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Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients

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Summary. Many randomized trials have evaluated α-interferon as myeloma therapy, some suggesting a benefit and others not. Most were too small to give reliable answers, so a systematic overview has been performed to provide a more reliable estimate of the effect of interferon. The main end-points were response rates (induction trials), progression-free survival (PFS) and overall survival (OS). Individual patient data were supplied for 24 trials involving 4012 patients, 12 induction trials (2469 patients) and 12 maintenance trials (1543 patients). In induction, response rates were slightly better with interferon (57·5% versus 53·1%, $P = 0{\cdot}01$). PFS was better with interferon (33% versus 24% at 3 years, $P < 0{\cdot}00001$), an effect seen in both induction ($P = 0{\cdot}0003$) and maintenance ($P < 0{\cdot}00001$) trials. Median time to progression was increased by about 6 months in both settings. OS was somewhat better with interferon (53% versus 49% at 3 years, $P = 0{\cdot}01$) with median survival increased by about 4 months. This benefit was restricted to the smaller trials. The effect of interferon was not significantly related to the dose or duration of interferon or to patients' characteristics. PFS was improved with interferon, but the survival benefit, if any, was small and needs balancing against cost and toxicity.

Keywords: myeloma, interferon, response, progression, survival.

Although patients with multiple myeloma may respond at first to induction chemotherapy, most will eventually suffer progression and death from the disease, irrespective of whether single-agent or combination chemotherapy is used (Myeloma Trialists' Collaborative Group, 1998). *In vitro*, α-interferon (IFN) has an anti-proliferative effect on myeloma cells (Cooper & Welander, 1987), and there have been many randomized trials of its addition to induction chemotherapy or of its use as maintenance therapy for patients who have already responded to their initial cytotoxic treatment (Bataille & Harousseau, 1997). The majority of these trials have been too small to give reliable answers when taken alone. Most individual trials have not reported a significant improvement in survival, showing that IFN does not have a substantial effect on survival. It might, nevertheless, have a moderate, but still clinically meaningful, benefit (cf. tamoxifen as adjuvant therapy for breast cancer; Early Breast Cancer Trialists' Collaborative Group, 1998). To determine reliably whether or not this is the case, a systematic overview ('meta-analysis') of all available trials is needed. This should preferably involve a central review of the data on each individual patient in each of the trials, not just the review of the published results from those trials (Stewart & Parmar, 1993; Clarke & Godwin, 1998; Fritz & Ludwig, 2000). We report such an overview.

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Members who supplied data are listed in the Appendix.

PATIENTS AND METHODS

Standard procedures for overviews based on individual patient data (IPD) were followed (Stewart & Clarke, 1995). Trials in which patients with myeloma were randomized to interferon versus no interferon in either the induction or maintenance phases of therapy were sought in registers and databases [the Cochrane Controlled Trials Register, PDQ (Physician Data Query), MEDLINE and EMBASE]; in abstracts of haematology or oncology meetings; by scrutiny of reports of trials and review articles; and by contact with individual trialists, trial groups and pharmaceutical companies. The cut-off for trial identification was mid 1997.

Baseline data were requested for each randomized patient on date of diagnosis, date of birth (or age), sex, Durie–Salmon stage (Durie & Salmon, 1975), haemoglobin,

Table I. Presentation features of the individual data patient population.

	Induction trials			Maintenance trials		
	Number of patients			Number of patients		
Type of Patient	IFN	None	Percentage* of patients	IFN	None	Percentage* of patients
All patients	1230	1239	100	767	776	100
Age (years):						
< 50	111	101	9	88	80	11
50–59	212	227	18	173	186	23
60–69	492	517	41	320	298	40
70+	415	394	33	186	212	26
Sex:						
Female	559	557	45	353	336	45
Male	669	681	55	412	440	55
Durie–Salmon stage:						
I	76	85	7	66	59	8
II	482	490	39	146	155	20
III	637	626	51	377	396	50
Haemoglobin (g/dl):						
< 9·0	174	192	15	79	88	11
9·0–10·9	314	288	24	186	170	23
11·0–11·9	148	138	12	142	130	18
12·0+	212	205	17	269	279	36
White cell count ($\times 10^9$/l):						
< 5·0	266	261	21	357	337	45
5·0–7·4	293	293	24	194	207	26
7·5+	191	189	16	127	124	16
Platelets ($\times 10^9$/l):						
< 150	108	99	8	111	111	14
150–249	317	347	27	297	303	39
250+	322	291	25	261	252	33
β_2-microglobulin (mg/l):						
< 4·0	305	310	25	320	307	41
4·0–7·9	239	232	19	130	134	17
8·0+	132	140	11	65	66	8
Creatinine (μmol/l):						
< 100	329	314	26	393	394	51
100–129	173	174	14	164	145	20
130+	215	223	17	136	154	19
Calcium (mmol/l):						
< 2·5	345	361	29	435	413	55
2·5–2·9	279	253	22	163	174	22
3·0+	103	96	8	42	42	5
M-band type:						
IgA	266	256	21	198	212	27
IgG	653	683	54	433	425	56
Light chain	198	184	15	57	55	7
Other	22	15	1	33	41	5
Bone lesions:						
None	148	156	12	146	155	20
Minimal	278	290	23	139	130	17
Multiple	436	391	33	321	327	42
Performance status:						
Asymptomatic	178	190	15	134	141	18
Minimal symptoms	506	523	42	153	174	21
Symptomatic	145	124	11	48	21	4
Status at randomization:						
Complete response	—	—	—	360	344	46
Partial response	—	—	—	185	178	24
Stable disease	—	—	—	76	89	11

*Percentages may not add up to 100 either because of rounding or because of missing data (for example, performance status is known for 15 + 42 + 11 = 68% of patients in induction trials and is unknown for 32%).

Table II. Response rates in induction trials.

Study start year, code and name		Number of patients	Complete response* (%)		Complete plus partial response* (%)	
			IFN	None	IFN	None
85B	GATLA 3-M-85	84	5	0	39	35
85I	EMSG 1985	33	67	33	93	83
86I	Rome IFN 1	50	41	21	95	68
86J	MGCS 1986	334	—	—	64	41
87E	EMSG 2 (I)	256	22	19	56	51
87O	Royal London	34	24	6	47	24
88A	ECOG 9486	485	18	10	66	64
89H	KIF, Avicenne	282	10	16	67	69
90D	NMSG 04–90	583	7	7	44	45
90H	ALSG Myeloma II	113	3	7	41	48
90J	Italian NHLSG (I)	67	53	55	72	68
91B	GMM (I), Mexico	148	41	29	53	55
Total		2469	17·1	13·7	57·5	53·1
Statistical tests:						
Observed-expected			17·8		26·3	
Variance			62·7		145·6	
Increase in odds of response			25%		17%	
Effect *P*-value			0·02		0·03	
Test for heterogeneity between trials			$X^2_{10} = 16{\cdot}7, P = 0{\cdot}08$		$X^2_{11} = 24{\cdot}2, P = 0{\cdot}01$	

*Response criteria were those used by each group.
References for each trial are listed in the Appendix.

platelets, white blood count, β_2-microglobulin, M-band type, creatinine, calcium, albumin, bone lesions, performance status, date of randomization and allocated treatment (data were not available for other parameters, e.g. cytogenetics, C-reactive protein, plasma cell labelling index). The data requested on events after randomization were type (complete or partial) and date of response, progression and its date, most recent status (dead or alive) and date of death or date of last follow-up. The data were checked for obvious inconsistencies and were amended as necessary through correspondence with the responsible trialists. The data used in the analyses were confirmed with the responsible trialists. This manuscript was circulated to all relevant trialists and amended in the light of their comments.

Statistical methods. All analyses presented are by allocated treatment (intention to treat). The main statistical methods for combining trials are described in detail elsewhere (Early Breast Cancer Trialists' Collaborative Group, 1990). To summarize, the number of events observed (O) in the interferon group of each trial is compared with the number expected (E) if the events in that trial had been equally distributed between the interferon and no interferon groups. The difference between these numbers, O − E, and its variance yields the log-rank test for each trial. The individual patient data allow these statistics to be calculated using the exact dates of events, which is more statistically reliable and clinically informative than basing the calculations on proportions alive at a particular point in time (Stewart & Parmar, 1993). The sum of the statistics for each trial provides the overall statistics, which are then used to calculate reductions in the odds of death. All *P*-values are two-tailed. Analyses were first performed in October 1997, with updated analyses over the subsequent few months as data queries were clarified.

The main end-points analysed were: (i) overall survival, (ii) complete response (CR) and complete plus partial response (PR) rates, for induction trials, (iii) progression-free survival, defined either as the time from response to recurrence (in induction trials) or as the time from randomization to recurrence or progression (in maintenance trials) ignoring (i.e. censoring at) death without recurrence or progression, and (iv) survival from progression. The criteria for CR and PR were those used in each individual trial. Response duration was also analysed, and was defined in the same way as progression-free survival except that deaths without recurrence were included as events.

RESULTS

Trials and patients

Thirty-six trials that compared IFN with control were

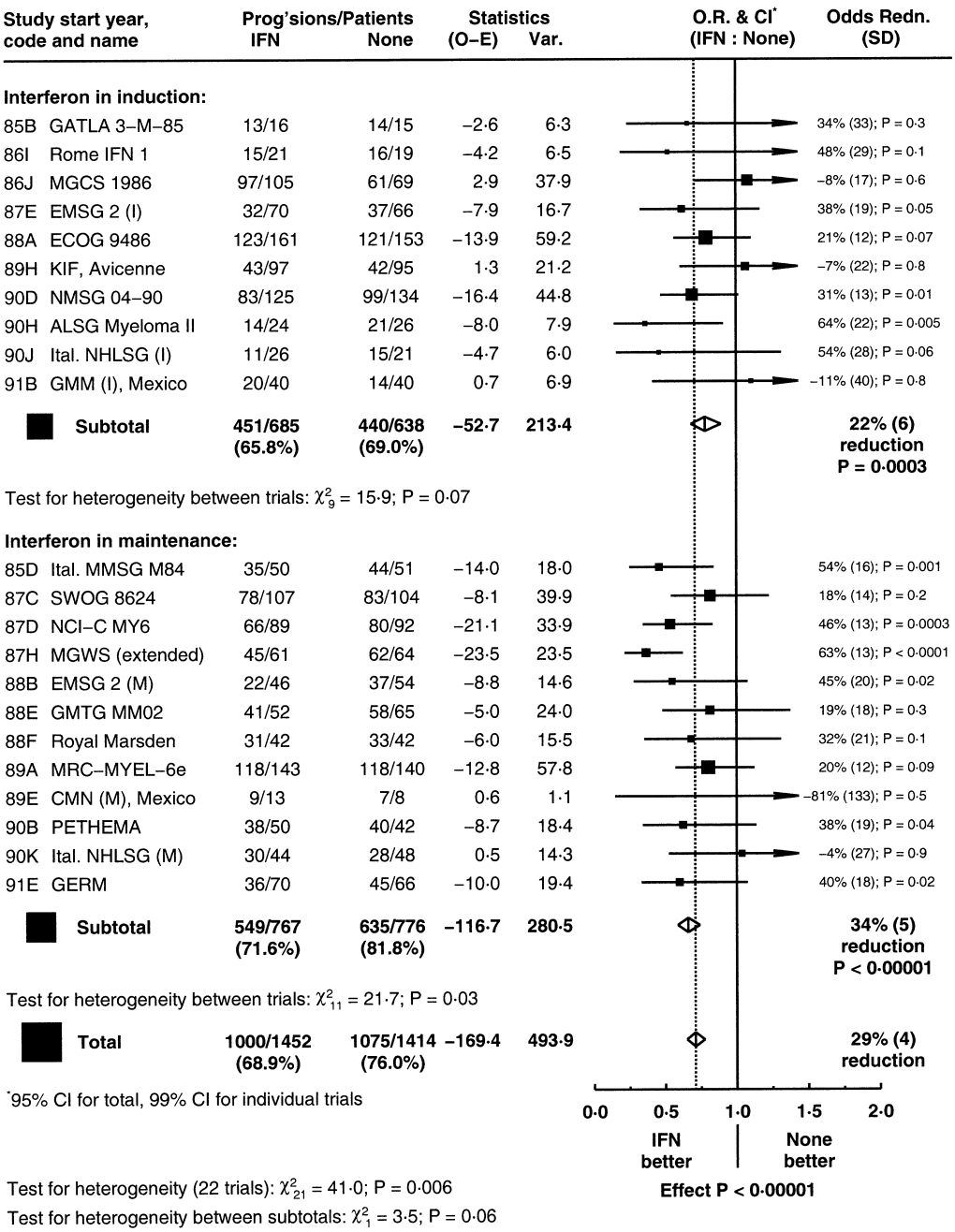

Fig 1. Progression in trials of interferon (IFN) versus none. Large squares indicate trials that provide more information and hence have narrower 99% confidence intervals (CI). If the square is to the left of the solid line then progression-free survival is better in the group allocated IFN, but if the CI crosses this line then this result is not statistically significant ($P < 0{\cdot}01$). An arrow at the right-hand end of the CI indicates that the CI extends further than the plotting area. The subtotals for induction and maintenance trials separately and the overall total are represented as diamonds centred on the odds ratio (OR) estimate, with 95% CI shown by the width of the diamond and with the odds reduction also given as a percentage along with its standard deviation (SD). Vertical dotted lines show the overall odds ratio estimate, i.e. the centre of the diamond. References for each trial are listed in the Appendix.

identified, involving about 4900 patients. Details of these are given in the Appendix. In some of the induction trials, interferon was continued into the maintenance phase (see Appendix). Individual patient data were supplied from 25 trials (4066 patients): 12 in induction (2469 patients) (Preis *et al*, 1989; Montuoro *et al*, 1990; Corrado *et al*, 1991; Aitchison *et al*, 1993; Österborg *et al*, 1993; Capnist *et al*, 1994; Ludwig *et al*, 1995; The Nordic Myeloma Study Group, 1996; Joshua *et al*, 1997; Oken *et al*, 1999; GMM(I), Mexico trial, unpublished observations, presented as an

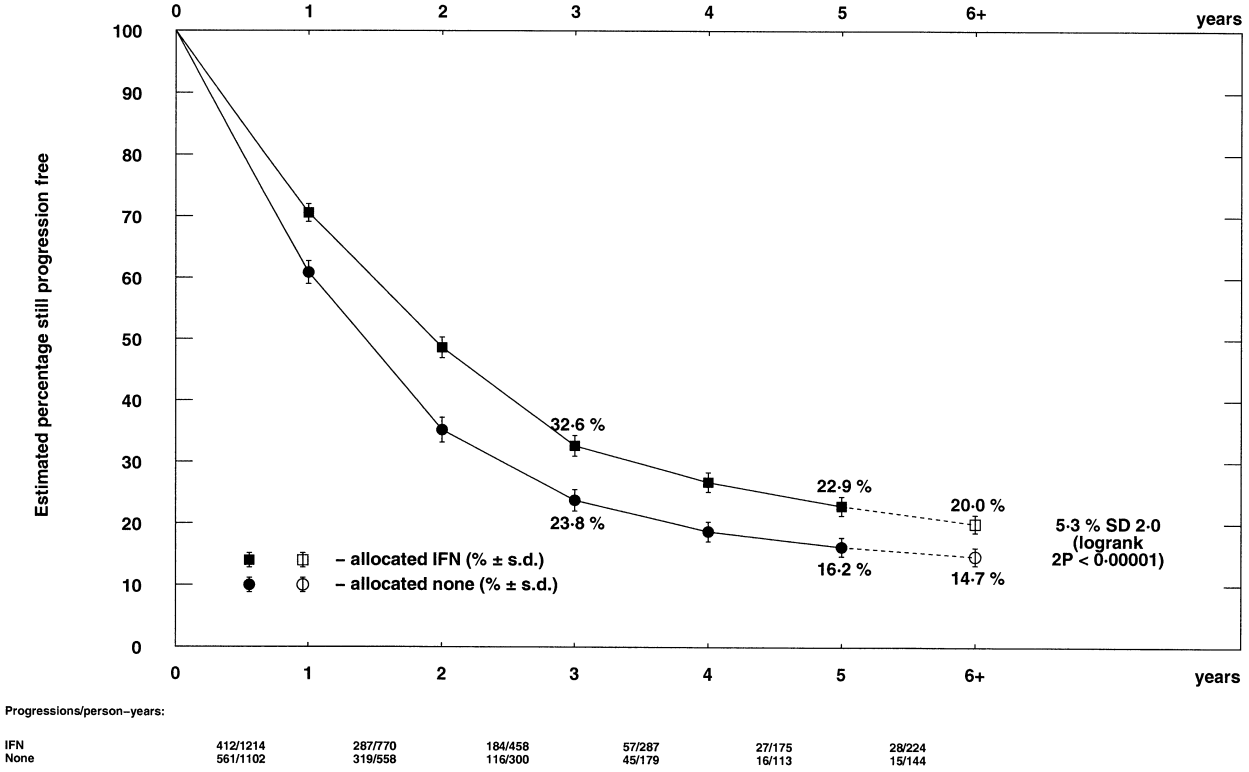

Fig 2. Progression-free survival in trials of interferon (IFN) versus none. Median progression-free survival was 23 months with IFN and 17 months without. Because of the small number of patients at risk, events beyond year 5 are combined.

abstract at the IV International Workshop on Multiple Myeloma, 1993; KIF, Avicenne trial, unpublished observations, poster 5-1, presented at the VI International Workshop on Multiple Myeloma, Boston, 1997), 12 in maintenance (1543 patients) (Aviles *et al*, 1991; Capnist *et al*, 1994; Salmon *et al*, 1994; Browman *et al*, 1995; Ludwig *et al*, 1995; Peest *et al*, 1995; Westin *et al*, 1995; Grosbois *et al*, 1997; Bladé *et al*, 1998; Cunningham *et al*, 1998; Drayson *et al*, 1998; Pulsoni *et al*, 1998) and one in refractory and relapsed disease (54 patients: as these small numbers do not permit reliable analysis, this trial is not considered further) (Gertz *et al*, 1995). Table I summarizes the presentation features of the 4012 patients in these induction and maintenance trials. There was generally good balance across treatment arms.

Response

Both complete response and complete plus partial response rates were slightly, but significantly, better with IFN (Table II).

Outcome after response

For patients who responded in induction trials, the response duration was significantly better with IFN than without (30% versus 25% at 3 years, log-rank $P = 0{\cdot}0005$). Similarly, for all patients in maintenance trials, response duration was better with IFN than without (27% versus 19% at 3 years, log-rank $P < 0{\cdot}00001$). For induction and maintenance trials together, response duration at 3 years was 28% with IFN and 20% without (log-rank $P < 0{\cdot}00001$). Among those who had not yet suffered disease progression, the death rates (expressed as deaths/person-years) did not differ significantly between the IFN and control groups: 5% versus 6% in induction trials ($P = 0{\cdot}7$) and 3% versus 4% in maintenance trials ($P = 0{\cdot}5$). There was, however, a definite effect of IFN on time to progression (censoring at death without progression) (Figs 1 and 2), both in induction trials ($P = 0{\cdot}0003$) and in maintenance trials ($P < 0{\cdot}00001$). Median time to progression was increased with IFN by about 6 months in both groups of trials, with large reductions in the risk of progression both in year 1 and in year 2 [odds reductions: 35% (SD 5) and 38% (SD 7), respectively, both log-rank $P < 0{\cdot}00001$]. There was no evidence of any additional benefit beyond year 2, but there was also no evidence that the early benefit was lost [odds increase 2% (SD 12), log-rank $P = 1{\cdot}0$], based on analysis from the start of year 3.

Survival from progression

Overall, survival from progression was worse for patients who had been allocated IFN than for control patients (22% versus 26% 3 years later, log-rank $P = 0{\cdot}02$). Although this was significant only in the maintenance trials (odds ratio 1·21, $P = 0{\cdot}007$) and not in the induction trials (odds ratio 1·04, $P = 0{\cdot}6$), this apparent difference between these two groups of trials could well be largely or wholly owing to

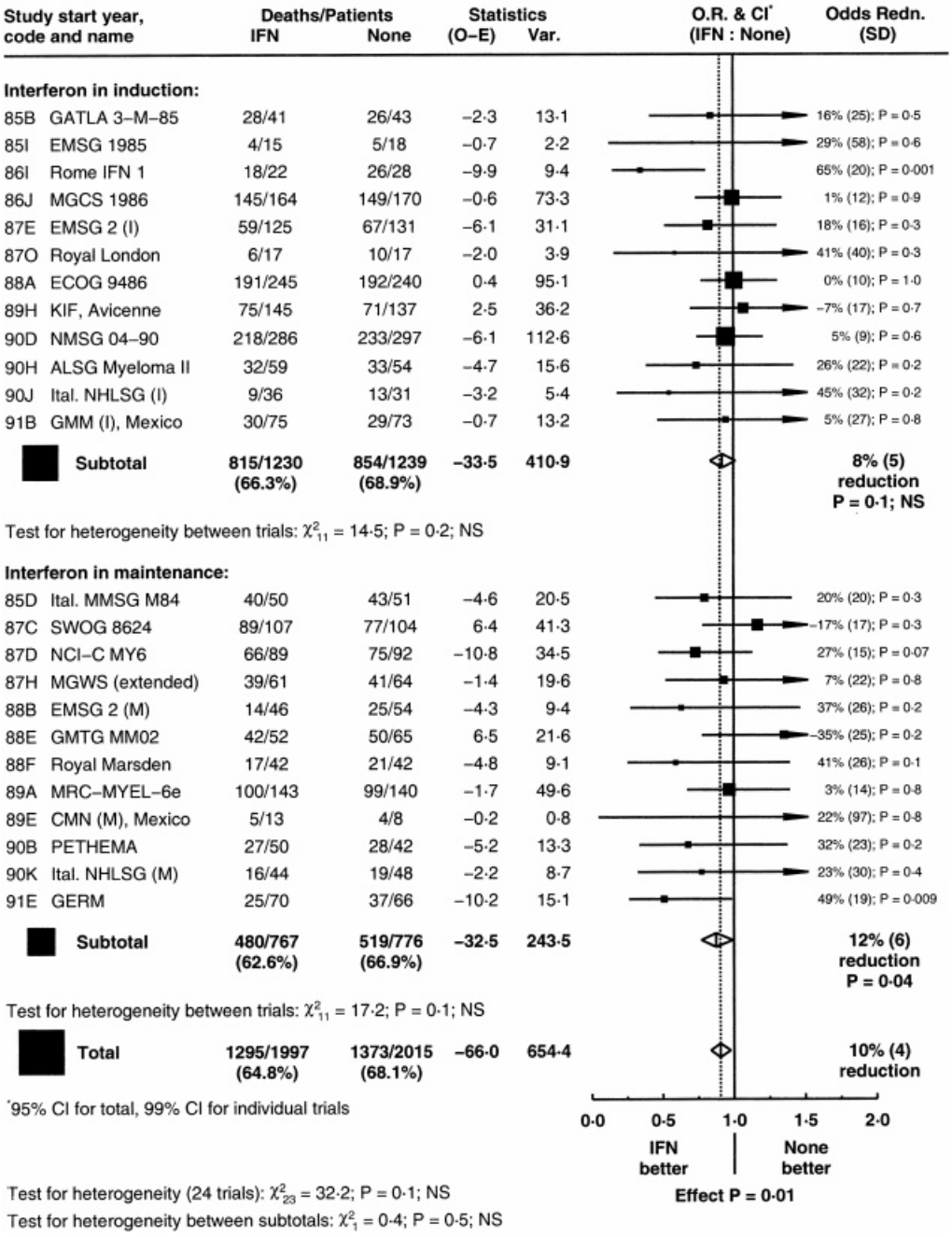

Fig 3. Mortality in trials of interferon (IFN) versus none. Format as Fig 1.

chance, as there was no significant heterogeneity between the two results ($P = 0{\cdot}2$).

Overall survival

Survival was significantly [odds reduction 10% (SD 4), log-rank $P = 0{\cdot}01$] improved with IFN (Figs 3 and 4). Although there was not a statistically significant benefit in the induction trials [odds reduction 8% (SD 5), log-rank $P = 0{\cdot}1$], while there was in the maintenance trials [odds reduction 12% (SD 6), log-rank $P = 0{\cdot}04$], there was again no significant heterogeneity between these two results ($P = 0{\cdot}5$). Increases in median survival of about 2 and 7 months were observed in the induction and maintenance trials, respectively, with overall an increase of about 4 months.

Subgroup analyses

Subgroup analyses were performed to explore whether the benefit of IFN was greater for some patients than for others, and whether IFN was superior in particular therapeutic situations.

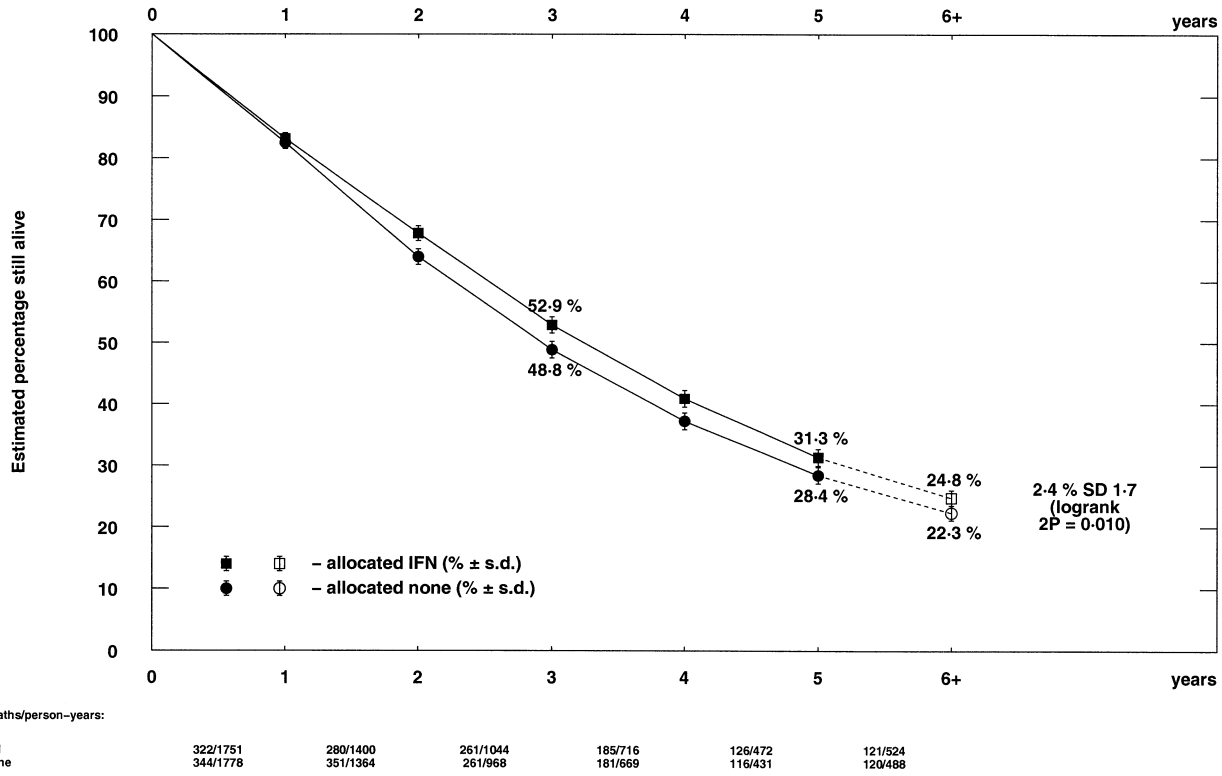

Fig 4. Survival in trials of interferon (IFN) versus none. Format as Fig 2. Median survival was 40 months with IFN and 36 months without.

Types of patient

The relative benefit of IFN on time to progression for the 12 presentation parameters listed in Table I is shown in Fig 5. There was no evidence, from any of these variables, that the benefit of IFN was importantly greater or worse in either good- or poor-risk patients. When the induction and maintenance trials were analysed separately, there was similarly no evidence of important differences between types of patient in their response to IFN within either category of trials. Nor was there evidence of heterogeneity between patient groups with respect to survival, either overall or within induction and maintenance trials separately (data not shown). In the maintenance trials, there was no evidence that the benefit of IFN differed between patients who were in CR, in PR or who had stable disease at the time of randomization (Fig 6).

Type of therapy

The trials can be grouped by certain features of their designs: for example, dose of IFN, duration of IFN, and type of concurrent or prior chemotherapy. This yielded no significant heterogeneity with respect to progression (Fig 7), or with respect to response rate (in the induction trials) or overall survival. There was one feature of the trials that produced a substantial trend, namely that the magnitude of the benefit of IFN on mortality was much greater in small trials than in larger ones (Fig 8), with no clear benefit for IFN in the latter. Similarly, there was a trend for the effects of IFN on progression-free survival to be better in the smaller trials, although there was still a significant benefit in the larger trials (Fig 8).

Trials for which individual patient data were not supplied

It was possible to extract data on response rates from reports of a further five trials (Cooper *et al*, 1993; Aviles *et al*, 1995; Rome IFN2 and Spanish Coop Group trials, unpublished observations, presented as abstracts, p299 and p301, at the 24th Congress of the International Society of Haematology, London, 1992; Buenos Aires trial, unpublished observations, presented as an abstract, p321, at the 18th International Congress of Chemotherapy, Stockholm, 1993), for two of which an estimate of the survival benefit could also be made. Inclusion of these data did not materially alter the results, with the benefit of interferon on both response rates and overall survival becoming slightly greater.

DISCUSSION

Overall effect of interferon

This overview of 24 randomized trials, using individual patient data, does demonstrate some clinical benefit for interferon as a treatment for myeloma. Response rates were slightly better when interferon was used during induction treatment (although the definition of response varied between studies, this analysis is valid as patients allocated interferon are only compared with controls in the same

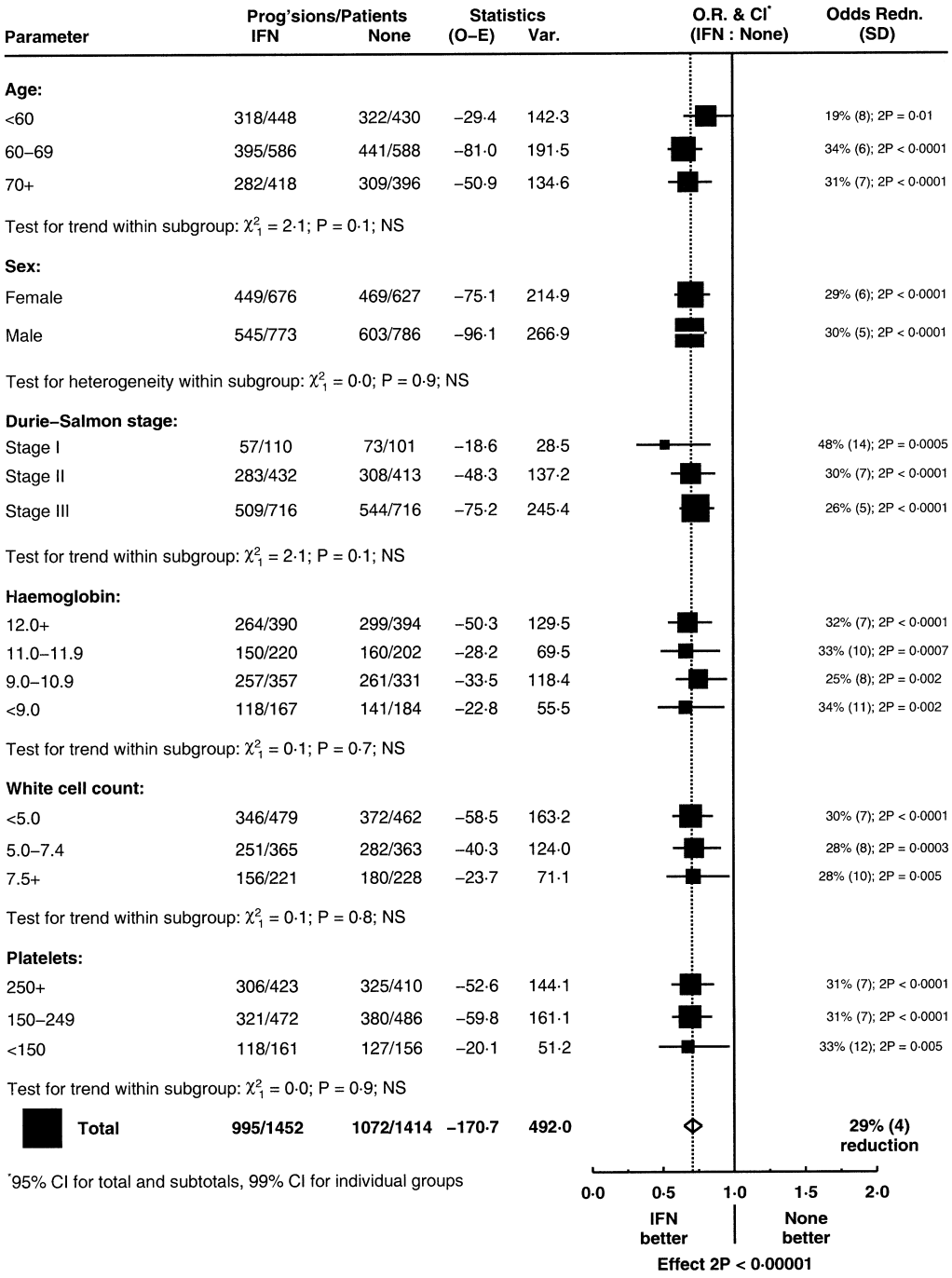

Fig 5. Progression in trials of interferon (IFN) versus none by patient presentation features. Format as Fig 1.

trial). Also, in both induction and maintenance trials, progression of the disease was delayed. Once progression did occur, subsequent survival was slightly worse in those previously given interferon, so the effect on progression was greater than the effect on survival. Overall therefore, there was at most only a small survival benefit.

There is a suggestion that the progression-free survival curve for the interferon arm might be showing a plateau consistently above that in the control arm (Fig 2), but the number of patients at risk beyond 3 years is still relatively small and longer follow-up will be required to determine reliably whether this really is the case. There is currently no apparent plateau in the survival curve (Fig 4).

The results presented here, based on intention-to-treat analyses of all randomized patients, will underestimate the true potential benefit of interferon as there will have been a

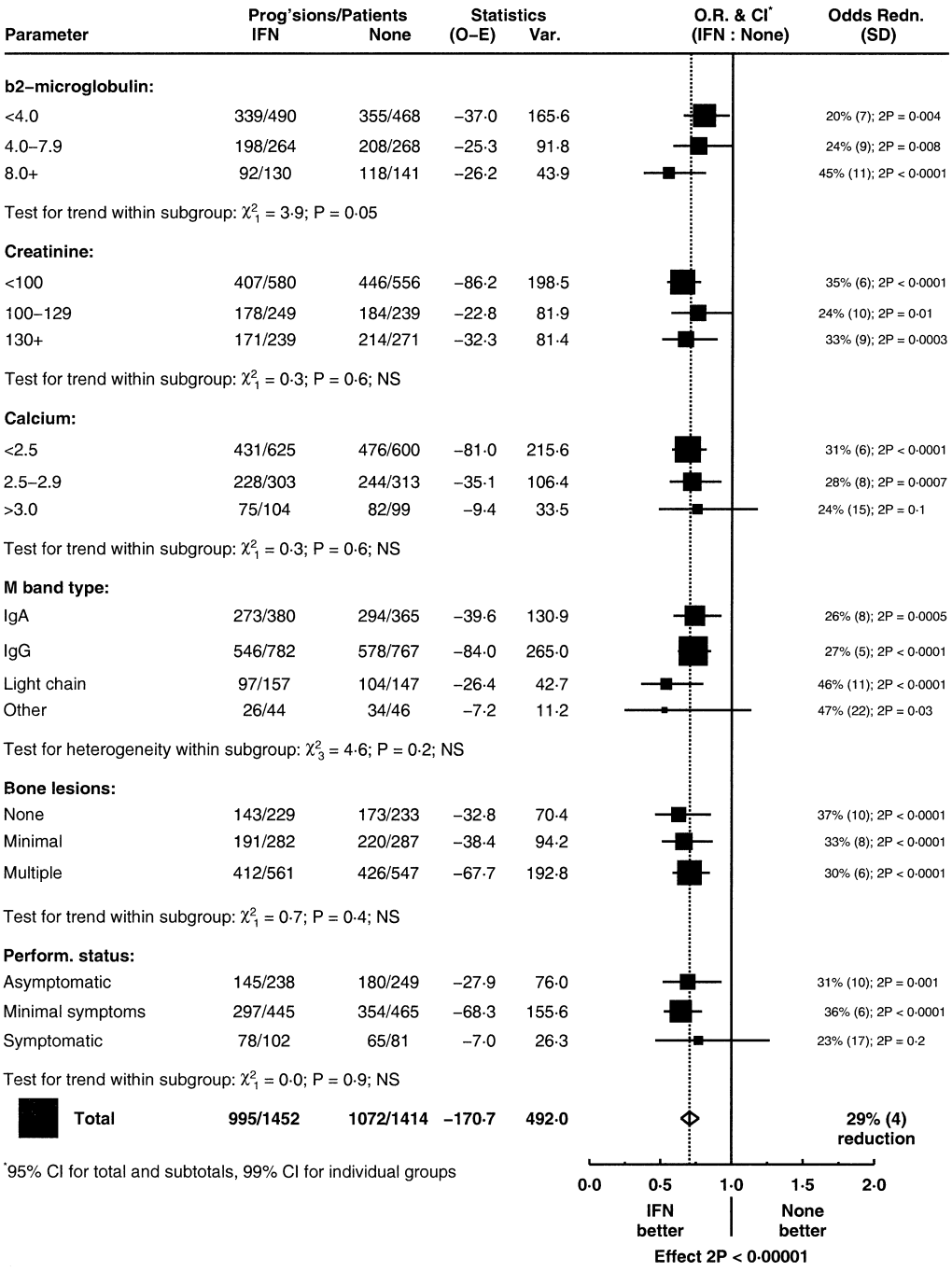

Fig 5. Continued.

degree of non-compliance with allocated treatment. However, this has the advantage that it represents the situation in regular clinical practice in which, inevitably, some patients will stop taking a drug that has side-effects.

A recent meta-analysis based on published data (Fritz & Ludwig, 2000) showed similar results to those reported here, with estimates of a 6·6% better response rate with interferon and median improvements of 4·6 months in relapse-free and 3·7 months in overall survival respectively (cf. 4·4%, 6 months and 4 months, respectively, in the present report). IPD overviews are much more time-consuming and labour-intensive than published data meta-analyses, but have a number of advantages. These include being able to assess trial quality, to include all randomized patients, to use updated data with longer follow-up, to investigate effects over time, to allow more

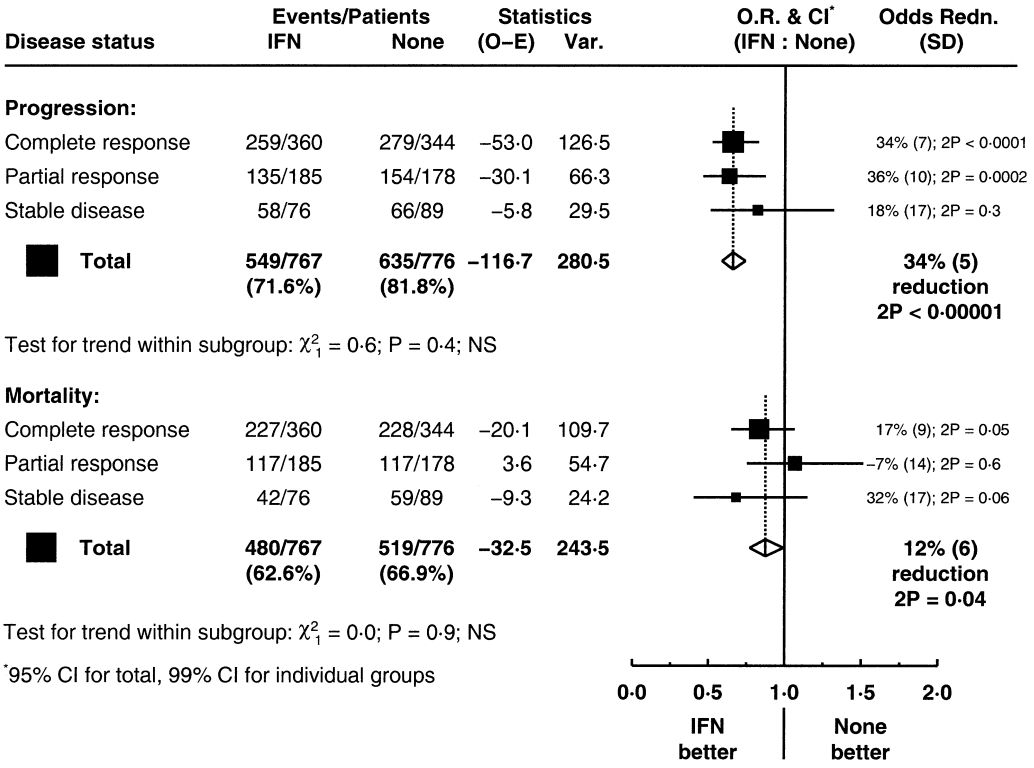

Fig 6. Outcome in maintenance trials by disease status at entry. Format as Fig 1.

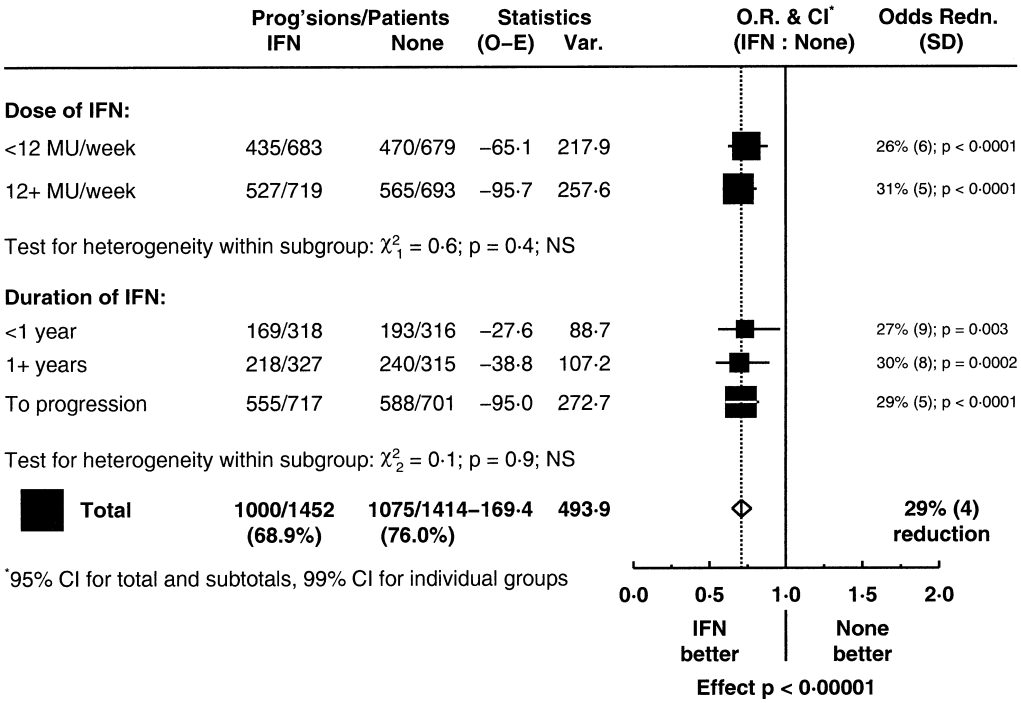

Fig 7. Progression in trials of interferon (IFN) versus none by scheduled dose and duration of interferon. Format as Fig 1. The cut-off points between higher and lower dose categories were selected so that about half the trials were in each group.

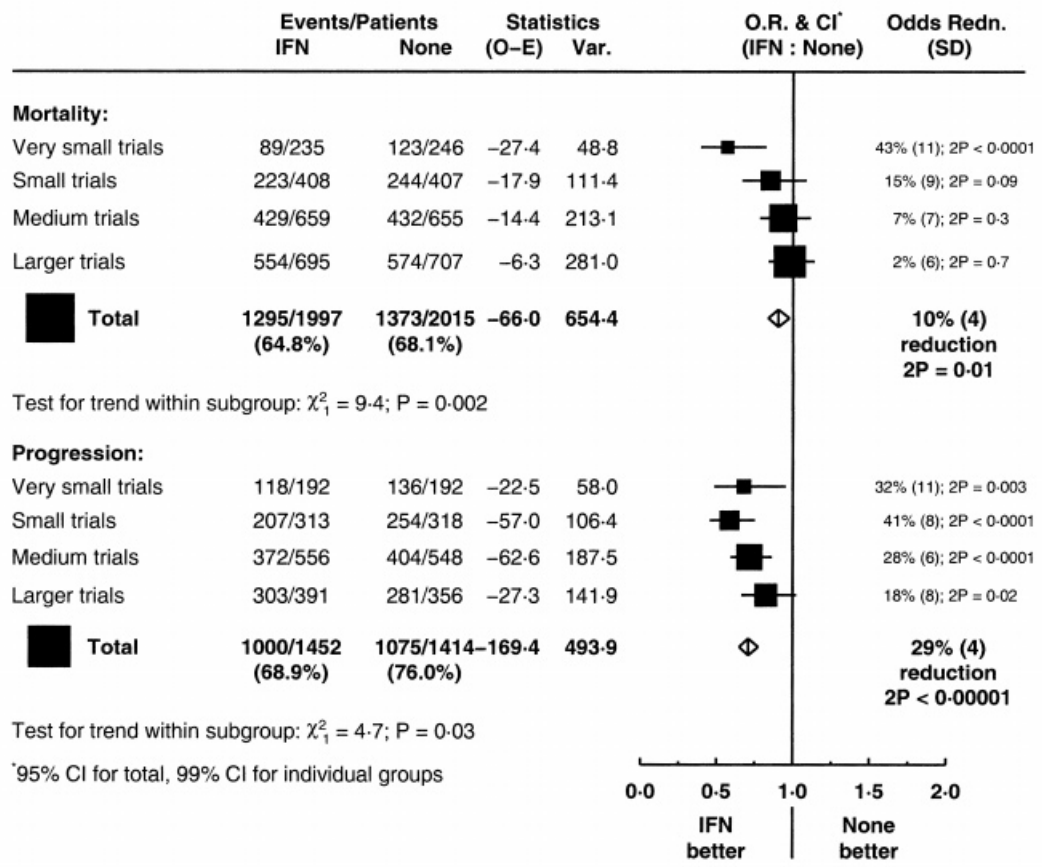

Fig 8. Effect of trial size on effect of interferon (IFN). Format as Fig 1. Trial size was defined by the variance obtained in the mortality analysis (with the number of deaths in parentheses): very small = 0–9·9 (9–39), small = 10·0–19·9 (54–80), medium = 20·0–49·9 (116–199), large = 50·0+ (294–451).

flexibility of patient subgroup analyses, to permit a consensus paper approved by all relevant trialists and, in this case, to use more standard meta-analysis methods.

A tendency for the smaller trials to indicate a greater survival benefit has also been seen in clinical trials in other diseases (CLASP Collaborative Group, 1994; Fourth International Study of Infarct Survival Collaborative Group (ISIS-4), 1995). The reasons are unclear, but one possible explanation is that there is a publication bias in which unpromising results from small trials never get reported, while promising ones do (Egger *et al*, 1997). We have vigorously sought to identify, and obtain data from, unpublished studies and so this seems unlikely to be a substantial source of bias. Another potential source of bias in smaller trials is less rigorous application of appropriately strict randomization procedures, but as protection against this we have obtained and extensively checked individual patient data from each trial without finding any indication of problems. Inclusion of published data from the five induction trials without IPD did not change the results or their interpretation in any important fashion. Two of the three maintenance trials with no data available were more recent studies that were still open, so this reason for exclusion is unlikely to introduce a bias. If there is any publication bias, or if the smaller studies are for some reason less reliable, then the true survival benefit for interferon would be even less than that observed, and there might actually be little or no benefit. This effect of trial size is the only factor identified that might explain some of the heterogeneity observed between trials (Fig 1), as there are no clear differences in the effect of interferon between patient types and trial designs (see below).

Effect of interferon in different types of patient

Although the overall benefit of interferon is relatively modest, there might be recognizable subgroups of patients who gain larger or smaller benefits from interferon. Twelve prognostic factors have been investigated, but there was no evidence that the benefit of interferon differed substantially between types of patients. In particular, there was no evidence that good-risk patients obtained a greater benefit than poorer-risk ones, or that patients in complete response at the time of maintenance randomization benefited more than those in partial response or with stable disease. With multiple comparisons being performed, it is probable that the effect of IFN will appear larger or smaller in some subgroups simply owing to the play of chance. It cannot therefore be concluded that patients with high β_2-microglobulin or light

Appendix. Details of trials of interferon as therapy for myeloma.

Year code	Trial name	Reference	Entry period	Scheduled IFN dose	Scheduled IFN duration	Prior/concurrent chemotherapy
Induction trials with individual patient data supplied						
85B	GATLA 3-M-85	Corrado *et al*, 1991	1985–89	5 MU/m^2 s.c. d 1,3,5,8,10,12/28 d	1 year	MP
85I	EMSG 1985	Preis *et al*, 1989	1985–86	2 MU × 5/w	6–12 months	VMCP
86I	Rome IFN 1	Montuoro *et al*, 1990	1986–88	5 MU d 1,3,5,8,10,12/28 d	2 years or progression	MP
86J	MGCS 1986	Österborg *et al*, 1993	1986–91	7 MU/m^2 d 1–5/21 d to response then 3 MU/m^2 3 d/w to progression	To progression	MP
87E	EMSG2 (I)	Ludwig *et al*, 1995	1987–93	2 MU × 5/w	To CR +3 cycles, PR +6 cycles, or stable disease +9 cycles	VMCP
87O	Royal London	Aitchison *et al*, 1993	1987–90	3 MU × 3/w w 1,2/3 w	If no response by 3 months change to 2nd line treatment	C
88A	ECOG 9486	Oken *et al*, 1999	1988–92	5 MU/m^2 × 3/w (w 1–3/6 w)	2 years	VBMCP
89H	KIF, Avicenne	Poster presentation, VI International Workshop on Multiple Myeloma, 1997	1989–95	3 MU/m^2 × 3/w in 2 w between 3 w courses	To plateau	VMCP/VBAP
90D	NMSG 04–90	The Nordic Myeloma Study Group,1996	1990–92	5 MU × 3/w	To failure	MP
90H	ALSG Myeloma II	Joshua *et al*, 1997	1990–92	3 MU 5d/w from 3rd month	To progression	CBAP
90J	Italian NHLSG (I)	Capnist *et al*, 1994	1990–92	3 MU × 3/w	9 months	MP
91B	GMM (I), Mexico	Abstract presentation, IV International Workshop on Multiple Myeloma, 1993	1991–97	5 MU d 1,3,5,7,9,11,13,15,17	?	MP or VMCP
Induction trials with no individual patient data received, but published data available						
85A	CALGB 8415	Cooper *et al*, 1993	1985–89	2 MU/m^2 d 1,3,5,8,10,12/28 d	2 years	MP
87L	CMN (I), Mexico	Aviles *et al*, 1995	1987–90	5 MU × 3/w	1 year	VMCP, CVNP, BEVD
88I	Buenos Aires	Abstract presentation, 18th International Congress of Chemotherapy, 1993	1988–92	5 MU × 3/w	To progression	VBAP
89G	Rome IFN 2	Abstract presentation, 24th Congress of the International Society of Haematology, 1992	1989-?	6 MU d1,3,5,8,10,12	?	MP
90G	Spanish Coop Grp	Abstract presentation, 24th Congress of the International Society of Haematology, 1992	199?	7 MU/m^2 5 d/21 d to response	To progression then 3 MU/m^2 3 d/7 d	MP
Maintenance trials with individual patient data supplied						
85D	Italian MMSG M84	Pulsoni *et al*, 1998	1985–88	3 MU/m^2 × 3/w	To progression	VMCP and VBAP (ind)
87C	SWOG 8624	Salmon *et al*, 1994	1987–90	3 MU × 3/w	To progression	VAD, VMCP and VBAP (ind)
87D	NCI-C MY6	Browman *et al*, 1995	1987–92	2 MU/m^2 (starting dose) × 3/w	To progression	MP (ind)
87H	MGWS (extended)	Westin *et al*, 1995	1987–90	5 MU × 3/w	To progression	MP (ind)
88B	EMSG 2 (M)	Ludwig *et al*, 1995	1988–93	2 MU × 3/w	1 year	VMCP ± IFN (ind)
88E	GMTG MM02	Peest *et al*, 1995	1988–91	5 MU d 1,3,5/8 d	To progression	MP then VBAMD (ind)
88F	Royal Marsden	Cunningham *et al*, 1998	1988–91	3 MU/m^2 × 3/w	To progression	CVAP then HD M and ABMT (ind)
89A	MRC-MYEL-6e	Drayson *et al*, 1998	1989–95	3–6 MU × 3/w	To progression	ABCM, MP, VAD, VMPC/VBAP, or HD M (ind)
89E	CMN (M), Mexico	Aviles *et al*, 1991	1989–90	5 MU × 3/w	18 months	? (ind), MP or VMCP (maint)
90B	PETHEMA	Bladé *et al*, 1998	1990–94	3 MU/m^2 × 3/w	To progression	VMCP and VBAP (ind)
90K	Ital. NHLSG (M)	Capnist *et al*, 1994	1990–94	3 MU × 2/w	To progression	MP (± IFN) or VMCP or VPP (ind)
91E	GERM	Grosbois *et al*, 1997	1991–95	3 MU/m^2 × 3/w	2 years	MP + IFN (ind)

Appendix. *continued*

Maintenance trials for which no data were available	
Grupo Multicentrico Mexicano (Mexico)	
Dutch Hemato Oncology Working Party (The Netherlands) HOVON 16	
South-west Oncology Group (USA) SWOG 9321/INT 0141	
Trials in refractory or relapsed myeloma	
University College Hospital London (UK)	
Bowman Gray School of Medicine (USA) BGSM 26285	
Eastern Cooperative Oncology Group (USA) ECOG 8489, individual patient data supplied (Gertz *et al*, 1995)	
Cape Town University (South Africa) SAFR CT MM 1	

IFN, Interferon; M, Melphalan; P, Prednisone; V, Vincristine; C, Cyclophosphamide; A, Adriamycin; B, BCNU; D, Dexamethasone; N, Mitozantrone; E, Epirubicin; HD, high dose; ABMT, autologous bone marrow transplant; ind, induction; maint, maintenance; d, day; w, week.

chain disease (both relatively small subgroups, with wide confidence intervals that overlap the overall effect estimate) obtain greater benefit from IFN.

Effect of trial design

The trials included in the overview differed substantially in their design and there was evidence of heterogeneity between trials with respect to the effect of interferon. It was not, however, possible to reliably identify any aspect of study design that materially affected the size of the benefit of interferon. The use of interferon in induction led to a prolongation of response duration among patients who achieved a response (either partial or complete), as did its use in maintenance among all patients entered. Although the survival benefit for induction trials was not statistically significant ($P = 0{\cdot}1$), while that for maintenance trials was of borderline significance ($P = 0{\cdot}04$), this does not provide good evidence that the survival benefit is restricted to the maintenance setting, as there was no significant heterogeneity of benefit between the induction trials and the maintenance trials. There was no evidence that the scheduled dose or duration of interferon was important.

Only one maintenance trial used interferon after high-dose therapy (Cunningham *et al*, 1998). The point estimate result for this one trial (32% odds reduction for progression) was consistent with the overall effect in the maintenance setting (34% odds reduction). This trial was, however, small with wide confidence intervals (99% CI: 74% odds reduction to 10% odds increase), so a greater, or indeed lesser, benefit for interferon in the context of high-dose therapy compared with other forms of chemotherapy cannot be ruled out. More randomized evidence is needed if this issue is to be addressed reliably and the results of a large ongoing intergroup trial in the USA are awaited.

Other factors

Interferon is an expensive drug and can have substantial side-effects that adversely affect a patient's quality of life. One study estimated a cost of $US 110 000 per quality-adjusted life-year gained (Nord *et al*, 1997). Information on side-effects was not collected for this overview, but the relatively large Nordic trial of interferon during induction did include a quality-of-life assessment (Wisløff *et al*, 1996), which showed an adverse impact of interferon during the first year of treatment. Against this must be set the fact that interferon keeps patients progression-free for longer and therefore free of the symptoms of myeloma, which may (at least for a time) improve the patients' quality of life, although the Nordic quality-of-life study did not find a late benefit. A survey of myeloma patients (Ludwig *et al*, 1997) showed that approximately half the patients interviewed would be willing to tolerate the side-effects of interferon if it improved progression-free or overall survival by 6 months.

CONCLUSION

This overview shows that interferon delays disease progression and that, even after several years, there still

appears to be a persistent reduction in the likelihood of having suffered recurrence. If this does eventually translate into a real difference in mortality, then it is possible that a few more years of follow-up of these same trials and an updated overview of them may yield a much more definite mortality advantage than is indicated by the current survival analyses. Until such evidence becomes available, the current analysis shows only a small survival benefit, if any, and decisions as to whether to use interferon or not will need to balance a modest clinical benefit on progression and mortality against cost and toxicity.

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