56	15
ASCT+Len	Skin	M	69	11	11
	Lung	F	60	8	9
	GI	M	62	19	23
	GI	M	65	30	24
	Breast	F	47	32	33
	Skin	M	69	28	45
	Lung	M	61	41	46
	GI	F	66	42	54

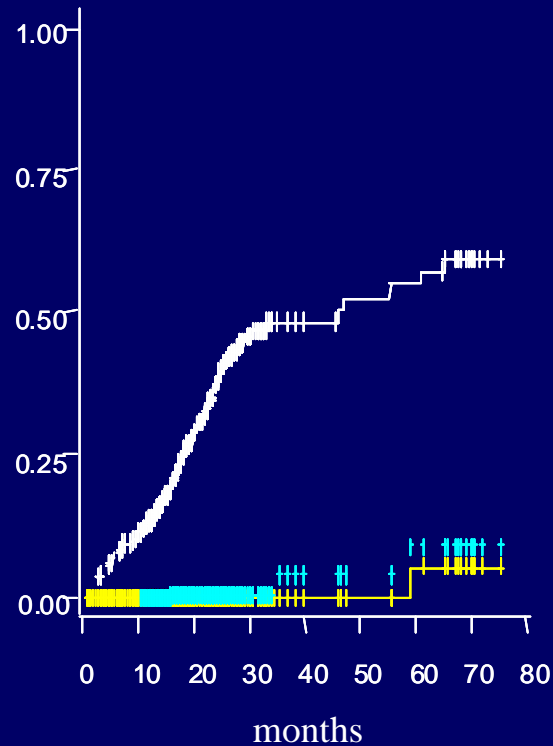
SPM, secondary primary malignancy; PFS, progression-free survival; Alkylating agents, melphalan or cyclophosphamide; ASCT, autologous stem cell transplantation; ALL, acute lymphocytic leukemia; GI, gastrointestinal; M, male; F, female.

Second primary malignancies and MM progression risk

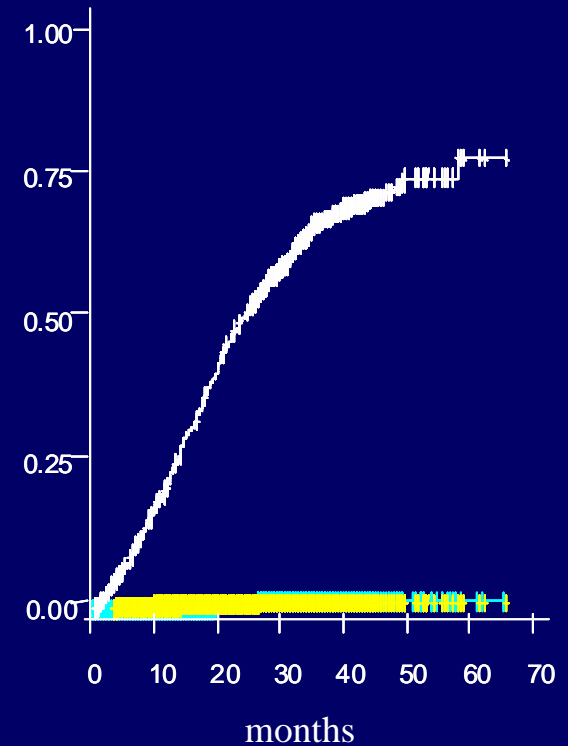
All patients



Lenalidomide



No Lenalidomide

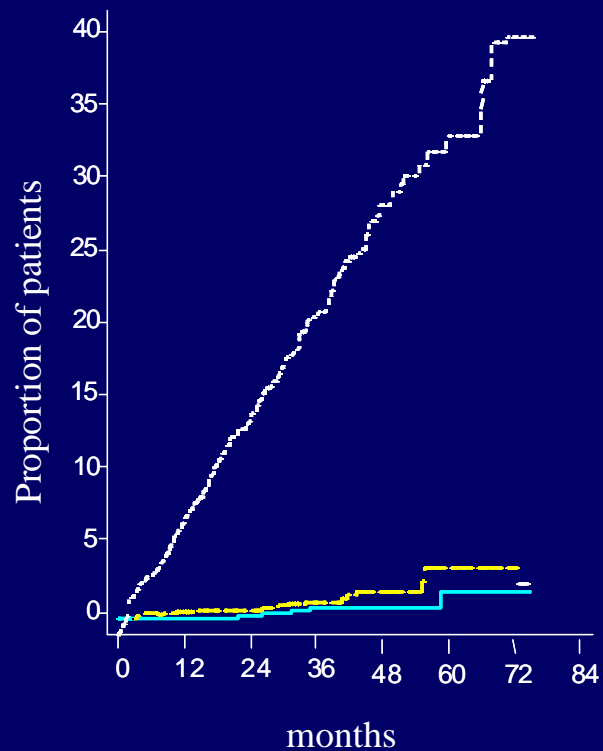


— Progression or death — Solid SPMs — Hematologic SPMs

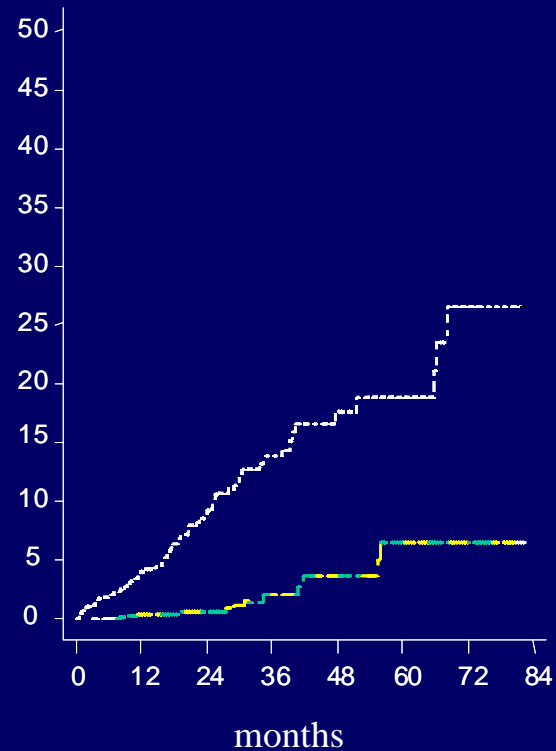
SPM, secondary primary malignancy.

Second primary malignancies and MM death risk

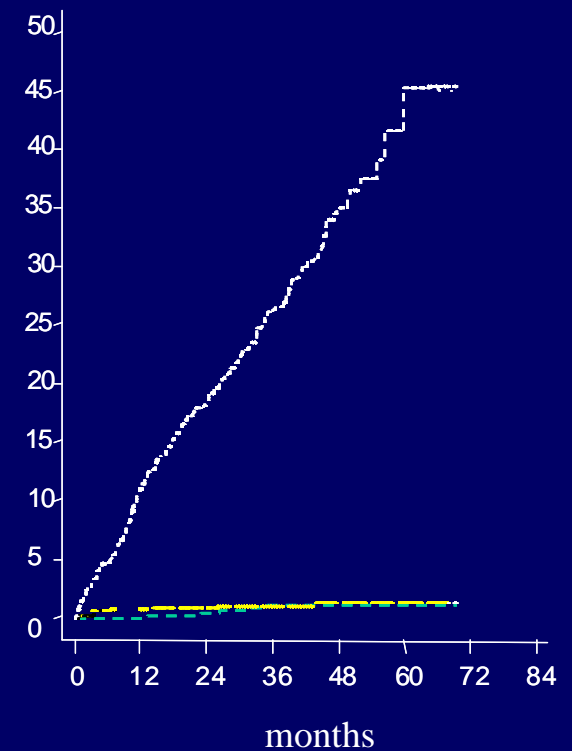
All patients



Lenalidomide



No Lenalidomide



— Death — Solid SPMs — Hematologic SPMs

SPM, secondary primary malignancy.

Comparison of observed to expected rate of second primary malignancies

SMPs observed in Italian patients

SMPs expected from Italian Cancer Registry (age- and sex-adjusted)

All patients	Observed	Expected	SIR	95% CI
All patients	27	48.11	0.56	0.37-0.82
Male	16	30.25	0.53	0.30-0.86
Female	11	17.86	0.62	0.31-1.10

Lenalidomide patients	Observed	Expected	SIR	95% CI
All patients	11	15.69	0.70	0.35-1.25
Male	8	9.20	0.87	0.38-1.71
Female	3	6.49	0.46	0.10-1.35

SPM, secondary primary malignancy; SIR, standardized incidence ratio; CI, confidence interval

Conclusions

- Longer follow-up is needed
- At present, observed and expected rates of SPMs are similar
- The risk of progression/death is higher than the risk of SPMs

We Are Grateful to All Patients, Nurses and Physicians of the Participating Centers

1. ALESSANDRIA	Levis, Baraldi	39. GENOVA	Carella, Spriano	77. RIMINI	Pasquini, Fattori
2. ANCONA	Leoni, Offidani	40. GENOVA	Bacigalupo, Dominietto	78. RIONERO VULTURE	Musto
3. AOSTA	Di Vito	41. IVREA	Giroto, Aitoro	79. RIETI	Capparella
4. ASCOLI PICENO	Galieni	42. LATINA	De Blasio	80. ROMA	Foà, Petrucci
5. ASTI	Favro, Ciravegna	43. LATINA	Cimino	81. ROMA	De Fabritiis, Caravita
6. AVELLINO	Cantore, Volpe	44. LECCE	Di Renzo	82. ROMA	Andriani
7. AVIANO	Tirelli, Rupolo	45. MATERA	Fragasso	83. ROMA	Annino, Bongarzoni
8. BARI	Vacca, Ria	46. MESSINA	Brugiatelli	84. ROMA	Leone, De Stefano
9. BARI	Liso	47. MESSINA	Musolino	85. ROMA	Petti, Pisani
10. BELLUNO	Pianezze	48. MILANO	Corradini, Montefusco	86. ROMA	Majolino, De Rosa
11. BENEVENTO	Di Lonardo, Vallone	49. MILANO	Morra	87. ROMA	Amadori
12. BERGAMO	Rambaldi, Galli	50. MILANO	Ciceri	88. ROMA	Avvisati
13. BOLOGNA	Baccarani, Cavo	51. MILANO	Lambertenghi, Baldini	89. ROMA	Recine
14. BOLZANO	Cortellazzo, Pescosta	52. MILANO	Gianni	90. ROZZANO	Santoro, Nozza
15. BRA	Vanni, Stefani	53. MODENA	Marasca	91. S. G. ROTONDO	Cascavilla, Falcone
16. BRESCIA	Rossi, Crippa	54. MODENA	Sacchi	92. SASSARI	Dore, Podda
17. BRESCIA	Russo, Malagola	55. MONZA	Pogliani, Rossini	93. SIENA	Lauria, Gozzetti
18. BRINDISI	Quarta	56. NAPOLI	Pane, Catalano	94. TARANTO	Mazza, Casulli
19. CAGLIARI	Angelucci, Derudas	57. NAPOLI	Ferrara	95. TERNI	Liberati
20. CAGLIARI	La Nasa, Ledda	58. NAPOLI	Mettivier	96. TORINO	Boccardo
21. CAMPOBASSO	Storti	59. NOCERA INF.	D'Arco, Califano	97. TORINO	Pregno, Benevolo
22. CANDIOLIO	Aglietta, Capaldi	60. NOVARA	Gaidano, Rossi	98. TORINO	Tarella, Gottardi
23. CATANIA	Di Raimondo	61. NUORO	Gabbas	99. TREVISO	Gherlinzoni
24. CATANZARO	Peta, Piro	62. ORBASSANO	Saglio, Guglielmelli	100. TRICASE	Pavone
25. CATTOLICA	Pasquini	63. PADOVA	Semenzato, Zambello	101. TRIESTE	De Sabbata
26. CESENA	Guardigni	64. PALERMO	Mirto, Cangialosi	102. UDINE	Fanin, Patriarca
27. CIRI'	Giroto, Freilone	65. PARMA	Rizzoli, Giuliani	103. VENEZIA	Chisesi
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31. FIRENZE	Bosi/Nozzoli	69. PESCARA	Fioritoni, Spadano	107. VICENZA	Rodeghiero, Elice
32. FOGGIA	Capalbo	70. PIACENZA	Cavanna, Lazzaro	108. VITERBO	Montanaro
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34. FROSINONE	Sala	72. PISA	Petrini/Benedetti	110. JERUSALEM	Ben Yehuda
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36. GENOVA	Gobbi, Canepa	74. RAVENNA	Zaccaria, Cellini	112. ZERIFIM	Komberg
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38. GENOVA	Gobbi, Canepa	76. REGGIO EMILIA	Gugliotta, Masini		