QUARTO CONGRESSO NAZIONALE DI IPPOCRATE

TRATTAMENTO E FOLLOW UP NEL MELANOMA AVANZATO

Cascina

3 - 4 Ottobre, 2009

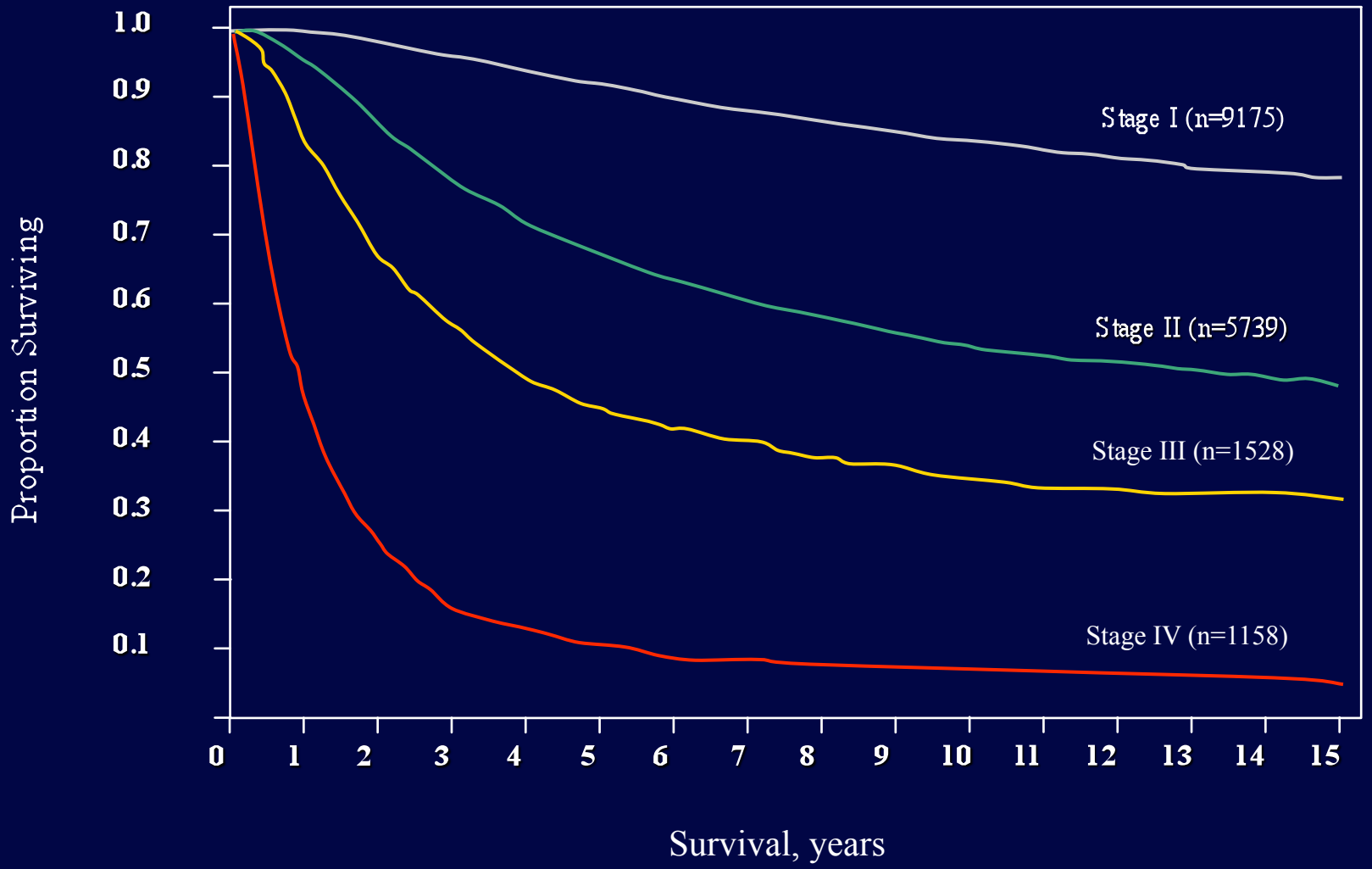
Antonella Romanini
a.romanini@ao-pisa.toscana.it

Dimensione del problema

Negli USA circa 45.000 nuovi casi di melanoma/anno

Balch CM et al. JCO 19:3622-3634, 2001

Survival curves

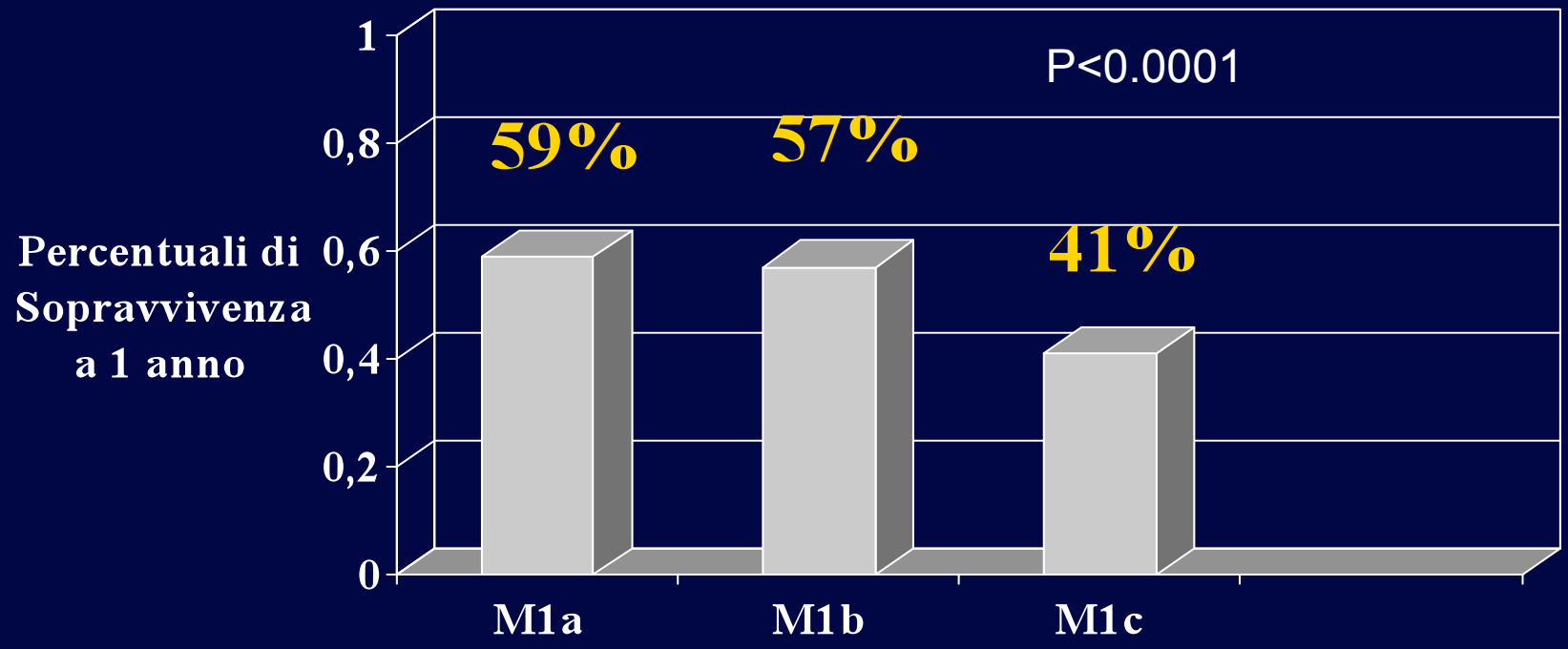


Reproduced with permission from Balch CM, Buzaid AC, Soong SJ, et al. *J Clin Oncol.* 2001;19:3635-3648.

CLASSIFICATION

AJCC	Site	LDH
M1a	distant cutis, subcutis or Lymph-node	normal
M1b	lung	normal
M1c	visceral metastasis	normal or elevated

One-year survival rates of M cathegories from AJCC data-base



FATTORI PROGNOSTICI MELANOMA METASTATICO Multivariata

Variabile	RR	95% CI	p
Elevazione LDH	1.89	1.46-2.44	.0001
Elevazione PAL	1.76	1.33-2.32	.0001
Mts app. GE	1.66	1.09-2.55	.02
Elevazione Plt	1.63	1.21-2.19	.001
N°sedi mts	1.30	1.16-1.46	.0001

Manola et al JCO, Nov 2000

Metastatic Melanoma
Meta-analysis

Korn '08 – 42 Phase II coop.groops trials , from 1975 to 2005

1-year survival prognostc factors:

PS Visceral disease Sex Brain Metastases excl/allowed

JCO, 26:527-34, 2008

Mocellin '06 – 53 studies, 5433 pts

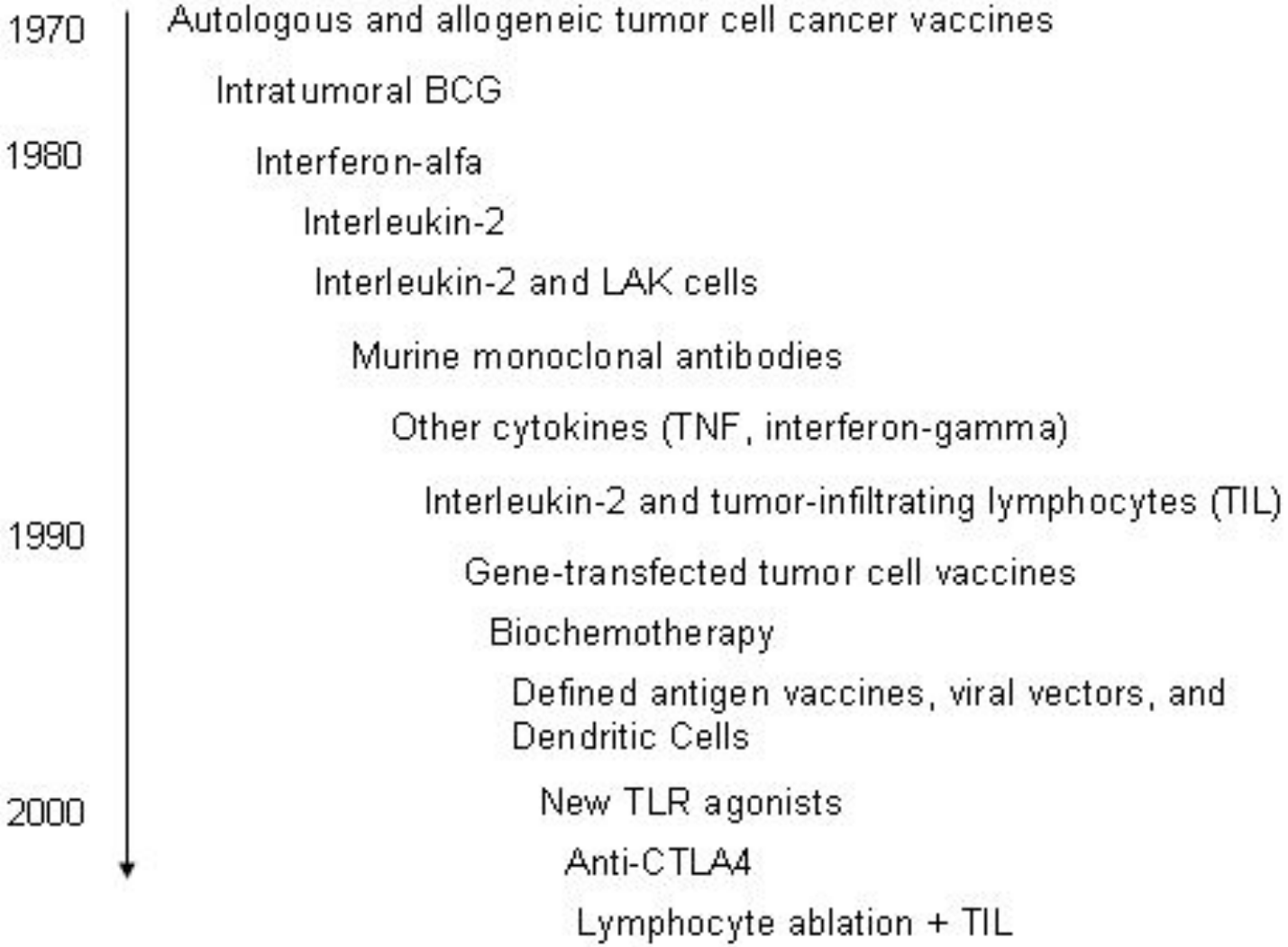
Prognostic value of circulating tumor cells

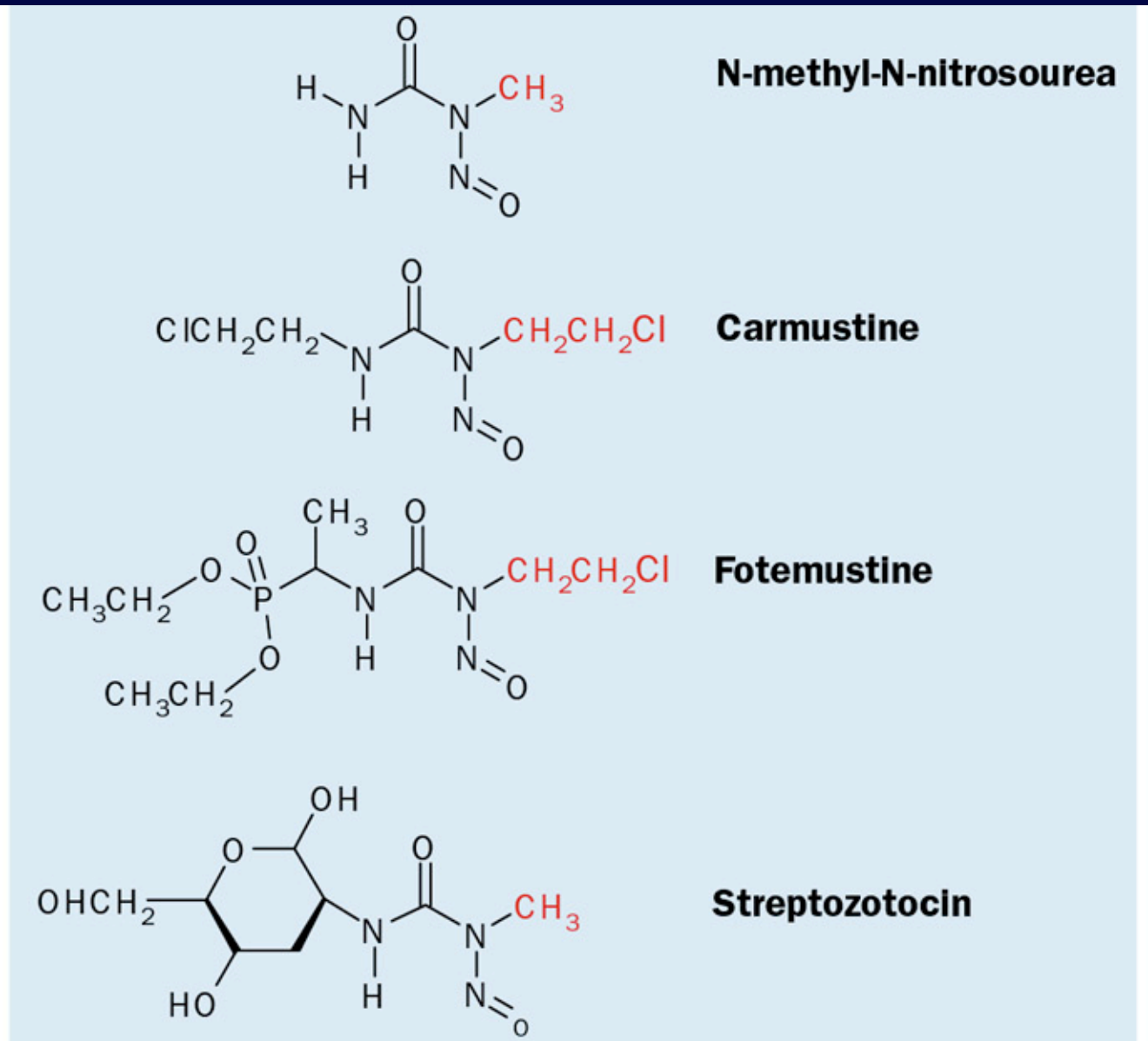
tumor-node-metastasis stage (stage I, 32%; stage II, 41.7%; stage III, 41.1%; stage IV, 47.4%; P trend < 0.0001)

survival (OS: hazard ratio, 2.42; 95%confidence interval, 1.7-3.45, P < 0.0001)

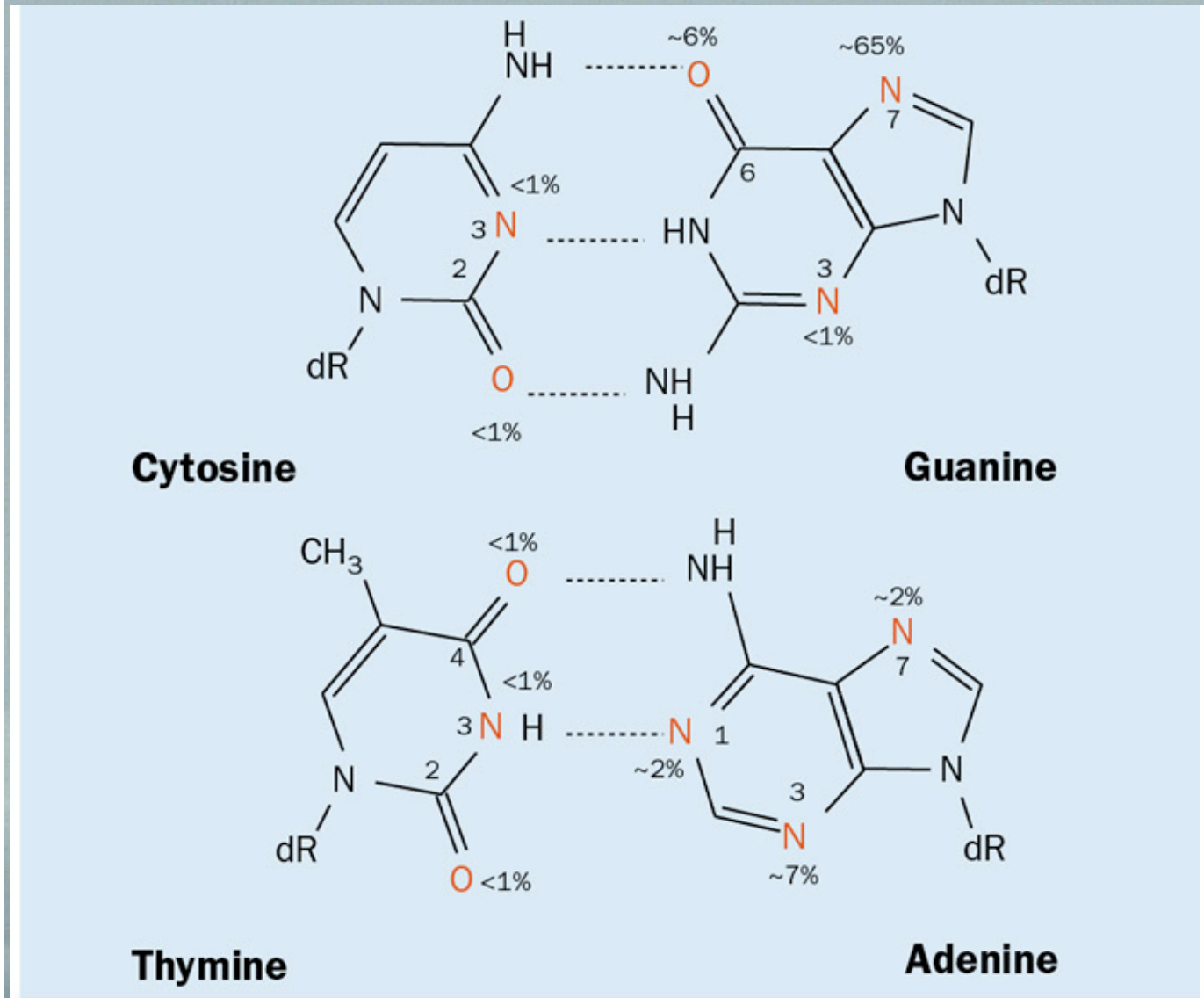
PFS: hazard ratio, 2.45; 95% confidence interval, 1.78-3.38; P < 0.0001

Clin Cancer Res 12:4605, 2006

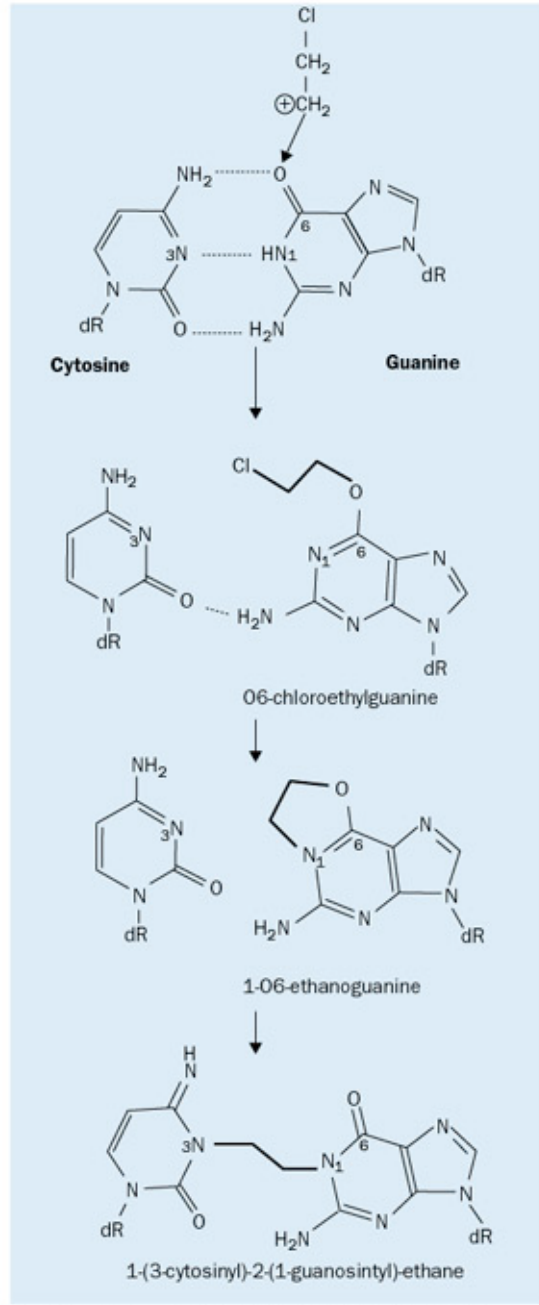

1970
1980
1990
2000
Autologous and allogeneic tumor cell cancer vaccines
Intratumoral BCG
Interferon-alfa
Interleukin-2
Interleukin-2 and LAK cells
Murine monoclonal antibodies
Other cytokines (TNF, interferon-gamma)
Interleukin-2 and tumor-infiltrating lymphocytes (TIL)
Gene-transfected tumor cell vaccines
Biochemotherapy
Defined antigen vaccines, viral vectors, and Dendritic Cells
New TLR agonists
Anti-CTLA4
Lymphocyte ablation + TIL



Chemical structures of N-methyl-N-nitrosourea and O6-alkylating agents in common clinical use (the-nitrosourea backbone is shown in bold and the alkylating moiety is shown in red).

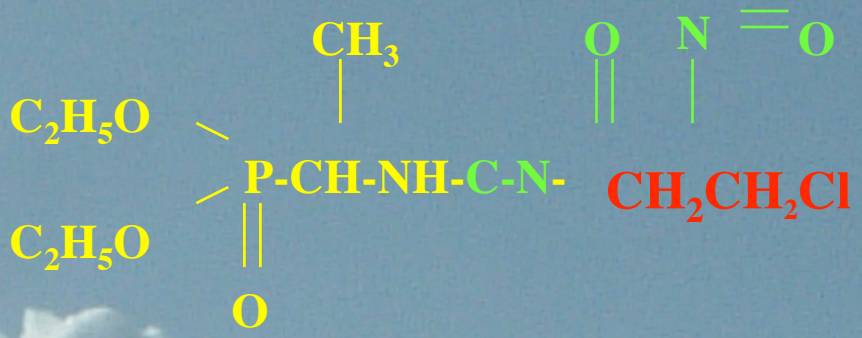


Alkylation sites in DNA base-pairs. The sites of attack are indicated in red and the relative amounts of the products are given for t methylating agent N-methyl-N-nitrosourea; phosphodiester alkylation constitutes the remaining ~12%.[2] dR, deoxyribose residue.



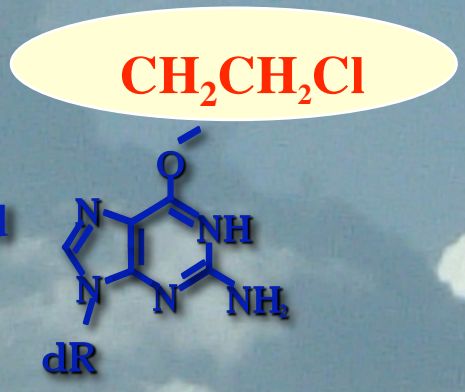
DNA interstrand crosslink formation after chloroethylation of guanine in DNA. dR, deoxyribose residue.

MECHANISM OF ACTION: alkylation O^6-Guanine

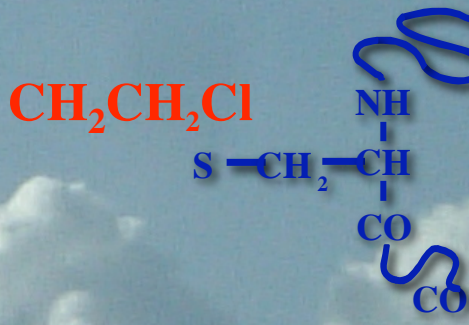


Guanine alkylated by FTMS

MECHANISM OF REPAIR: MGMT



Guanine alkylated by FTMS



MGMT

Irreversible inactivation

ATase expression in tumour tissues[26]

Tumour tissue	Number of samples	ATase (fmol/mg protein) Mean (SD)	Range
Breast	9	1071 (374)	444–1470
Stomach	7	515 (107)	400–689
Lung (small-cell)	5	509 (251)	265–867
Lung (non-small-cell)	24	461 (227)	0–890
Renal cell	5	329 (246)	49–713
Oesophagus	5	273 (376)	0–747
Brain	14	244 (175)	0–520
Colon	5	242 (308)	0–761
Melanoma	2	201 (161)	87–315

VOLUME 26 · NUMBER 14 · MAY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Extended-Dose Temozolomide in Patients With Melanoma

Petra Rietschel, Jedd D. Wolchok, Susan Krown, Scott Gerst, Achim A. Jungbluth, Klaus Busam, Katherine Smith, Irene Orlow, Katherine Panageas, and Paul B. Chapman

J Clin Oncol 26:2299-2304 2008

Purpose

We conducted a phase II trial of extended-dose temozolomide (TMZ) in patients with melanoma to test the hypothesis that the approximately 30% response rate observed in patients treated with extended-dose TMZ with antiangiogenic agents was caused by TMZ alone. We hypothesized that expression of methylguanine methyltransferase (MGMT) in the tumor would correlate with drug resistance to TMZ.

Patients and Methods

Patients with stage IV or unresectable stage III melanoma were treated with TMZ 75 mg/m^2/d for 6 weeks followed by a 2-week rest period. Cycles were repeated until progression. Patients were stratified by M1c disease or not. The primary end point was objective response proportion. MGMT expression was assessed by methylation-specific pyrosequencing of the promoter and by immunohistochemistry.

Results

Forty-nine patients (25 with M1c disease) were assessable. Three patients (12.5%) in each cohort experienced partial responses; there were no complete responses. Ten patients (21%) had stable disease lasting more than 24 weeks. Median time to progression was 3.3 months. Median survival was 10.1 months; survival was similar in the two cohorts. The estimated 18-month survival was 27%. There was no correlation between response and either immunohistochemistry staining for MGMT or for MGMT promoter methylation. Seventy-five percent of patients developed CD4$^+$ lymphopenia after three cycles.

Conclusion

Extended-dose TMZ therapy did not result in a 30% responses rate, which has been observed using extended-dose TMZ with antiangiogenic agents. Response did not correlate with MGMT expression or promoter methylation as a continuous variable, suggesting that other resistance mechanisms are important.

TEMOZOLOMIDE

- alchilante convertito chimicamente a monometiltriazenoimidazolcarboxiimide (MTIC) il metabolita attivo del DTIC

- Middleton MR et al. JCO 18:158, 2000

#305	schema	SLP	Sm
156 T	T 200x5 q28	7.7 m	1.9 m
149 D	DTIC 250 x 5q21	6.4 m	1.5 m

Temozolomide for the Treatment of Brain Metastases Associated With Metastatic Melanoma: A Phase II Study

Sanjiv S. Agarwala, John M. Kirkwood, Martin Gore, Brigitte Dreno, Nicholas Thatcher, Beate Czarnetski, Michael Atkins, Antonio Buzaid, Dimosthenis Skarlos, and Elaine M. Rankin

Table 2. Summary of Best Response to Temozolomide in Brain Metastases

Parameter	No Prior Chemotherapy (n = 117)		Prior Chemotherapy (n = 34)		Total (N = 151)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Objective response	8	7	1	1	9	6
Complete	1	1	—	—	1	1
Partial	7	6	1	1	8	5
Stable disease	34	29	6	18	40	26
Progressive disease	54	46	19	56	73	48
Missing*	20	17	9	26	29	19

*Indicates patients who did not have a best objective response recorded by the investigator. Primary reasons were disease progression identified before scheduled scans; investigator decided not to perform scan; patients refused scheduled scans; or patients progressed more quickly than anticipated and died, or were not medically stable to undergo scan procedures.

J Clin Oncol 22:2101-2107, 2004

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-based Series #8-4: Section 1

Temozolomide for the Treatment of Metastatic Melanoma: A Clinical Practice Guideline

I. Quirt, S. Verma, T. Petrella, K. Bak, M. Charette, and members of the Melanoma Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 20, 2006

Qualifying Statements

- Dacarbazine is the only chemotherapy drug currently approved for the treatment of patients with metastatic malignant melanoma, with response rates ranging from 6% to 15% observed in large randomized trials. Virtually all responses are partial, with median durations of response of only seven to eight months. Given these overall disappointing results, there is consensus among most physicians treating patients with metastatic malignant melanoma that it is appropriate to recommend more convenient treatments or experimental treatments to these patients.
- Due to oral dosing, temozolomide is a reasonable choice, particularly for patients who would have difficulty travelling to cancer centres for intravenous chemotherapy.
- Temozolomide has demonstrated an efficacy equal to that of dacarbazine in a randomized phase III trial. However, unlike dacarbazine, temozolomide is a convenient oral treatment that penetrates the blood-brain barrier and has shown activity against brain metastases. Although surgery is the preferred treatment modality for patients with solitary brain metastases from melanoma, temozolomide is the preferred chemotherapy for patients with brain metastases who require systemic treatment.

- **Trattamento conveniente per la sua formulazione orale**
- **Di efficacia uguale a quella di DTIC**
- **Supera la barriera EE**

Temozolomide (TMZ) as prophylaxis for melanoma brain metastases (BrM): Results from a phase III, multicenter study.

V. Chiarion-Sileni, M. Guida, R. Ridolfi, A. Romanini, S. Brugnara, P. Del Bianco, E. Perfetti, R. Cavallo, J. Pigozzo, D. Donati, G. De Salvo

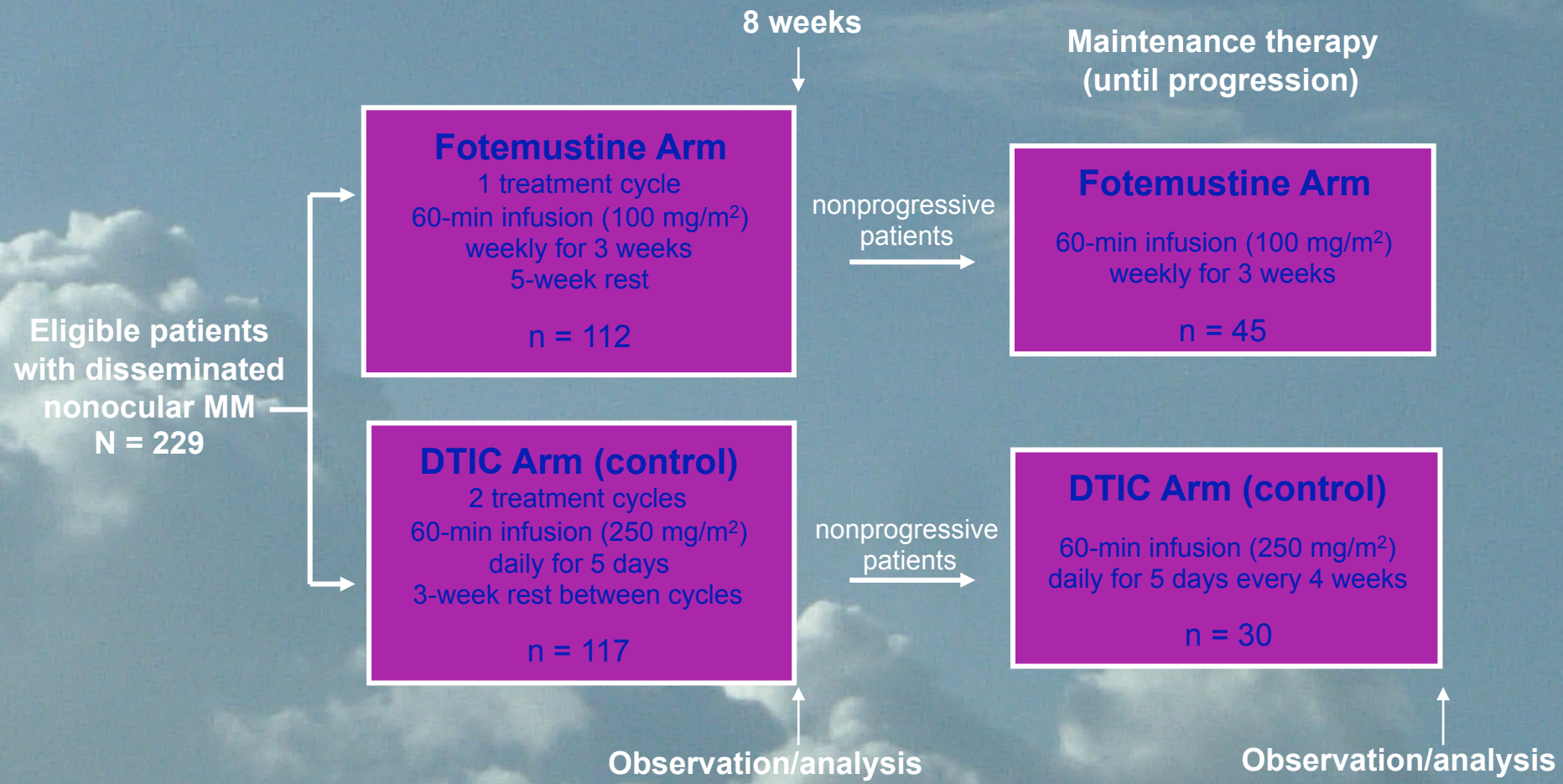
J Clin Oncol 26: 2008 (May 20 suppl; abstr 20014)

Background: Almost 170,000 patients developed CNS metastases in 2007 and melanoma is the 4th leading cause. Some authors reported a possible role for TMZ in preventing BrM. In 2002, the IMI started a randomized study with the primary end point of evaluating whether TMZ is able to reduce the expected incidence of BrM at 12 months from 30 % to 12 % (α= 5%, β= 80%, two tailed test). Methods: 150 pts with untreated metastatic melanoma were randomly assigned (1:1) to receive cisplatin 75 mg/m2 day 1, and IL-2 3 MU X 2/d on days 9-18 plus TMZ 200 mg/m2/d on days 1-5, or DTIC 800 mg/m2 on day 1 every 28. (arm CTI=75 pts, arm CDI=75). Brain CT or MRI were planned every four months in the first 2- years and every six months after. Results: 147 patients (CTI=73 pts, CDI=74) were valuable. The two arms were well balanced for sex, PS, LDH serum level, metastatic site. The overall incidence of BrM was 31% in CTI and 40% in CDI arm (p=ns) with a median time to BrM of 15 vs 13 mos respectively. The 1-year BrM progression free survival was 57% in CTI vs 53% in CDI. Considering only responsive pts (13 in CTI and 16 in CDI), the overall incidence of BrM was 55% with a median time to BrM of 23 mos in CTI and 21 in CDI arm. The median PFS and OS for all patients were 4 and 8.4 mos in CTI and 4 and 9.5 mos in CDI. Conclusions: The BrM incidence was higher than previously reported, especially in responsive patients. The relative 22% reduction of BrM occurrence obtained using a TMZ-based CT was less than planned and therefore did not translate in a significant benefit.

Pts #	schema	% inc. BrM	m Time to BrM	m PFS	m OS
74	CDI	40	13	4	9.5
73	CTI	31	15	4	8.4

Summary of Study Design

Randomized, comparative, phase III trial



Avril, et al. J Clin Oncol. 2004;22:1118-1125.

Main findings

- Higher ORR in the fotemustine arm
  - 15.5% vs 7.2% with DTIC (*P* = .053) (odds ratio = 2.35)
  - 15.2% vs 6.8% (*P* = .043) (Intent-to-treat group)
  - 17.8% vs 7.6% (*P* = .040) (no brain metastases at inclusion)
- Overall survival favored fotemustine (*P* = .067)
  - 7.3 (95% CI, 6.01-8.84) vs 5.6 months (95% CI, 5.03-6.54)
- Extended median time to brain metastases (*P* = .59)
  - 22.7 months (95% CI, 9.62-23.33) for fotemustine
  - 7.2 months (95% CI, 6.28-11.70) for DTIC

Avril, et al. J Clin Oncol. 2004;22:1118-1125.

Metastatic Melanoma Meta-analysis: CT or bio vs bioCT

Au 'y	# pts	# studies	years	%RR	mS
Allen'98	7711	168	up to 1990	29 vs 41*	8.6 vs 9.8
Tomsu '97	5392	74	1974 to 1995	-	7 vs 8.8/9.2
Huncharek '01	3273	20	1970 to 1999	53°	=
Ives '07	2621	18	1966 to 2006	59°	=
Lui '07	7135	48	1966 to 2006		=
Sasse '07	2625	18	1982 to 2006	46°	=
Allen '97				17 vs 41*	=
Maral '98				9 vs 33*	=
Keilholz '98	631			21 vs 45*	=

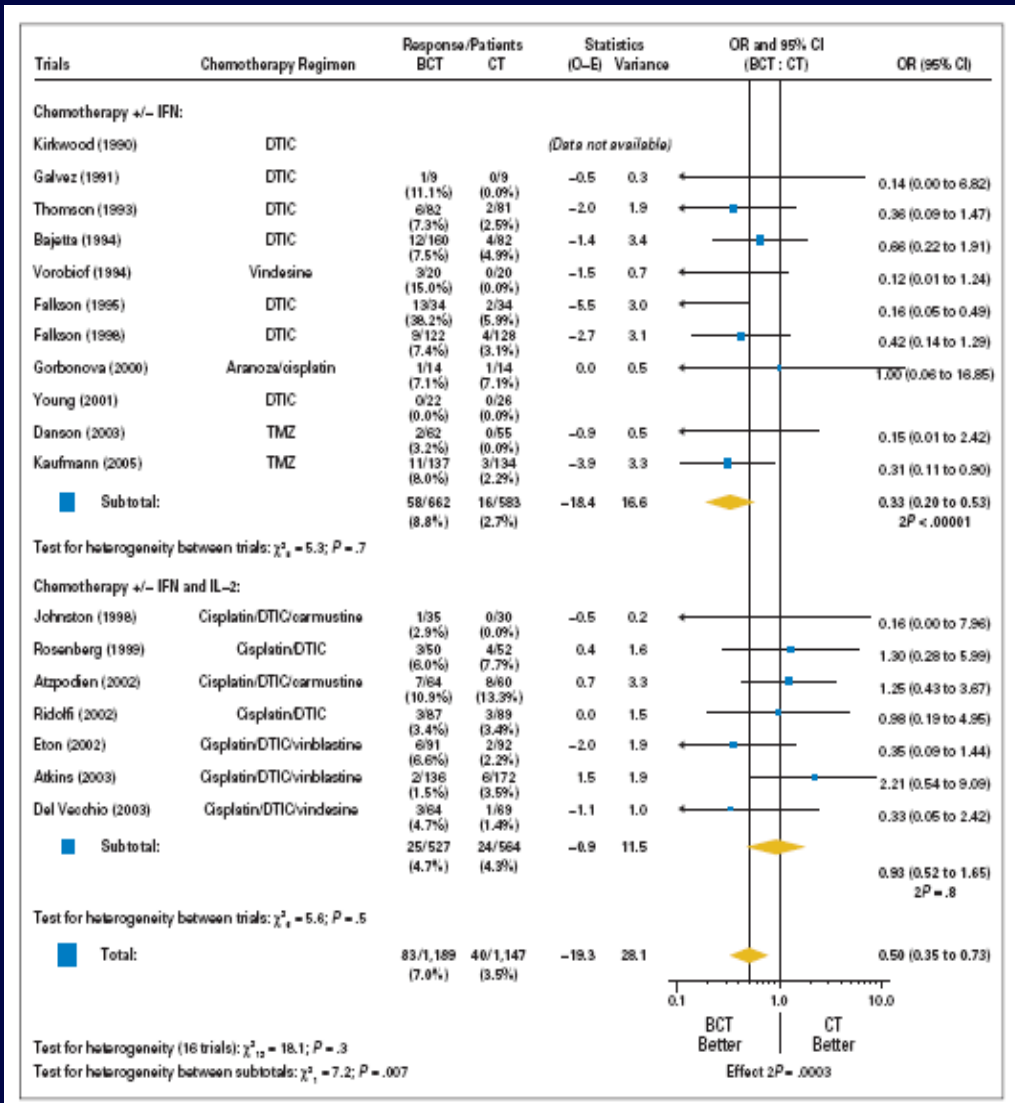
* Statistically significant
° increase over single agent DTIC

Complete responses better with IFN

9% vs 3%

5% vs 4%

7% vs 3.5%



Trials	Chemotherapy Regimen	Response/Patients BCT	Response/Patients CT	Statistics (O–E)	Statistics Variance	OR (95% CI)
Chemotherapy +/– IFN:						
Kirkwood (1990)	DTIC			(Data not available)		
Galvez (1991)	DTIC	1/9 (11.1%)	0/9 (0.0%)	–0.5	0.3	0.14 (0.00 to 6.82)
Thomson (1993)	DTIC	6/82 (7.3%)	2/81 (2.5%)	–2.0	1.9	0.36 (0.09 to 1.47)
Bajetta (1994)	DTIC	12/160 (7.5%)	4/82 (4.9%)	–1.4	3.4	0.66 (0.22 to 1.91)
Vorobiof (1994)	Vindesine	3/20 (15.0%)	0/20 (0.0%)	–1.5	0.7	0.12 (0.01 to 1.24)
Falkson (1995)	DTIC	13/34 (38.2%)	2/34 (5.9%)	–5.5	3.0	0.16 (0.05 to 0.49)
Falkson (1998)	DTIC	9/122 (7.4%)	4/128 (3.1%)	–2.7	3.1	0.42 (0.14 to 1.29)
Gorbonova (2000)	Aranoza/cisplatin	1/14 (7.1%)	1/14 (7.1%)	0.0	0.5	1.00 (0.06 to 16.85)
Young (2001)	DTIC	0/22 (0.0%)	0/26 (0.0%)			
Danson (2003)	TMZ	2/62 (3.2%)	0/55 (0.0%)	–0.9	0.5	0.15 (0.01 to 2.42)
Kaufmann (2005)	TMZ	11/137 (8.0%)	3/134 (2.2%)	–3.9	3.3	0.31 (0.11 to 0.90)
Subtotal:		58/662 (8.8%)	16/583 (2.7%)	–18.4	16.6	0.33 (0.20 to 0.53) $2P < .00001$
Test for heterogeneity between trials: $\chi^2_9 = 5.3$; $P = .7$						
Chemotherapy +/– IFN and IL–2:						
Johnston (1998)	Cisplatin/DTIC/carmustine	1/35 (2.9%)	0/30 (0.0%)	–0.5	0.2	0.16 (0.00 to 7.96)
Rosenberg (1999)	Cisplatin/DTIC	3/50 (6.0%)	4/52 (7.7%)	0.4	1.6	1.30 (0.28 to 5.99)
Atzpodien (2002)	Cisplatin/DTIC/carmustine	7/64 (10.9%)	8/60 (13.3%)	0.7	3.3	1.25 (0.43 to 3.67)
Ridolfi (2002)	Cisplatin/DTIC	3/87 (3.4%)	3/89 (3.4%)	0.0	1.5	0.98 (0.19 to 4.95)
Eton (2002)	Cisplatin/DTIC/vinblastine	6/91 (6.6%)	2/92 (2.2%)	–2.0	1.9	0.35 (0.09 to 1.44)
Atkins (2003)	Cisplatin/DTIC/vinblastine	2/136 (1.5%)	6/172 (3.5%)	1.5	1.9	2.21 (0.54 to 9.09)
Del Vecchio (2003)	Cisplatin/DTIC/vindesine	3/64 (4.7%)	1/69 (1.4%)	–1.1	1.0	0.33 (0.05 to 2.42)
Subtotal:		25/527 (4.7%)	24/564 (4.3%)	–0.9	11.5	0.93 (0.52 to 1.65) $2P = .8$
Test for heterogeneity between trials: $\chi^2_6 = 5.6$; $P = .5$						
Total:		83/1,189 (7.0%)	40/1,147 (3.5%)	–19.3	28.1	0.50 (0.35 to 0.73)

0.1 1.0 10.0

BCT Better | CT Better

Test for heterogeneity (16 trials): $\chi^2_{15} = 18.1$; $P = .3$

Test for heterogeneity between subtotals: $\chi^2_1 = 7.2$; $P = .007$

Effect $2P = .0003$

Fig 1. Complete response in trials of biochemotherapy (BCT) versus chemotherapy (CT) for metastatic melanoma. O–E, observed minus expected; var, variance; OR, odds ratio; DTIC, dacarbazine; TMZ, temozolomide.

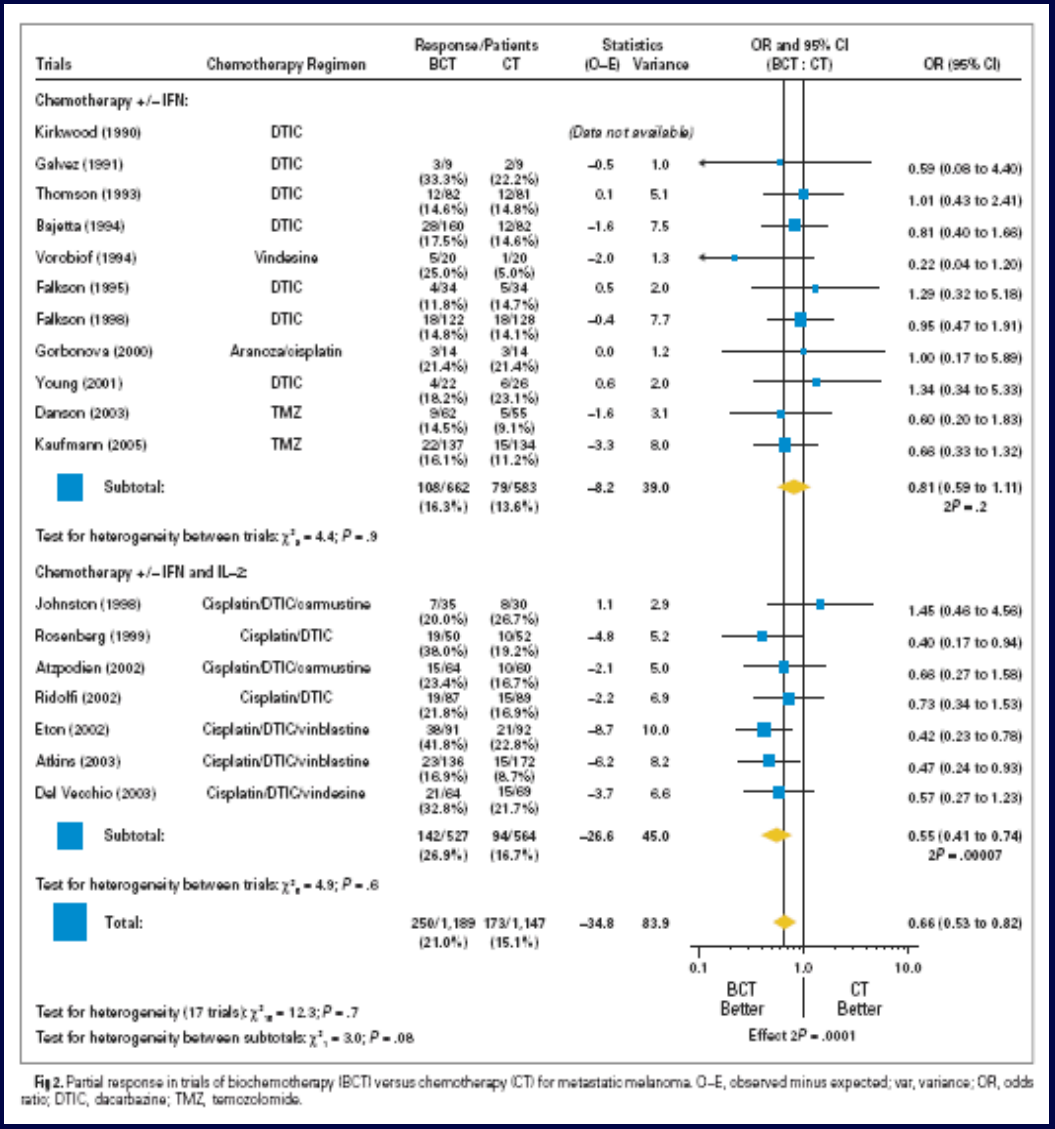
Ives, 2007

Partial responses better with IFN+ IL-2

16% vs 14%

27% vs 17%

21% vs 15%



Trials	Chemotherapy Regimen	Response/Patients BCT	Response/Patients CT	Statistics (O–E)	Statistics Variance	OR (95% CI)
Chemotherapy +/– IFN:						
Kirkwood (1990)	DTIC			(Data not available)		
Galvez (1991)	DTIC	3/9 (33.3%)	2/9 (22.2%)	–0.5	1.0	0.59 (0.08 to 4.40)
Thomson (1993)	DTIC	12/82 (14.6%)	12/81 (14.8%)	0.1	5.1	1.01 (0.43 to 2.41)
Bajetta (1994)	DTIC	28/160 (17.5%)	12/82 (14.6%)	–1.6	7.5	0.81 (0.40 to 1.66)
Vorobiof (1994)	Vindesine	5/20 (25.0%)	1/20 (5.0%)	–2.0	1.3	0.22 (0.04 to 1.20)
Falkson (1995)	DTIC	4/34 (11.8%)	5/34 (14.7%)	0.5	2.0	1.29 (0.32 to 5.18)
Falkson (1998)	DTIC	18/122 (14.8%)	18/128 (14.1%)	–0.4	7.7	0.95 (0.47 to 1.91)
Gorbonova (2000)	Aranoza/cisplatin	3/14 (21.4%)	3/14 (21.4%)	0.0	1.2	1.00 (0.17 to 5.89)
Young (2001)	DTIC	4/22 (18.2%)	6/26 (23.1%)	0.6	2.0	1.34 (0.34 to 5.33)
Danson (2003)	TMZ	9/62 (14.5%)	5/55 (9.1%)	–1.6	3.1	0.60 (0.20 to 1.83)
Kaufmann (2005)	TMZ	22/137 (16.1%)	15/134 (11.2%)	–3.3	8.0	0.68 (0.33 to 1.32)
Subtotal:		108/662 (16.3%)	79/583 (13.6%)	–8.2	39.0	0.81 (0.59 to 1.11) 2P = .2
Test for heterogeneity between trials: $\chi^2_8 = 4.4$; $P = .9$						
Chemotherapy +/– IFN and IL–2:						
Johnston (1998)	Cisplatin/DTIC/carmustine	7/35 (20.0%)	8/30 (26.7%)	1.1	2.9	1.45 (0.46 to 4.56)
Rosenberg (1999)	Cisplatin/DTIC	19/50 (38.0%)	10/52 (19.2%)	–4.8	5.2	0.40 (0.17 to 0.94)
Atzpodien (2002)	Cisplatin/DTIC/carmustine	15/64 (23.4%)	10/60 (16.7%)	–2.1	5.0	0.66 (0.27 to 1.58)
Ridolfi (2002)	Cisplatin/DTIC	19/87 (21.8%)	15/89 (16.9%)	–2.2	6.9	0.73 (0.34 to 1.53)
Eton (2002)	Cisplatin/DTIC/vinblastine	38/91 (41.8%)	21/92 (22.8%)	–8.7	10.0	0.42 (0.23 to 0.78)
Atkins (2003)	Cisplatin/DTIC/vinblastine	23/136 (16.9%)	15/172 (8.7%)	–6.2	8.2	0.47 (0.24 to 0.93)
Del Vecchio (2003)	Cisplatin/DTIC/vindesine	21/64 (32.8%)	15/69 (21.7%)	–3.7	6.6	0.57 (0.27 to 1.23)
Subtotal:		142/527 (26.9%)	94/564 (16.7%)	–26.6	45.0	0.55 (0.41 to 0.74) 2P = .00007
Test for heterogeneity between trials: $\chi^2_8 = 4.9$; $P = .8$						
Total:		250/1,189 (21.0%)	173/1,147 (15.1%)	–34.8	83.9	0.66 (0.53 to 0.82)
Test for heterogeneity (17 trials): $\chi^2_{16} = 12.3$; $P = .7$						
Test for heterogeneity between subtotals: $\chi^2_1 = 3.0$; $P = .08$						

OR and 95% CI (BCT : CT)

0.1 1.0 10.0

BCT Better | CT Better

Effect 2P = .0001

Fig 2. Partial response in trials of biochemotherapy (BCT) versus chemotherapy (CT) for metastatic melanoma. O–E, observed minus expected; var, variance; OR, odds ratio; DTIC, dacarbazine; TMZ, temozolomide.

Ives, 2007

Overall Response better with bioCT

25% vs 16.5%

32% vs 21%

28% vs 19%

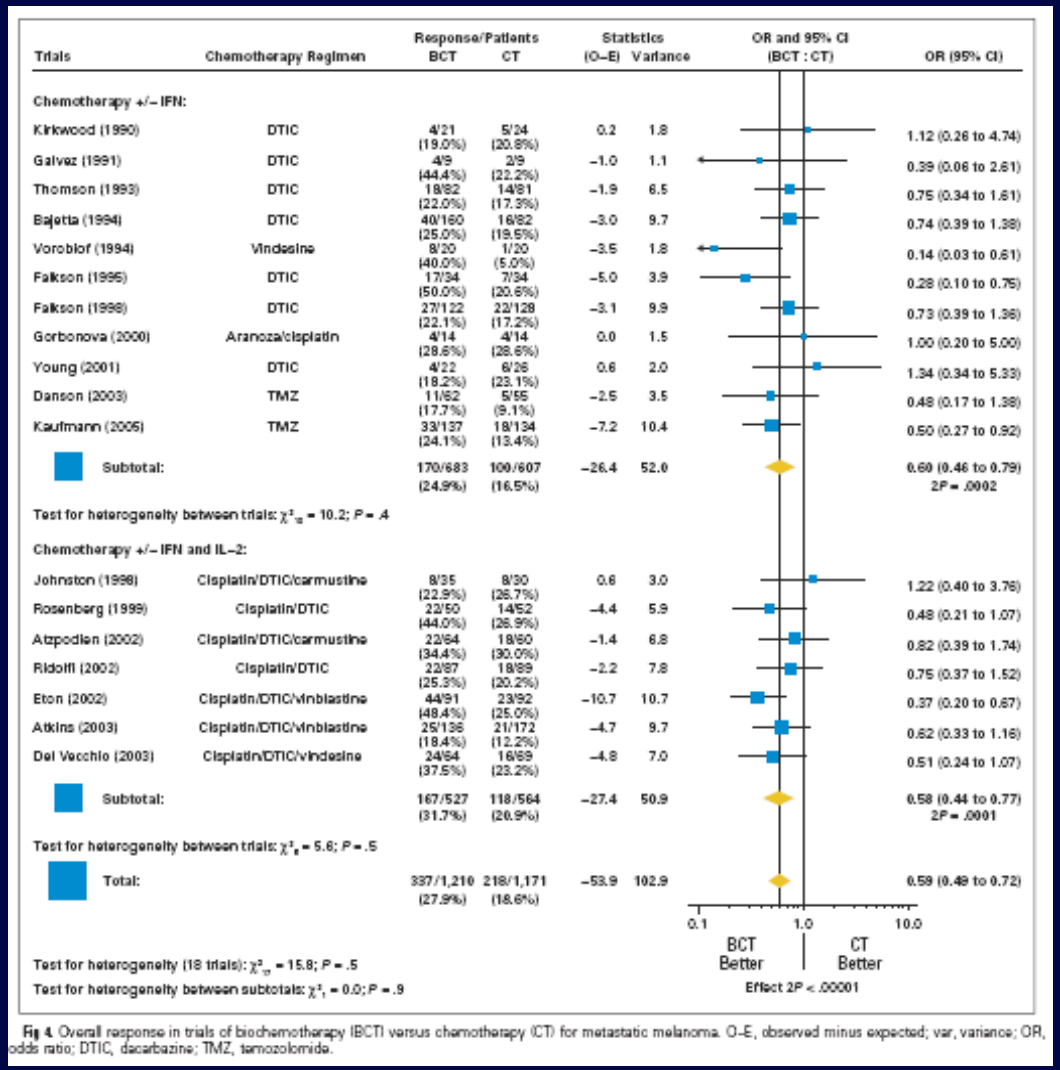


Fig 4. Overall response in trials of biochemotherapy (BCT) versus chemotherapy (CT) for metastatic melanoma. O-E, observed minus expected; var, variance; OR, odds ratio; DTIC, dacarbazine; TMZ, temozolomide.

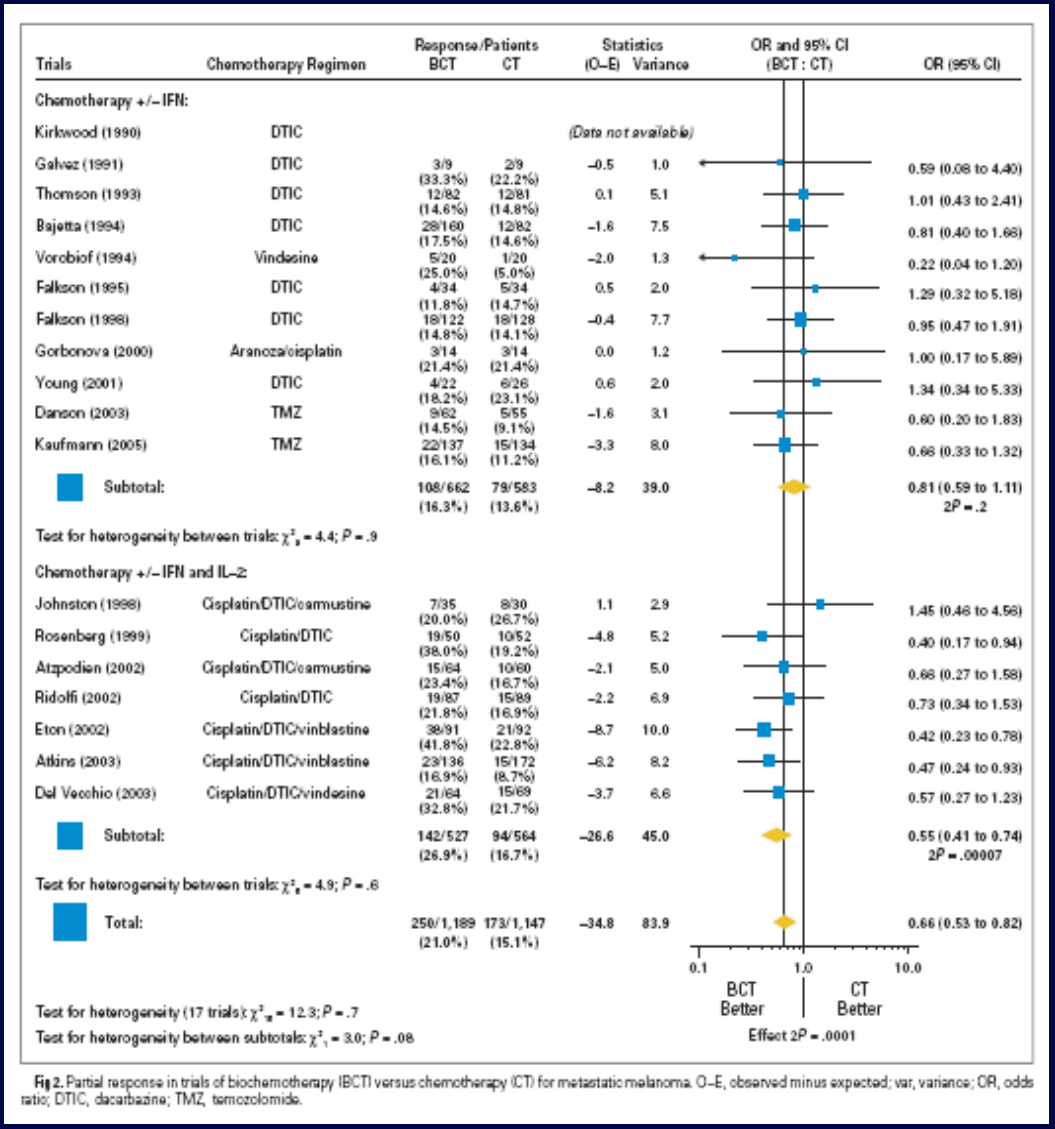
Ives, 2007

No difference in OS

98 vs 78

122 vs 129

220 vs 207



Trials	Chemotherapy Regimen	Response/Patients BCT	Response/Patients CT	Statistics (O–E)	Statistics Variance	OR (95% CI)
Chemotherapy +/– IFN:						
Kirkwood (1990)	DTIC			(Data not available)		
Galvez (1991)	DTIC	3/9 (33.3%)	2/9 (22.2%)	–0.5	1.0	0.59 (0.08 to 4.40)
Thomson (1993)	DTIC	12/82 (14.6%)	12/81 (14.8%)	0.1	5.1	1.01 (0.43 to 2.41)
Bajetta (1994)	DTIC	28/160 (17.5%)	12/82 (14.6%)	–1.6	7.5	0.81 (0.40 to 1.66)
Vorobiof (1994)	Vindesine	5/20 (25.0%)	1/20 (5.0%)	–2.0	1.3	0.22 (0.04 to 1.20)
Falkson (1995)	DTIC	4/34 (11.8%)	5/34 (14.7%)	0.5	2.0	1.29 (0.32 to 5.18)
Falkson (1998)	DTIC	18/122 (14.8%)	18/128 (14.1%)	–0.4	7.7	0.95 (0.47 to 1.91)
Gorbunova (2000)	Aranoza/cisplatin	3/14 (21.4%)	3/14 (21.4%)	0.0	1.2	1.00 (0.17 to 5.89)
Young (2001)	DTIC	4/22 (18.2%)	6/26 (23.1%)	0.6	2.0	1.34 (0.34 to 5.33)
Danson (2003)	TMZ	9/62 (14.5%)	5/55 (9.1%)	–1.6	3.1	0.60 (0.20 to 1.83)
Kaufmann (2005)	TMZ	22/137 (16.1%)	15/134 (11.2%)	–3.3	8.0	0.68 (0.33 to 1.32)
Subtotal:		108/662 (16.3%)	79/583 (13.6%)	–8.2	39.0	0.81 (0.59 to 1.11) 2P = .2
Test for heterogeneity between trials: $\chi^2_8 = 4.4$; $P = .9$						
Chemotherapy +/– IFN and IL–2:						
Johnston (1998)	Cisplatin/DTIC/carmustine	7/35 (20.0%)	8/30 (26.7%)	1.1	2.9	1.45 (0.46 to 4.56)
Rosenberg (1999)	Cisplatin/DTIC	19/50 (38.0%)	10/52 (19.2%)	–4.8	5.2	0.40 (0.17 to 0.94)
Atzpodien (2002)	Cisplatin/DTIC/carmustine	15/64 (23.4%)	10/60 (16.7%)	–2.1	5.0	0.66 (0.27 to 1.58)
Ridolfi (2002)	Cisplatin/DTIC	19/87 (21.8%)	15/89 (16.9%)	–2.2	6.9	0.73 (0.34 to 1.53)
Eton (2002)	Cisplatin/DTIC/vinblastine	38/91 (41.8%)	21/92 (22.8%)	–8.7	10.0	0.42 (0.23 to 0.78)
Atkins (2003)	Cisplatin/DTIC/vinblastine	23/136 (16.9%)	15/172 (8.7%)	–6.2	8.2	0.47 (0.24 to 0.93)
Del Vecchio (2003)	Cisplatin/DTIC/vindesine	21/64 (32.8%)	15/69 (21.7%)	–3.7	6.6	0.57 (0.27 to 1.23)
Subtotal:		142/527 (26.9%)	94/564 (16.7%)	–26.6	45.0	0.55 (0.41 to 0.74) 2P = .00007
Test for heterogeneity between trials: $\chi^2_8 = 4.9$; $P = .8$						
Total:		250/1,189 (21.0%)	173/1,147 (15.1%)	–34.8	83.9	0.66 (0.53 to 0.82)
Test for heterogeneity (17 trials): $\chi^2_{16} = 12.3$; $P = .7$						
Test for heterogeneity between subtotals: $\chi^2_1 = 3.0$; $P = .08$						

OR and 95% CI (BCT : CT)

0.1 1.0 10.0

BCT Better CT Better

Effect 2P = .0001

Fig 2. Partial response in trials of biochemotherapy (BCT) versus chemotherapy (CT) for metastatic melanoma. O–E, observed minus expected; var, variance; OR, odds ratio; DTIC, dacarbazine; TMZ, temozolomide.

Ives, 2007

REVIEW ARTICLE

Systemic therapy of disseminated malignant melanoma: an evidence-based overview of the state-of-the-art in daily routine

D Nashan,*† ML Müller,† S Grabbe,‡ S Wustlich,§ A Enk¶

JEADV 2007,21, 1305–1318

Results Monotherapy with DTIC (dacarbazine) is the standard. Based on overall survival data, polychemotherapies cannot be recommended. Combination of polychemotherapy with the cytokines interferon-α and interleukin-2 substantially augments chemotherapy induced response rates, but a meta-analysis for survival does not support its therapeutic superiority. Biological therapies such as vaccinations have not yet delivered results on a higher evidence level. Thus, immunotherapies as well as chemo-immunotherapies will have to be evaluated in further studies.

Conclusions Although the therapeutic efficacy is very limited, dacarbazine cannot be rejected as standard therapy for disseminated melanoma, because no other therapeutic regimen exhibits a survival benefit over DTIC in an evidence-based analysis. This lack of therapeutic progress over the past 40 years clearly calls for further clinical studies, and patients should be enrolled into clinical trials whenever possible.

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-based Series #8-3: Section 1

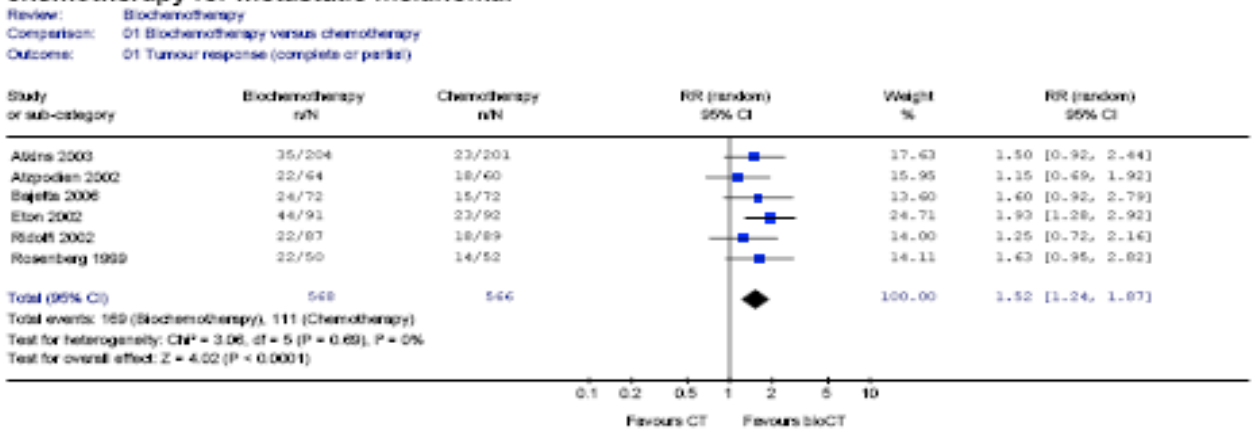
Biochemotherapy for the Treatment of Metastatic Malignant Melanoma: A Clinical Practice Guideline

S. Verma, T. Petrella, C. Hamm, K. Bak, M. Charette, and the Melanoma Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

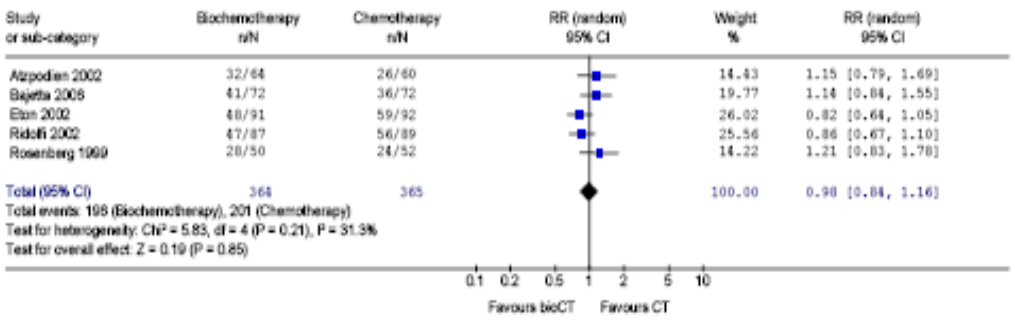
Report Date: April 30, 2007

Figure1. Pooled response rates from randomized trials of biochemotherapy versus chemotherapy for metastatic melanoma.



www.cancercare.on.ca

Figure 2. Pooled mortality rates at 12 months from randomized trials of biochemotherapy versus chemotherapy for metastatic melanoma.



Recommendation

Due to the inconsistent results of the available studies with regard to benefit (response, time-to-progression, and survival) and consistently high toxicity rates, biochemotherapy is not recommended for the treatment of metastatic melanoma.

NCCN Clinical Practice Guidelines in Oncology™ Principles of systemic therapy for advanced or metasttic Melanoma

First or second line chemotherapy

- **Clinical trial preferred**
- **Dacarbazine**
- **Temozolomide**
- **High-dose Interleukin-2**
- **Combination CT or bioCT**
- **Paclitaxel**
- **Paclitaxel/Cisplatin**
- **Pactilitaxel/Carboplatin**

All raccomandations are cathegory 2B
High-dose IL-2 should not be used for patients with untreated/active brain metastasis

Volume 11 • Number 2 • 2008
VALUE IN HEALTH

Advanced Cutaneous Malignant Melanoma: A Systematic Review of Economic and Quality-of-Life Studies

Richard P. Cashin, PharmD,[1] Philip Lui, PharmD,[1] Márcio Machado, PhD,[1,2]
Michiel E. H. Hemels, MSc, Drs,[3] Patricia K. Corey-Lisle, PhD, RN,[4] Thomas R. Einarson, PhD, FISPE[1]

[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; [3]Bristol-Myers-Squibb, Brussels, Belgium; [4]Bristol-Myers-Squibb, Wallingford, CT, USA

13 QOL studies

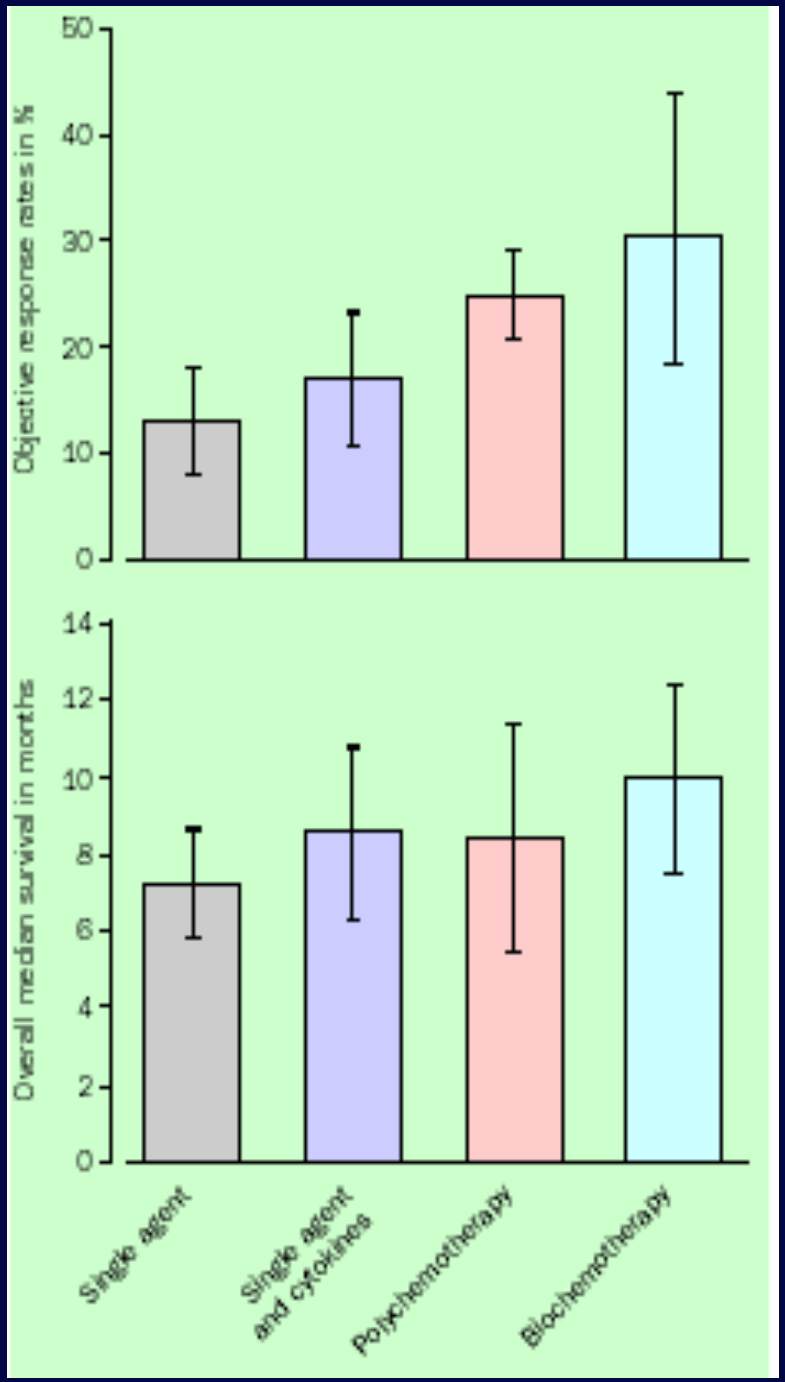
5 economic studies

- **3 cost-effectiveness**
- **2 cost-utility**

Different tests

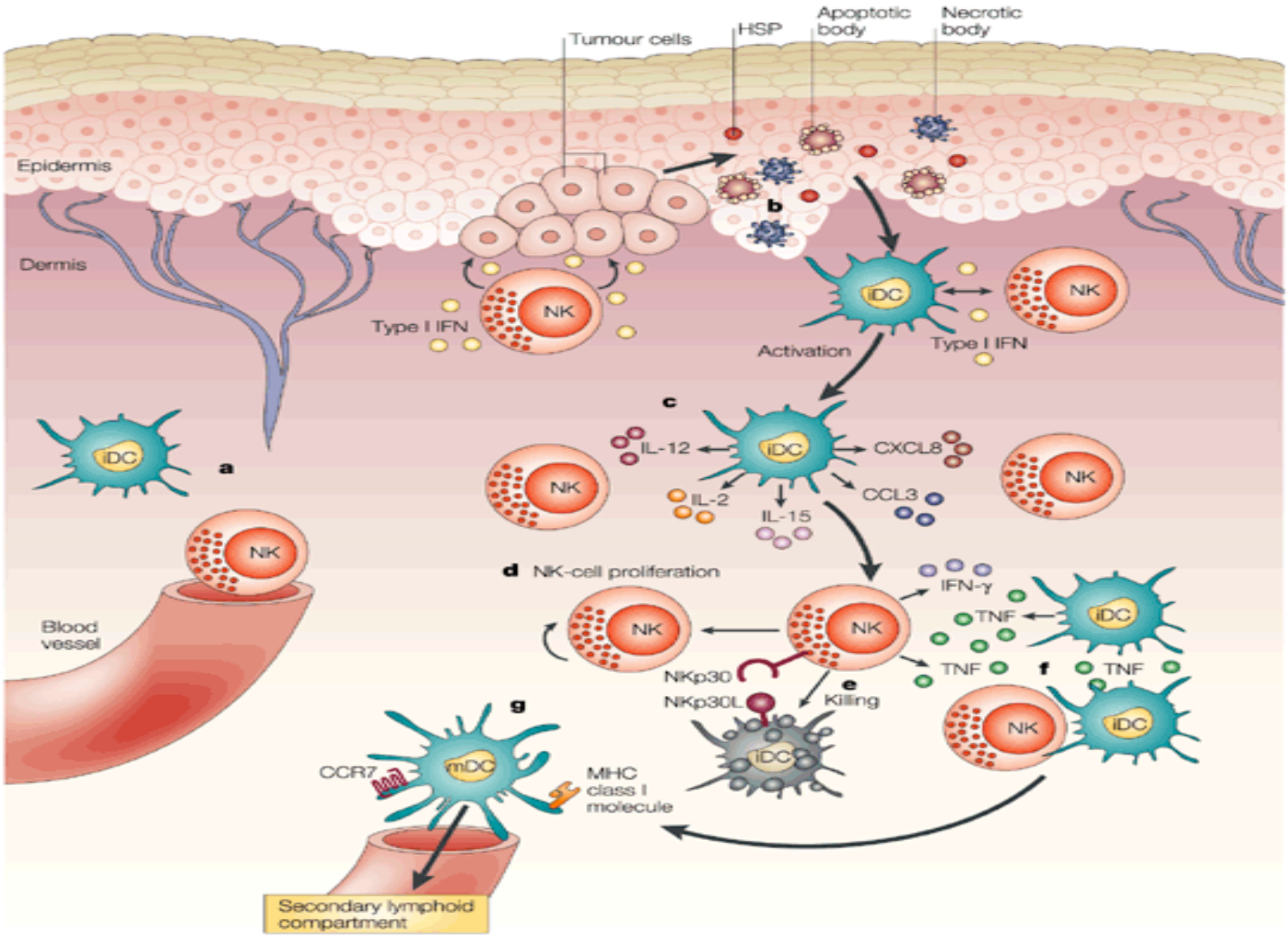
Small number of patients with data

Conclusions: Cost-effectiveness has not been widely demonstrated for treatment of MM. Only two studies with unimpressive results exist for treatments. Screening was not cost-effective in the United States or Germany. Generally, no significant improvements in QoL were found for any alternative for treating MM. A need exists for effective treatments that improve duration and QoL.



Compaison of response rate and overall survival in metastatic melanoma

Eigentler TK et al.
Lancet Oncol 2003; 4: 748–59



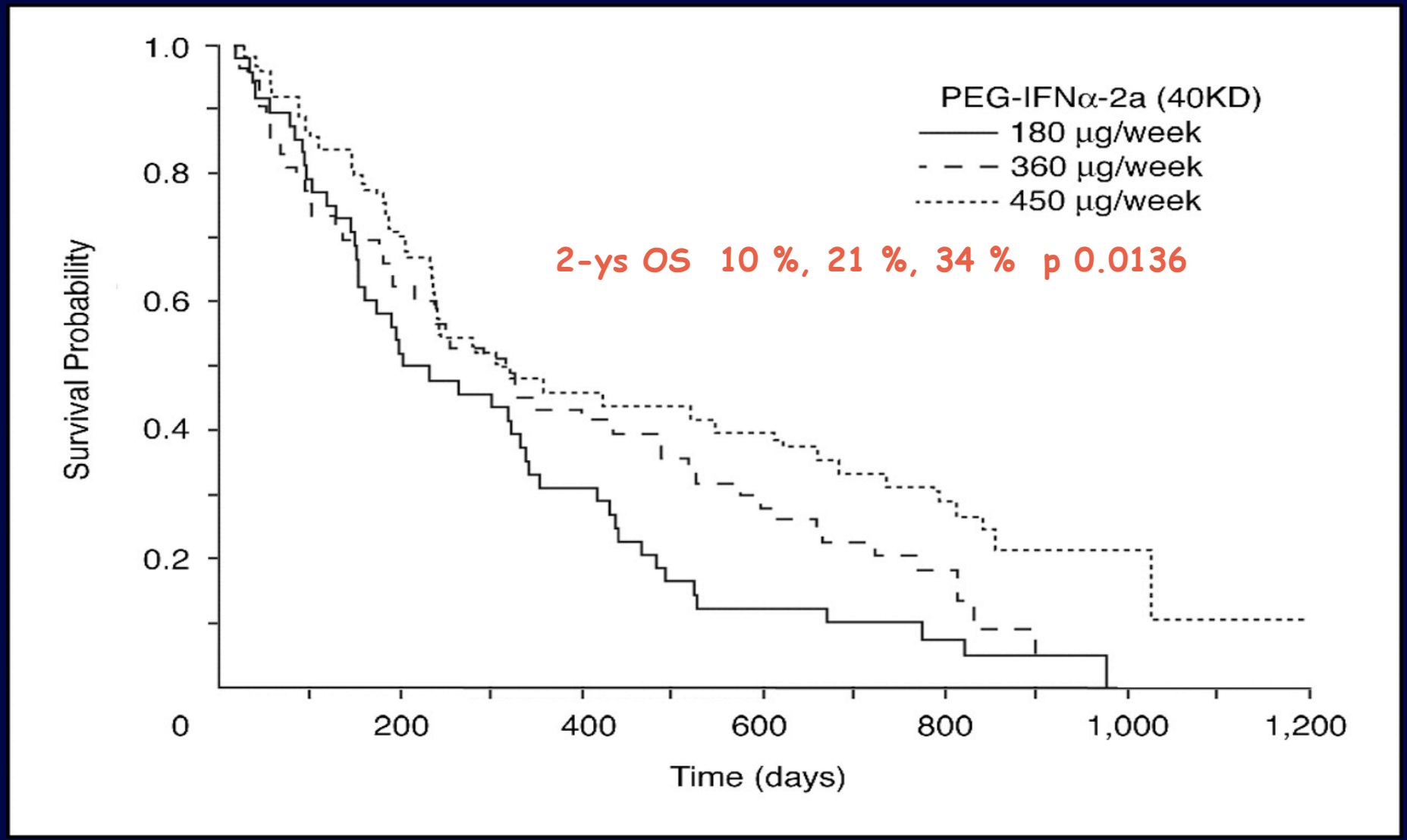
Nature Reviews | Immunology

High Dose IL-2 for Metastatic Melanoma

Atkins et al, J Clin Oncol, 1999

Number of Patients	**270**
Responders	**43 (16%)**
Complete Responders	**17 (6%)**
Durable Responses > 24 months	**12 (4.4%)**
Median Survival	**12 months**
Median duration of response	**8.9 months**
Durable Ongoing Responses > 24 months (in months) (staging based on disease site only)	**CR: 24,40,41,59,62,65,72,86, 103,106 (all M1a/b)** **PR: 55,92 (both M1c)** **+Salvage Surgery (4/5 M1c): survival: 54,60,64,66,87,103**
Treatment-related deaths (all sepsis-related)	**6 (2.2%)**

Overall survival rates by peginterferon alfa-2a (PEG-IFN{alpha}-2a) dose, based on Kaplan-Meier estimates



Dummer, R. et al. J Clin Oncol; 24:1188-1194 2006

METASTATIC MELANOMA FACTS

- There is no standardized treatment defined through randomized phase III trials (>40 published) with established prolungation of ovarall survival
- No drug combination, chemo-immunotherapy or immunotherapy gave better survival than DTIC alone in randomized trials
- DTIC alone is a drug with very limited clininically meaninful activity
- Investigational agents justified as 1st line treatment

Leptomeningeal Metastases: Still a Challenge

By Morris D. Groves, MD, JD

THE TERM leptomeningeal metastases (LM) refers to the dissemination of cancer to the pia mater, subarachnoid space, cerebrospinal fluid (CSF), and arachnoid membrane.

Incidenza fino al 25% dei casi di melanoma

Sopravvivenza mediana 8-26 sett

Causa di morte LM nel 24-34% dei casi

Sintomi neurologici centrali. Sensibilità diagnostica di un prelievo singolo di CSF: 44%, 2: 77%. Almeno 10,5 ml. Dianosi molto probabile se:

- **pressione > 150 mm H2O**
- **aumento GB**
- **proteine > 50 mg/dL**
- **glucosio < 60 mg/dL**

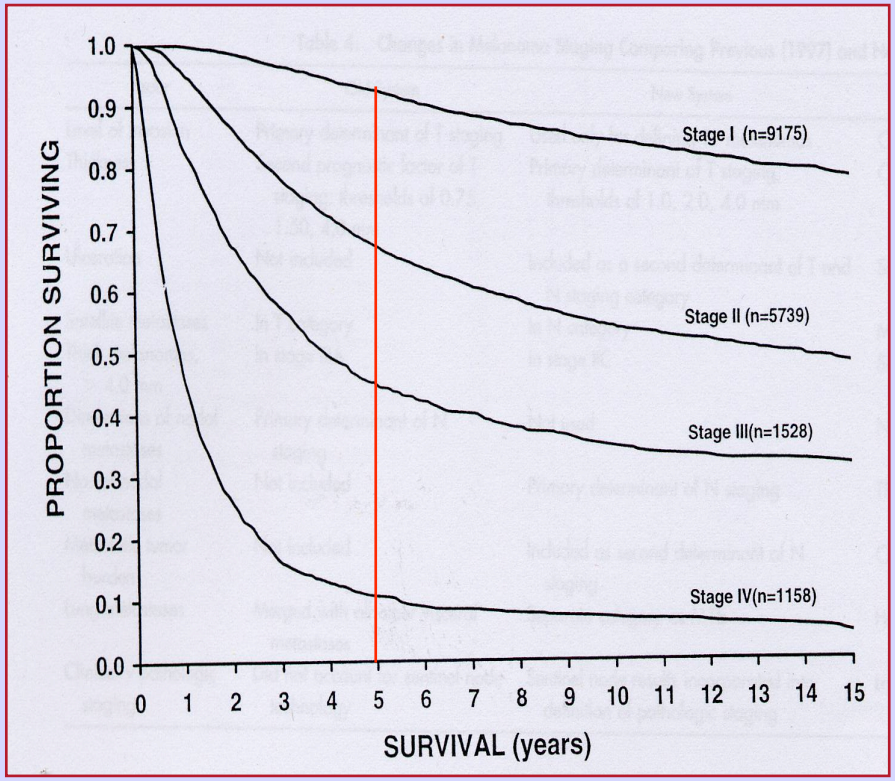
RM diagnostica

Trattamento (RT) controverso: spesso non migliora la sintomatologia neurologica e non impatta su sopravvivenza

MANAGEMENT DEL PAZIENTE CON MELANOMA
VALENZA E METODICHE DI FOLLOW UP

BACKGROUND E PROBLEMATICHE

SOPRAVIVENZA IN RAPPORTO ALLO STADIO



Sopravvivenza a 5 anni

Stadio I-II	95-45%
Stadio III	70-24%
Stadio IV	5%

Balch, JCO '01 for AJCC

MELANOMA STADIAZIONE

Stadio	% 5 y Surv	% 10 y surv
IA (1 mm without ulceration and Clark level II/III, T1aN0M0)	95	88
IB: 1 mm with ulceration or level IV/V (T1bN0M0); 1.01-2 mm without ulceration (T2aN0M0)	91 89	83 79
IIA: 1.01-2 mm with ulceration (T2bN0M0) 2.01-4 mm without ulceration (T3aN0M0)	77 79	64 64
IIB: 2.01-4 mm with ulceration (T3bN0M0) 4 mm without ulceration (T4aN0M0)	63 67	51 54

Balch CM, Buzaid AC, Soong SJ, et al. *J Clin Oncol.* 2001;19:3635-3648

MELANOMA STADIAZIONE

Stadio	% 5 y Surv	% 10 y surv
IIC 4 mm with ulceration (T4bN0M0)	45	32
IIIA:		
Single regional nodal micrometastasis, nonulcerated primary (T1-4aN1aM0);	69	63
2 to 3 microscopic regional nodes, nonulcerated primary (T1-4aN2aM0)	63	57
IIIB:		
Single regional nodal micrometastasis, ulcerated primary (T1-4bN1aM0)	59	36
2 to 3 microscopic regional nodes, nonulcerated primary (T1-4bN2aM0)	59	48
2 to 3 microscopic regional nodes, nonulcerated primary (T1-4a/bN2cM0)	46	39
IIIC:	29-24	24-15

Balch CM, Buzaid AC, Soong SJ, et al. *J Clin Oncol.* 2001;19:3635-3648

OBIETTIVI DEL FOLLOW UP

1° OBIETTIVO:
Diagnosi di ricorrenze/ "second primary" melanoma

- **Istruzione del paziente**
  - Autoesame per ricorrenze loco-regionali
  - Rilevazione dei sintomi
    (50-70% autodiagnosi)

- **Visita medica periodica**
  (25-50% di diagnosi)

- **Rx torace/Eco addome e LN/Es. emato-chimici (???)**
  (<5% di diagnosi)

Jillella et al, ASCO 1995

MANAGEMENT DEL PAZIENTE CON MELANOMA
VALENZA E METODICHE DI FOLLOW UP

"The German Society of Dermatology Guidelines"

	Stadio I-II			*Stadio III*	
ESAME	3 mesi	6 mesi	12 mesi	3 mesi	6 mesi
Es. clinico	*			*	
Eco loco-regionale		*	*	*	
Eco addome			*		*
Rx torace			*		*

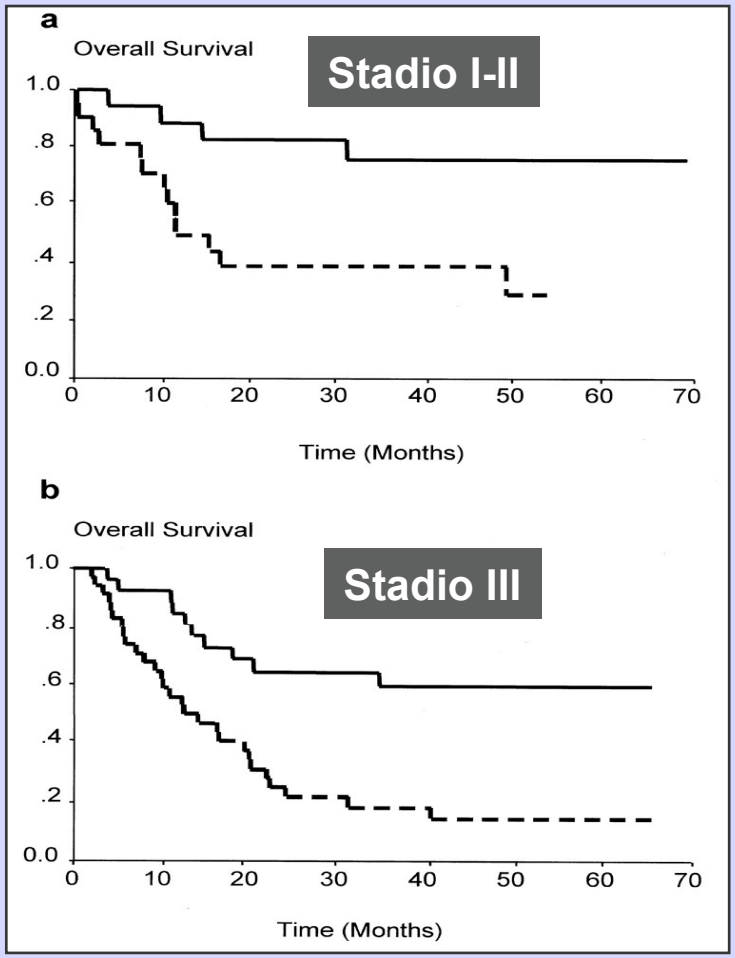
* in stadio II ogni 6 mesi

Orfanos et al, 1994

VALUTAZIONE PROSPETTICA DI UNA SCHEDULA DI FOLLOW-UP IN PTS AFFETTI DA MELANOMA

Garbe et al, JCO 2003

"early vs late detection"



Conclusioni:

1. Diagnosi precoce nel 48% dei casi che hanno avuto un beneficio significativo in sopravvivenza

2. < 1 mm: solo es. Clinico;
   > 1 mm: aggiungere ECO LN ed S100

3. In stadi I-II: Es Clinico a intervalli regolari fondamentale (25% delle dx)
   Intensità ridotta e scarso apporto di Es. chimico-strumentali
   (Si Ecografia: 2% delle diagnosi)

4. Stadio III: Intensità incrementata; importante apporto di Eco (15% delle diagnosi) e TAC (30% di diagnosi)

MANAGEMENT DEL PAZIENTE CON MELANOMA
VALENZA E METODICHE DI FOLLOW UP
"The German Society of Dermatology Guidelines"

	Stadio I-II			*Stadio III*	
ESAME	**3 mesi**	**6 mesi**	**12 mesi**	**3 mesi**	**6 mesi**
Es. clinico	*			*	
Eco loco-regionale		*	*	*	TAC
Eco addome			*		
Rx torace			*		

In stadio II e III +Es. emato-chimici (LDH, S100)

Garbe et al, JCO 2003

MANAGEMENT DEL PAZIENTE CON MELANOMA
VALENZA E METODICHE DI FOLLOW UP

TAC IN STADIO III

Pro:

- Migliora lo staging (capacità di diagnosticare il 30% delle metastasi) e quindi il trattamento nello stadio III

Garbe et al, JCO 2003

Contra:

- Scarsa capacità di diagnosticare metastasi occulte
- Veri positivi circa 10%
- No beneficio prognostico

NO raccomandata (SI in trials?)

- Falsi positivi 2-3 x dei veri positivi
- Se eseguita e positiva → conferma istologica

Buzaid et al, ASCO 1995

Autier el al. J. Clin. Oncol., 2003

MANAGEMENT DEL PAZIENTE CON MELANOMA

VALENZA E METODICHE DI FOLLOW UP

FOLLOW UP INTENSIFICATO IN STADIO III ?

QUALI OBIETTIVI ?

- **NO beneficio in OS**
- **SI cambiamento di strategia terapeutica nel 10-15% dei pts**
- **Rapporto costi/benefici?**

Tyler et al, Cancer 2000

MANAGEMENT DEL PAZIENTE CON MELANOMA
VALENZA E METODICHE DI FOLLOW UP

TAC versus PET

SENSIBILITA' SOVRAPPONIBILE
(capacità di identificare i veri positivi):
85-90%

SPECIFICITA' SOVRAPPONIBILE
(capacità di identificare i veri negativi)
45-50%

-Buzaid et al, J Clin Oncol 1995
-Kuvshinoff et al, Ann Surg Oncol 1997
-Johnson et al, Ann Surg Oncol 1997
-Tyler et al, Cancer 2000

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Confirm. Trial: Follow-up Schedule

	Physical examination /year	Lymph node sonography /year	Imaging techniques /year	Blood tests/ year (LDH, AP,S100)
≤ 1 mm Stage I				
Group A	2x	0x	0x	0x
Group B	4x	0x	1x	4x
> 1 mm Stage I-II				
Group A	4x	4x	0x	2x
Group B	4x	0x	2x	4x
Stage III				
Group A	4x	4x	2x	4x
Group B	4x	0x	2x	4x

Group A: Tübingen, Group B: Kiel and Mannheim

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Confirm. Trial: Stages and Recurrences

	Group A		Group B	
Strata	Patients	Recurrences	Patients	Recurrences
≤1mm tumor thickness	1,588 (62%)	8 (0.5%)	701 (56%)	15 (2.1%)
>1mm tumor thickness	741 (29%)	37 (5.0%)	391 (31%)	31 (8.0%)
Stage III	248 (9%)	67 (27.0%)	164 (13%)	53 (32.3%)
Total	2,577 (100%)	112 (4.4%)	1,256 (100%)	99 (7.9%)

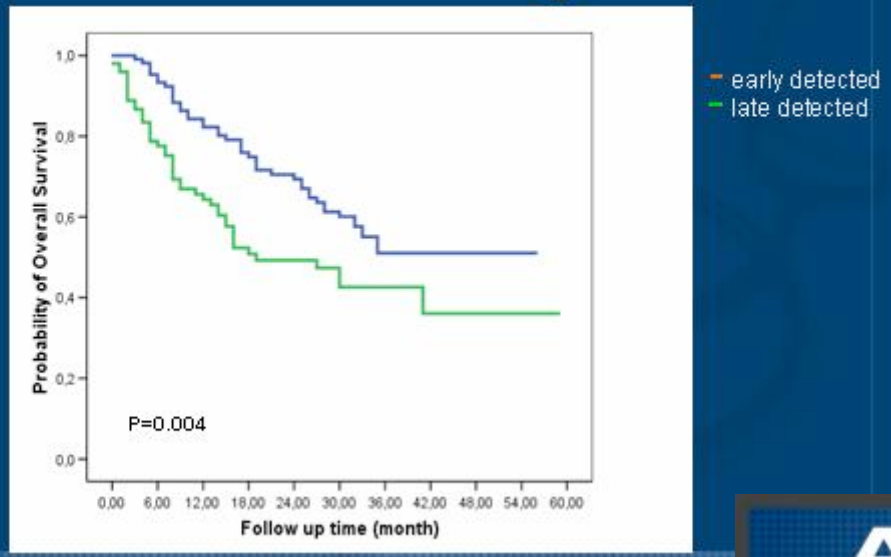
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Detection of first Recurrences by Examination Methods

	Group A		Group B	
Physical examination	68	60.7%	71	71.7%
LN Sonography	16	14.3%	7	7.1%
Chest X-ray	4	3.6%	1	1.0%
Abdomen Sonography	0	0%	0	0%
CT/MRI	15	13.4%	17	17.2%
S100	9	8.0%	3	3.0%
Total	112		99	

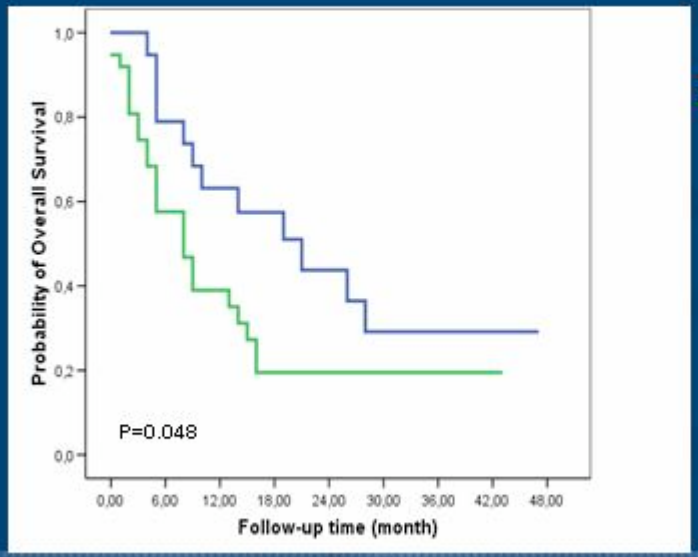
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Overall Survival of Patients with Locoregional Metastases



ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Overall Survival of Patients with Distant Metastases



"Management of Melanoma Patients: Benefit of Intense Follow-Up Schedule Is Not Demonstrated"

Assenza di studi prospettici randomizzati

Autier el al. for the EORTC

J. Clin. Oncol., October 1, 2003; 21(19): 3707 - 3707

PROPOSTA DI STUDIO