Temozolomide Oncology Drug Advisory Committee Review

March 23, 1999

Schering-Plough Research Institute

Indication

Temozolomide capsules are indicated for the first-line treatment of patients with metastatic melanoma.

Introduction

- Temozolomide is a structural analog of Dacarbazine (DTIC)
- Both temozolomide and dacarbazine are prodrugs for the active moiety MTIC
- Dacarbazine
  - IV administration
  - Hepatic metabolism
- Temozolomide
  - 100% orally bioavailable
  - Spontaneously forms MTIC

Introduction

- Rationale for developing temozolomide in metastatic melanoma
  - Same mechanism of action as dacarbazine
  - Objective responses in Phase I / II trials
  - Oral dosage form

Introduction

- Temozolomide/Melanoma - Key Issues
  - Demonstration of effectiveness
  - Equivalence to dacarbazine
  - Validity of dacarbazine as a comparator

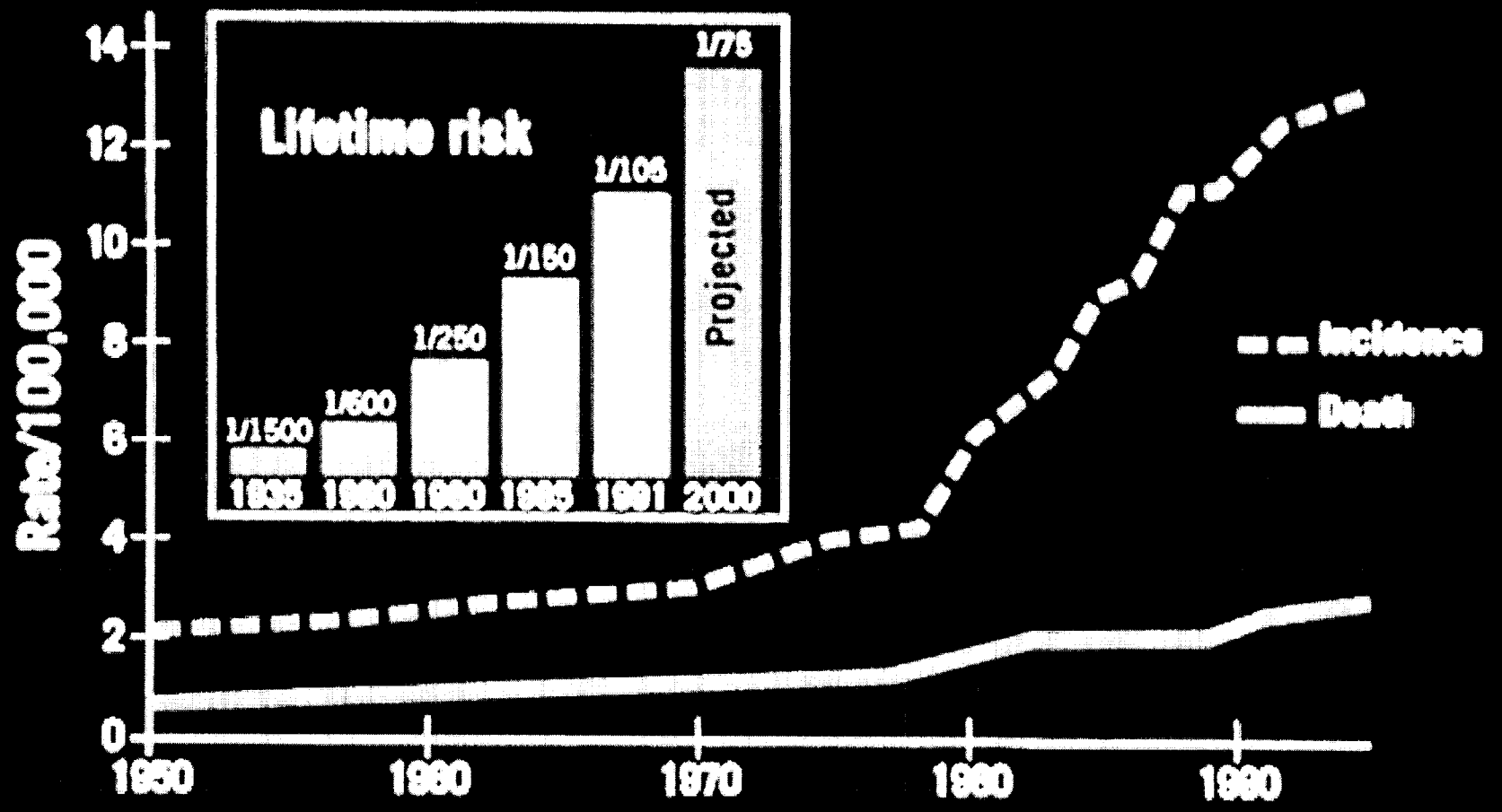
Agenda

Introduction	Colin Turnbull, PhD Schering-Plough Research Institute
Disease Background	John Kirkwood, MD University of Pittsburgh School of Medicine
Pharmacokinetics/ Metabolism	David Cutler, MD Schering-Plough Research Institute
Clinical Data	Robert Spiegel, MD Schering-Plough Research Institute
Clinical Perspective	Hilary Calvert, MD Northern Centre for Cancer Treatment Newcastle, UK
Discussion	Robert Spiegel, MD

Disease Overview

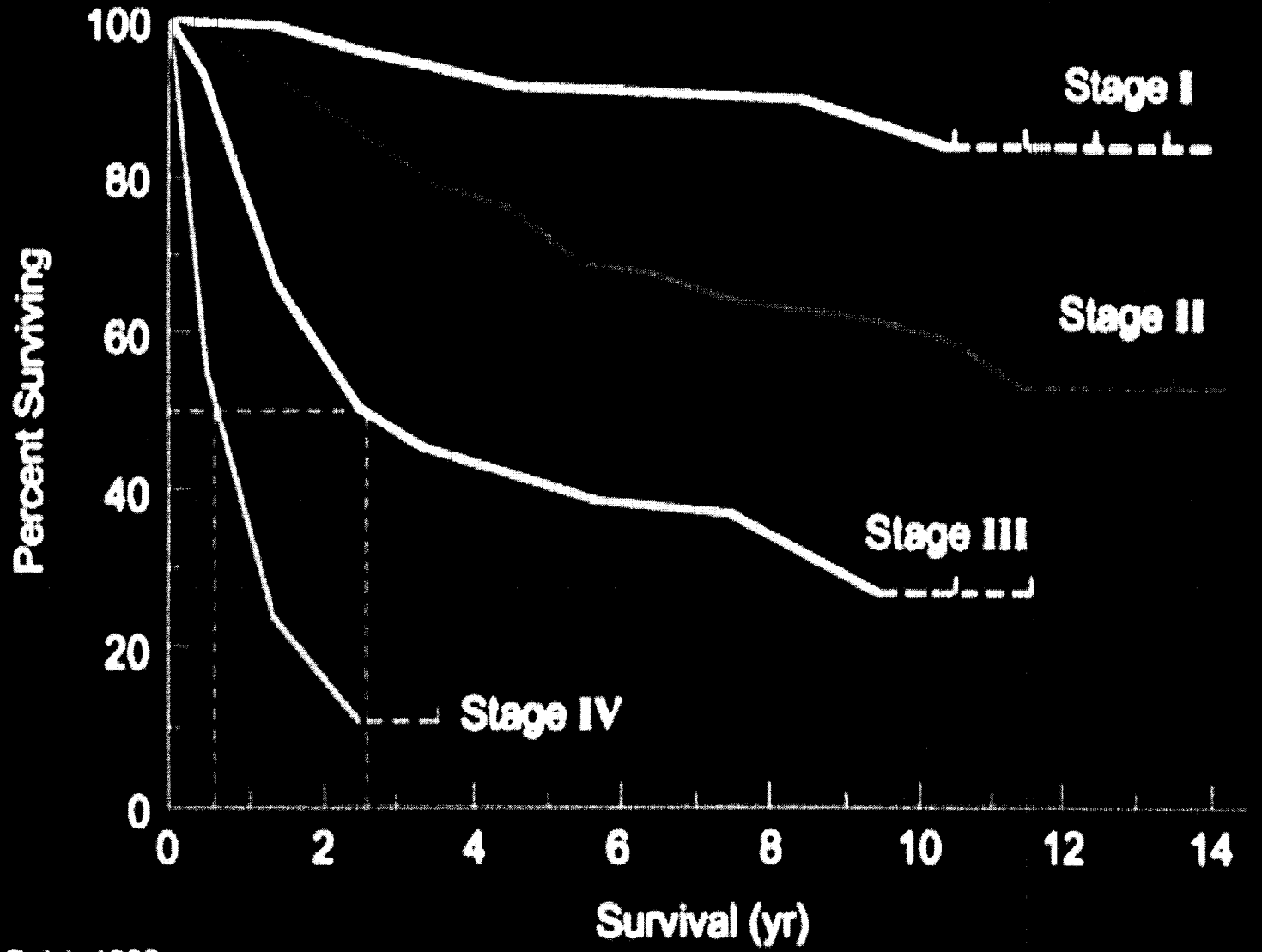
John Kirkwood, MD
University of Pittsburgh School of Medicine

Death Rate, Incidence, and Lifetime Risk



Adapted from Rigel, et al. *J Am Acad Dermatol.* 1996;34:839.

MELANOMA STAGING AND PROGNOSIS



AJCC Current System	
IA	T1N0M0
IB	T2N0M0
IIA	T3N0M0
IIB	T4N0M0
III	Any T,N1M0
IV	Any T,N2M0-2

Balch 1985

Stage IV Melanoma: Prognostic Factors

- Site of metastasis
  - Visceral versus nonvisceral
  - Hepatic
- Performance Status
- Gender
- Number of metastatic sites
- Remission duration

Survival

- Median, ~ 6 months (range, 5 to 9 mos.)
- Significant variability in individual patients and among studies
  - Role of prognostic factors and patient selection
- Long-term survivors 1.5- 5%

Goals of Treatment

- Palliation of symptoms
  - Preservation of quality-of-life
  - Toxicity of treatment key
- Prolongation of survival
  - Modest potential gains
  - Consider quality-of-life
- Cure or long-term survival
  - Low probability

Treatment Options

- Observation
- Surgical Resection
- Radiation Therapy
- Systemic
  - Immunotherapy
  - Chemotherapy
    - Single Agents, Combinations
  - Biochemotherapy

Dacarbazine (DTIC)

- Overall response rate = 10% to 20%
- CR rate = 2-5%
- Median response duration: 3 to 6 months
- Approximately 25% of CRs durable

Pooled Analysis of All Reported Studies of Dacarbazine

- 22 randomized trials
- 1095 pts received dacarbazine
- Cumulative mean RR 16.2%
- 95% CI 14.1 - 18.3%
- RRs range from 6 - 25%

Dacarbazine Literature Summary

- No randomized comparisons to placebo or best supportive care
- Only cytotoxic agent approved for metastatic melanoma
- Commonly used as a single agent
- Included in combinations routinely

Randomized Trials of Dacarbazine vs. Non-Dacarbazine Agents and Combinations

		Median Survival (Mo.)	
TRIAL	PATIENTS #	Dacarb	Non-Dacarb
vs. BCNU/VCR	50	8	6
vs. BVP	77	5	4.3
vs. BCNU/VCR	120	5.3	3.7
vs. VCR/NMU/Dact	114	N/A	N/A
vs. TIC Mustard	178	N/A	N/A

E3690
ECOG 2 X 2 Study of Dacarbazine Combined with IFN, TMX, or Both

REGIMEN	MEDIAN SURVIVAL (Mo.)
Dacarbazine	9.99
D + IFN	9.33
D + TMX	7.97
D + IFN + TMX	9.54

Dacarbazine Overview cont'd

- No single agent superior in randomized trials
  - response rate or survival
- No combination superior in randomized trials
  - M91-140/ECOG Intergroup (Dartmouth vs. dacarbazine)
  - E3695 Biochemotherapy CVD+IFN+IL-2 proposed reference arm = dacarbazine

Toxicity of Dacarbazine

- IV administration
  - 1-5 day schedules
  - Phlebitis/local pain
- Nausea and vomiting
- Neutropenia
- Veno-occlusive disease

Dacarbazine in Stage IV Melanoma Conclusions

- Useful palliation for symptomatic disease
- Consistent efficacy across numerous trials
- Only approved chemotherapy for Stage IV
- Standard of care
- Component of nearly all combinations
- Only appropriate comparator for new agents

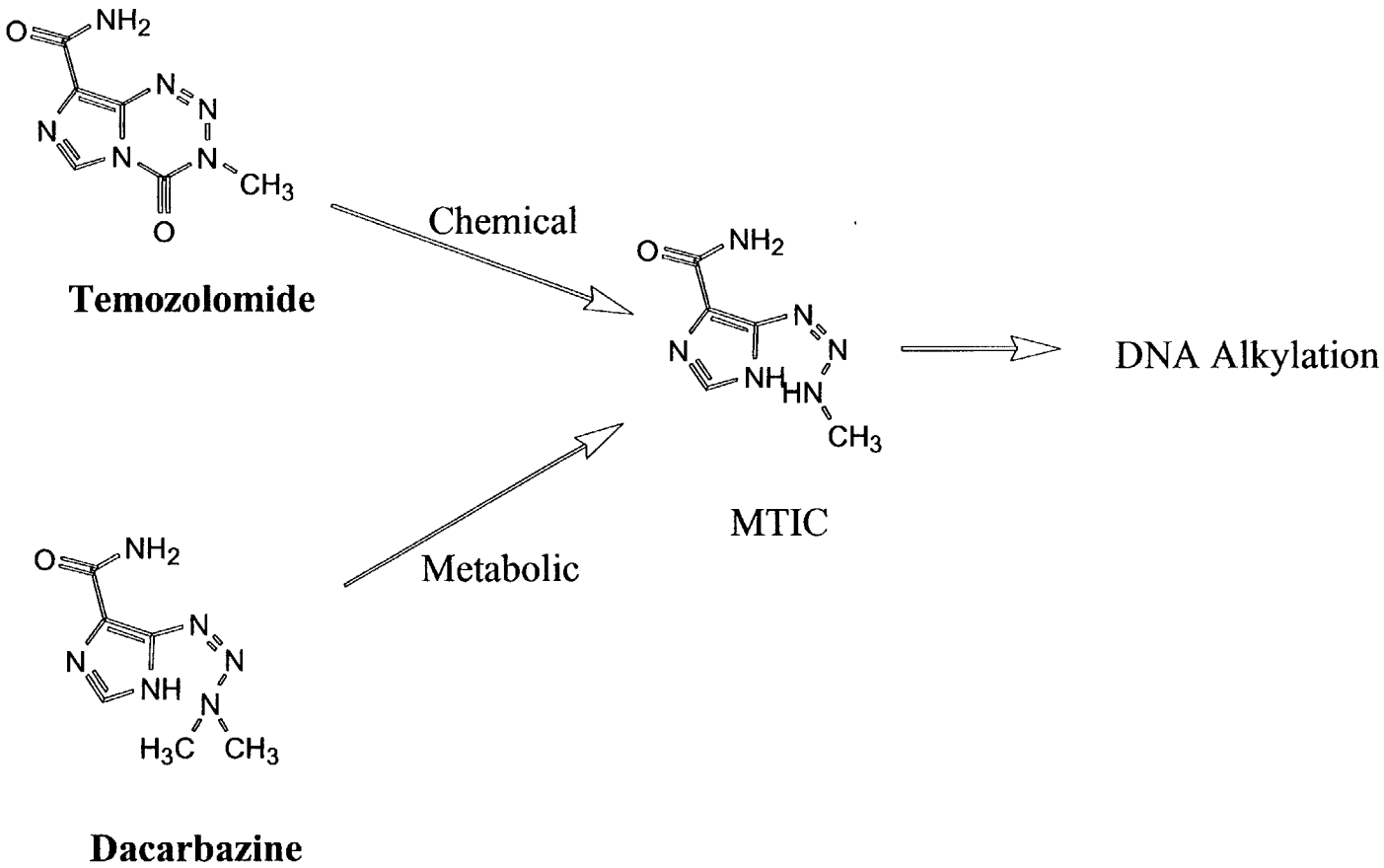
Pharmacokinetics/ Metabolism

David Cutler, MD
Schering-Plough Research Institute

Metabolism of Temozolomide and Dacarbazine

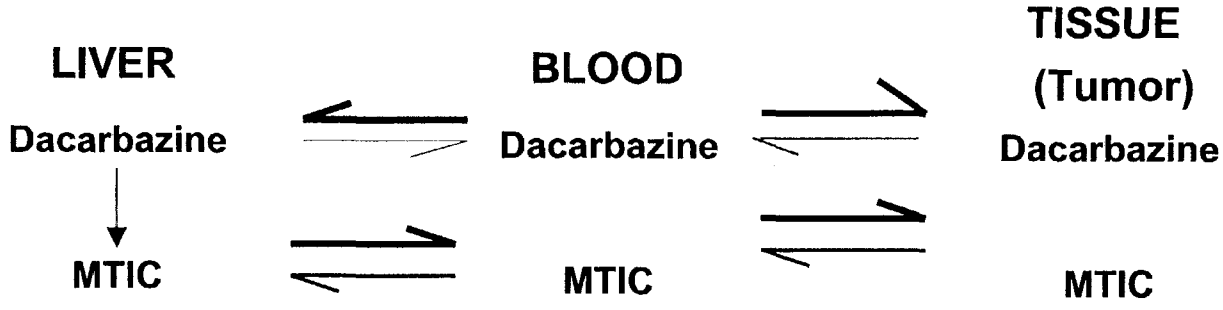
- Metabolism of Temozolomide and dacarbazine
- Implications of metabolic versus chemical transformation to active species (MTIC)
- Review of pharmacokinetics of MTIC derived from Study I95-018

Metabolism of Temozolomide and Dacarbazine

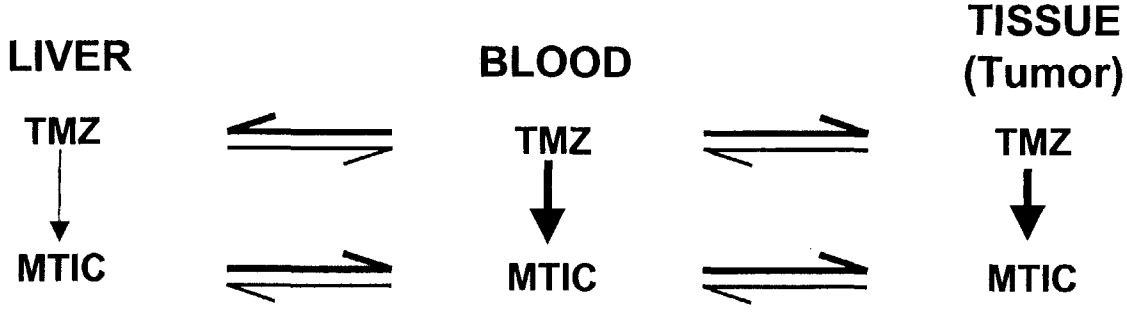


Metabolism of Dacarbazine and Temozolomide

Dacarbazine



Temozolomide

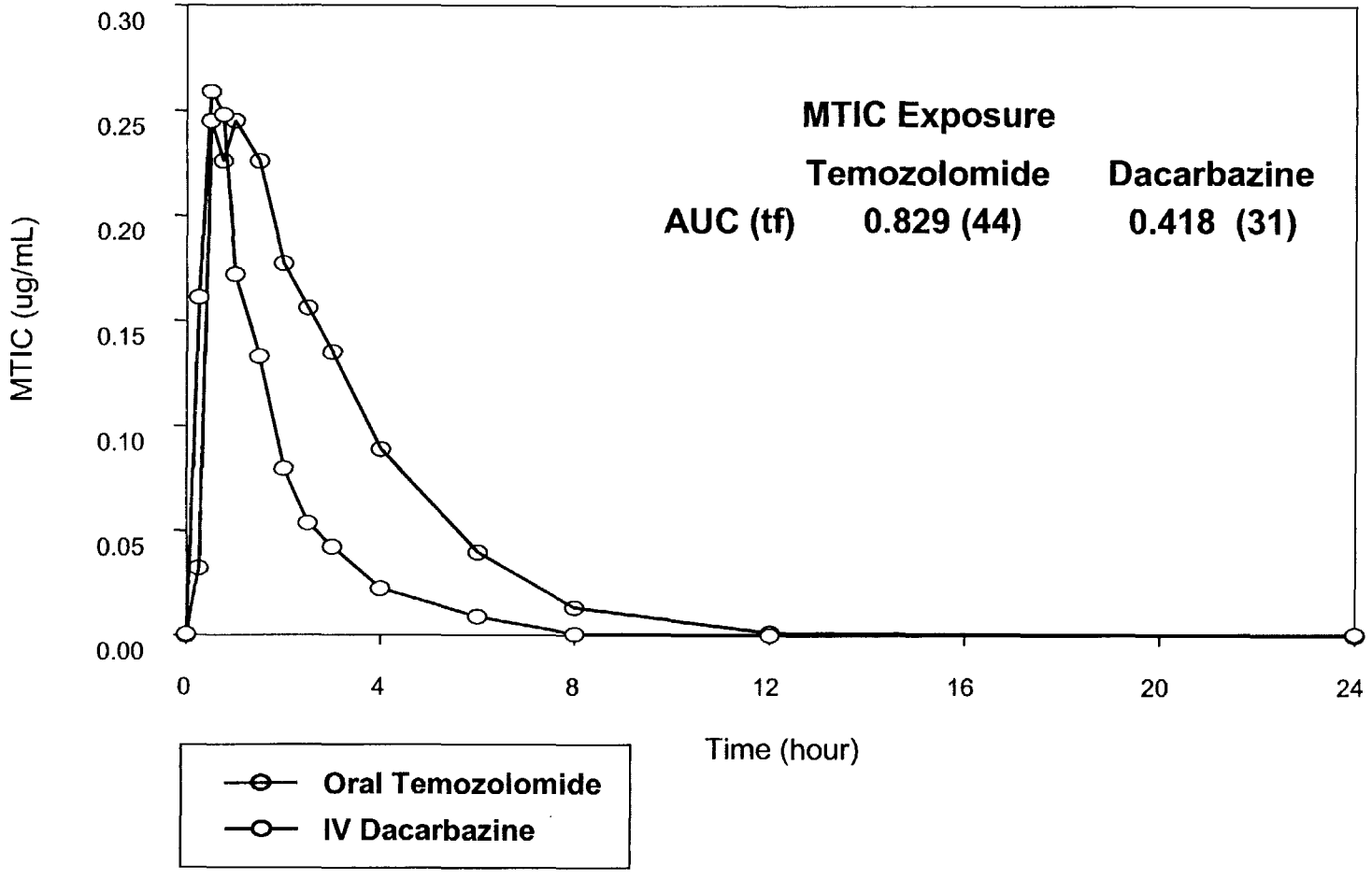


Study I95-018

- Dose
  - Temozolomide: 200 mg/m^2/day PO × 5
  - Dacarbazine: 250 mg/m^2/day IV × 5

- Multiple dose pharmacokinetics of MTIC obtained from 17 patients on each treatment

MTIC Concentration-Time Curve After IV Dacarbazine or Oral Temozolomide



Conclusions

- Temozolomide and dacarbazine are chemically related prodrugs of the active compound MTIC

- Compared with IV dacarbazine, the nonmetabolic conversion of temozolomide to the active species MTIC results in increased concentrations of MTIC in plasma

I95-018: Pivotal Trial

A Randomized, Phase III Study of Temozolomide Versus Dacarbazine (DTIC) in the Treatment of Patients With Metastatic Melanoma

Robert Spiegel, MD

Schering-Plough Research Institute

Trial Characteristics

- Population: Patients with first presentation of metastatic melanoma
- Design: Randomized, controlled, Phase III trial
- Location: 34 sites in 14 countries
- Enrollment: 305 patients (7/95 to 2/97)
  - 156 pts. temozolomide
  - 149 pts. dacarbazine
- Central randomization
- Stratification for prognostic factors

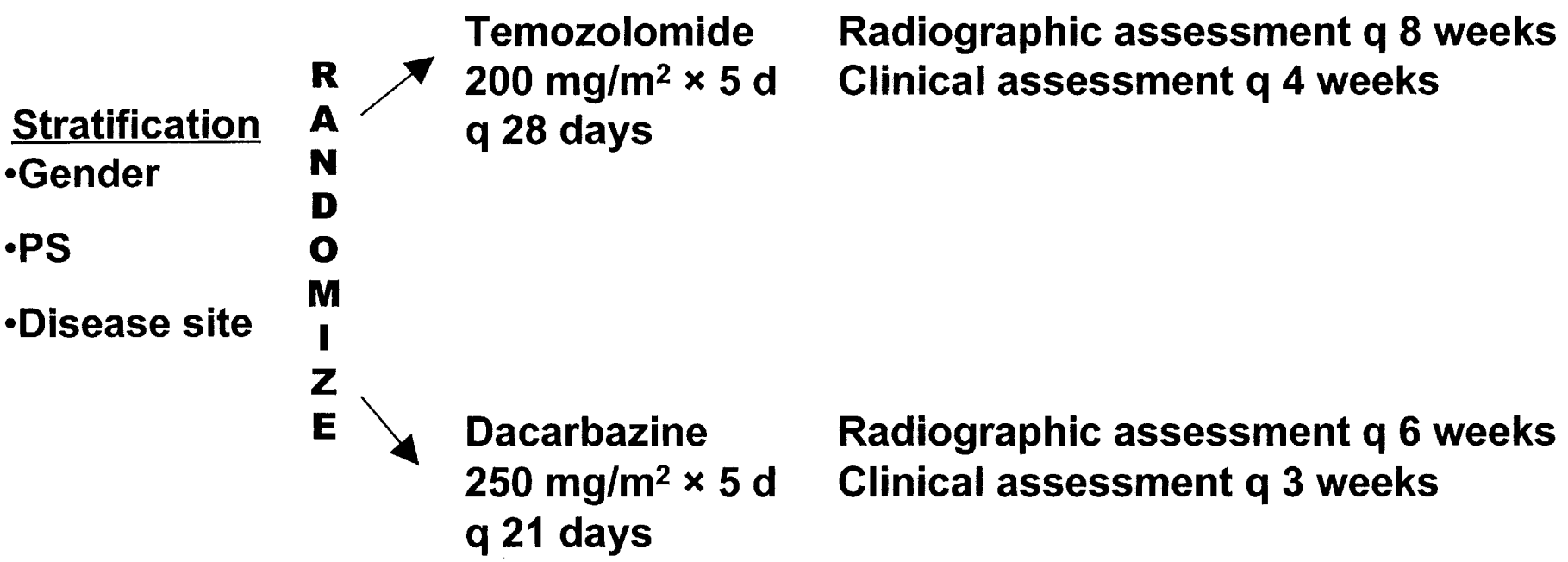
End Points / Statistical Design

- End Points:
  - Primary — Overall survival
  - Secondary — Progression-free survival
    Response rate
- Statistical design:
  - Target Hazard Ratio 1.5, assumption:
    Dacarb. 6 mos. vs temozolomide 9 mos. median survival
  - 260 patients, 210 deaths
  - Two interim analyses
  - Final p-value = 0.045 (adjusted for interim analyses)

Key Eligibility Criteria

- Histologically confirmed metastatic melanoma at first presentation with measurable disease
- No previous systemic treatment for metastatic disease
- Patients may have received one adjuvant regimen
- No CNS metastases

Trial Schema



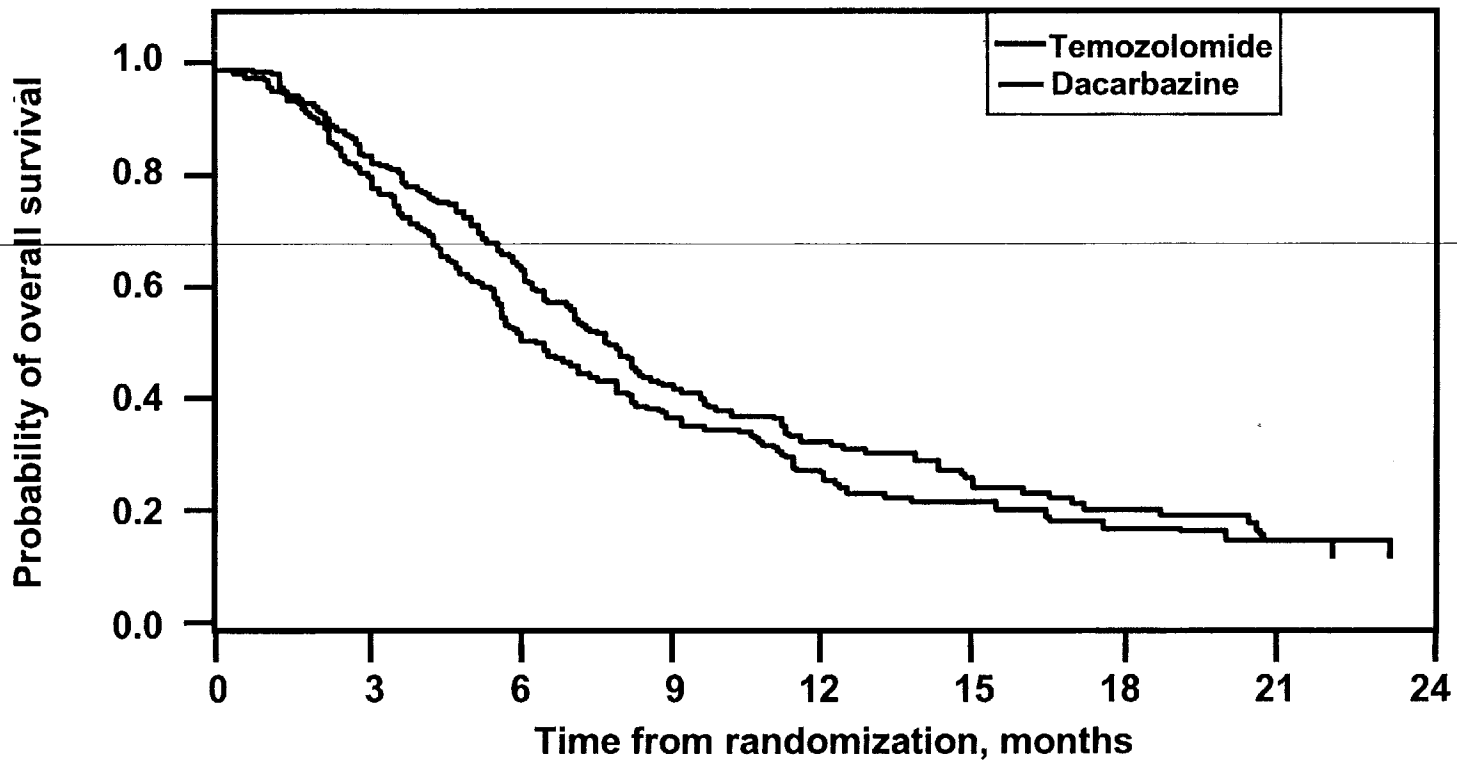
Demographics: Intent-to-Treat Population

	Patients, no. (%)	
	Temozolomide (n = 156)	Dacarbazine (n = 149)
Age, years		
Median	58.5	58.8
Range	20.7 - 82.1	23.6 - 88.4
Gender		
Male	98 (62.8)	80 (53.7)
Female	58 (37.2)	69 (46.3)
WHO Performance Status		
0	90 (58)	78 (52)
1	51 (33)	56 (38)
$\geq$ 2	14 (9)	14 (9.4)
Not reported	1 (0.6)	1 (0.7)

Baseline Disease Characteristics: Intent-to-Treat Population

	Temozolomide (n = 156)	Dacarbazine (n = 149)
Site of metastatic disease		
Hepatic and any other	49 (31.4%)	48 (32.2%)
Subcutaneous / skin only	13 (8.3%)	11 (7.4%)
Other	94 (60.3%)	90 (60.4%)
Time from initial diagnosis to metastatic disease, median	22.4 mos.	20.8 mos.
Time from metastatic disease to randomization, median	0.8 mos.	1.0 mos.

Overall Survival: Intent-to-Treat Population



Treatment group	No. patients	Median OS, months	p - *value**	Hazard ratio (HR)	95% CI for HR
Temozolomide	156	7.7	0.20	1.18	0.92 - 1.52
Dacarbazine	149	6.4			

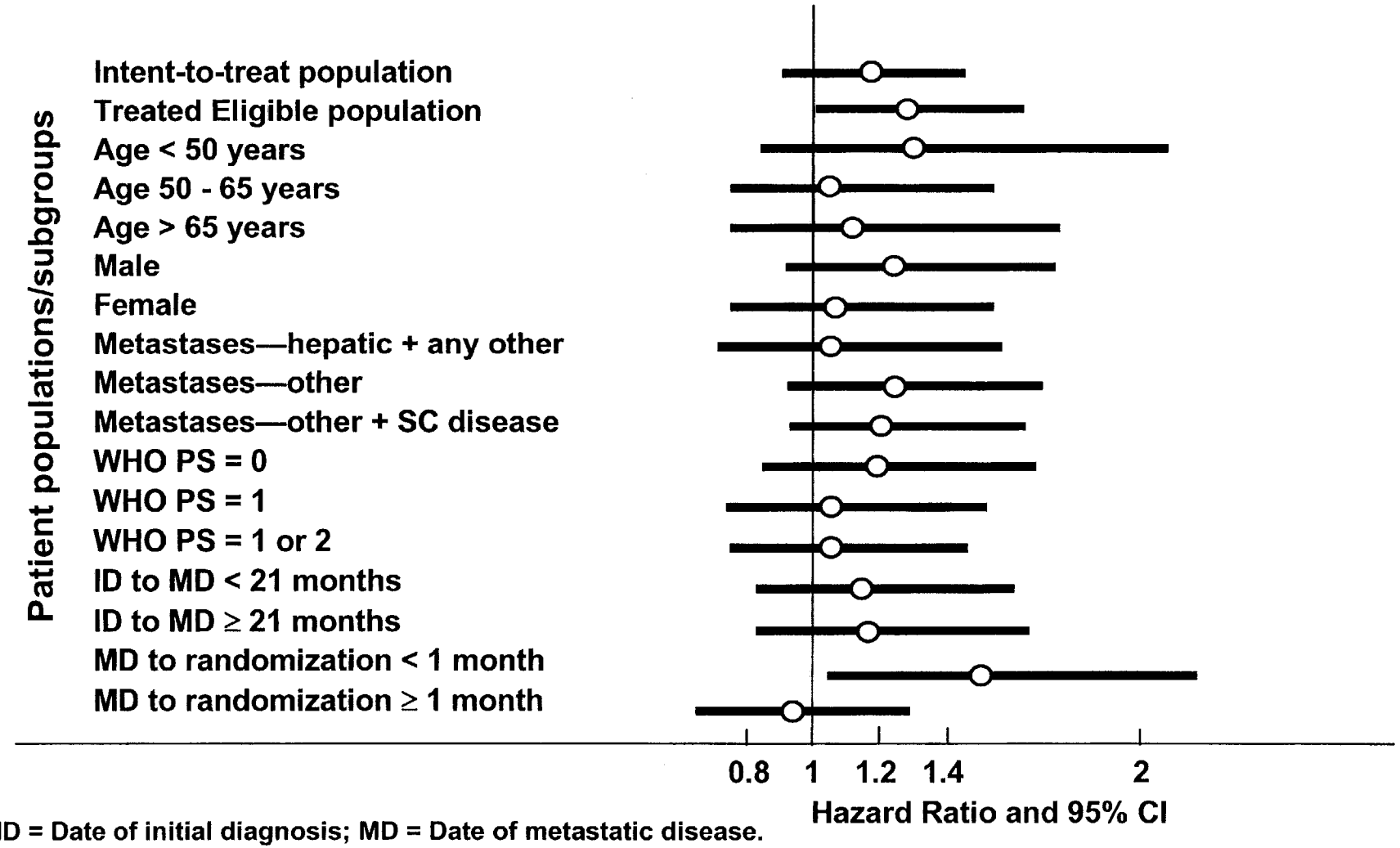
*Log rank *p* - value; nominal *p* - value for this comparison based on O'Brien-Fleming rule is 0.045.

Overall Survival Result

	Median OS	p - value	HR	95% CI
Temozolomide	7.7 mos.	0.20	1.18	0.92 - 1.52
Dacarbazine	6.4 mos.			

- Conclusion of equivalence is justified by the following:
  - Lower bound of the 95% CI (0.92) is well above the usual convention for equivalence
  - The worst case scenario of 8% inferiority equates to approximately 14 days difference

Subgroup Analysis for Overall Survival: Hazard Ratio Analysis



ID = Date of initial diagnosis; MD = Date of metastatic disease.

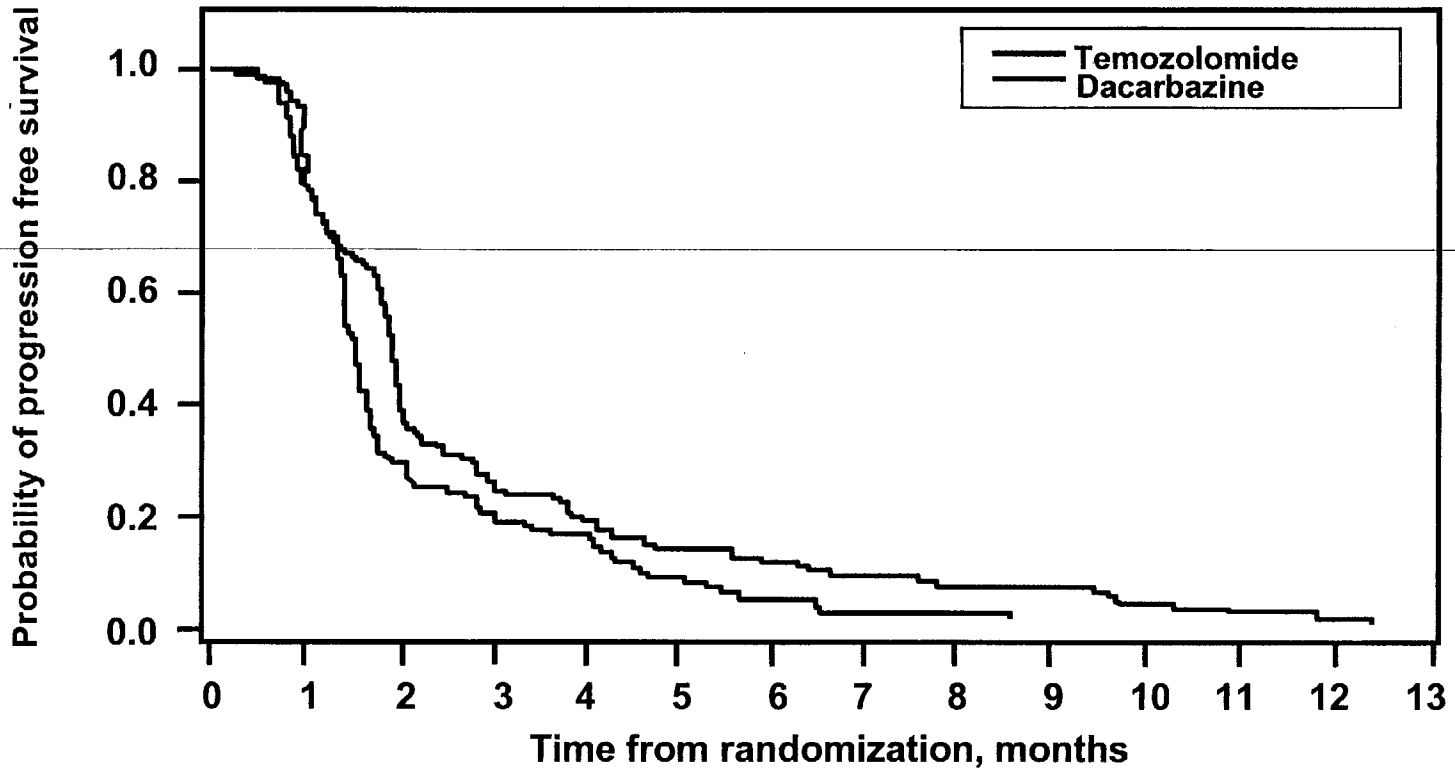
Patient Populations and Reason for Exclusion From ITT Populations

	Patients no. (%)	
	Temozolomide	Dacarbazine
Intent-to-treat population	156 (100)	149 (100)
Reason for exclusion from Treated Eligible population		
CNS metastases	2 (1)	3 (2)
Previous systemic treatment for metastatic disease	2 (1)	1 (1)
Incorrect histology	2 (1)	0
No metastatic melanoma	1 (1)	2 (1)
Did not receive study medication	5 (3)	7 (5)
Treated Eligible population	144 (92)	136 (91)

Overall Survival

Subgroup	Treatment	n	Median survival, months	*p* - value	HR (95% CI)
Intent-to-treat population	Temozolomide	156	7.7		
	Dacarbazine	149	6.4	0.20	1.18 (0.92 - 1.52)
Treated Eligible population	Temozolomide	144	7.9		
	Dacarbazine	136	5.7	0.054	1.29 (0.99 - 1.70)
Eligible population (FDA)	Temozolomide	129	7.7		
	Dacarbazine	126	5.8	0.14	1.23 (0.93 - 1.61)

Progression-Free Survival: Intent-to-Treat Population



Treatment	No. patients	Median PFS, months	*p* - value*	Hazard ratio (HR)	95% CI for HR
Temozolomide	156	1.9	0.012	1.37	1.07 - 1.75
Dacarbazine	149	1.5			

*Log rank *p* - value; nominal *p* - value for this comparison based on O'Brien-Fleming rule is 0.045.

Objective Response Rate

	SPRI Results		FDA Results	
	TMZ n=156	Dacarb. n=149	TMZ n=156	Dacarb. n=149
	n (%)	n (%)	n (%)	n (%)
CR	4(2.6)	4(2.7)	4(2.6)	4(2.7)
PR	17(10.9)	14(9.4)	15(9.6)	10(6.7)
CR+PR	21(13.5)	18(12.1)	19(12.2)	14(9.4)
95% C.I. for RR	(8.1%,18.9%)	(6.9%,17.3%)	(7.1%,17.3%)*	(4.7%,14.1%)*

* Calculated

Objective Response Duration

	Number of Responders	Median Response Duration (mo)	95% C.I.	p-value
TMZ	19	5.53	4.3 – 8.7	0.003*
Dacarbazine	14	3.22	2.4 – 4.1	

* Log Rank (FDA analysis)

Complete Responders

Pt. #	Sex /Age	PS	Skin/SQ	Lymph Nodes	Soft Tissue	Lung	Liver	Bone	Other	Response Duration	Surv.
Temozolomide											
11-009	M/64	0					○			NA+	45.3+
14-004	M/30	0	○							34.7+	36.5+
14-014	M/74	2	○							3.7	29.9+
22-001	M/43	0	○			○				16.6	36.1+
Dacarbazine											
01-001	F/ 50	0			○					35.6+	41.1+
02-009	M/70	0		○						12.1	12.1
16-017	F/ 88	2	○	○						19.1	29.0+
36-001	M/28	0	○	○						31.0	39.7+

Partial Responders - Temozolomide

Pt. #	Sex /Age	PS	Skin/SQ	Lymph Nodes	Soft Tissue	Lung	Liver	Bone	Other	Response Duration	Surv.
02-002	M/59	0		○						5.6	14.7
04-004	M/51	2	○	○		○				8.8	16.7
04-007	M/66	0				○	○			8.0	19.8
07-001	M/47	1					○			1.1	7.3
11-006	M/65	1			○			○		4.1	25.3
12-001	M/57	0		○			○	○	○	30.3+	40.6+
14-005	F/ 56	0	○							9.1	18.6
14-007	F/ 69	1	○	○						32.5+	34.3+
14-013	F/ 67	1		○						5.7	29.6+
19-013	M/52	0		○						5.5	26.0+
24-001	F/ 58	1		○						2.1	24.3
24-004	M/44	0				○				7.7	36.6+
24-005	M/75	0	○	○						3.7	29.8+
27-001	F/ 48	0	○	○		○			○	31.5+	33.3+
27-005	M/42	0							○	5.1	7.5
28-001	F/ 65	0				○		○		9.9	14.2
37-003	M/68	0				○				2.3	12.7

Survival of Responders

	Temozolomide (n=21)		Dacarbazine (n=18)	
Survival	alive (censored)	% alive*	alive (censored)	%alive*
12 months	19 (0)	90%	13 (0)	72%
18 months	15 (0)	71%	10 (1)	56%
24 months	13 (2)	62%	5 (2)	36%
Median Survival	26.1+ mos		20.9 mos.	

+ = estimated
*Based on Kaplan-Meier estimates
Based on updated data, 3/99

Safety

Dose Reduction Patients Receiving >1 Cycle of Study Drug

	Temozolomide (n =125)		Dacarbazine (n =117)	
	Number of Patients	Percent	Number of Patients	Percent
Received Full Dose Over Course of Study	106†	85%	109	93%
1 Dose Level Reduction	15	12%	3	3%
2 Dose Level Reductions	4	3%	5‡	4%

* Cumulative percent is based on the number of patients who received more than 1 cycle of study drug.

† 1 patient had a dose reduction to 150 mg/m^2 at cycle 3 due to thrombocytopenia but for all subsequent cycles received 200 mg/m^2.

‡ Three of these patients went directly to 125 mg/m^2 from the starting dose without first receiving a single dose reduction to 187.5 mg/m^2.

Adverse Events (Grade 3 / 4) in > 5% of Treated Patients

Adverse event	Patients, no. (%)	
	Temozolomide (n = 156)	Dacarbazine (n = 149)
Vomiting	7 (5)	5 (4)
Pain	10 (7)	19 (13)
Headache	9 (6)	2 (1)

Myelotoxicity Summary

	Patients with change from grade 0 to 2 at baseline to grade 3 or 4 during treatment, no. (%)*	
Parameter	**Temozolomide**	**Dacarbazine**
Hemoglobin	10/148 (7)	9/142 (6)
Neutrophils	31/144 (22)	20/134 (15)
Platelets	29/148 (20)	19/142 (13)
WBC	13/148 (9)	18/142 (13)

* Based on patients with a baseline evaluation and at least one subsequent evaluation.

Safety

- Acceptable safety profile
- Comparable safety to dacarbazine:
  - Rate of overall adverse events
  - Similar Grade 3/4 adverse events
  - Myelotoxicity
  - Similar low drop-out rate (<5%)
- Similar safety profile to overall experience in 1017 patients

Conclusion

Substantial Evidence of Effectiveness:

- Temozolomide and dacarbazine are both active as indicated by objective responses
- Temozolomide response durations were longer than dacarbazine
- Progression-free survival favors temozolomide
- Overall survival estimate demonstrates temozolomide is at least equivalent to dacarbazine and not meaningfully worse
- Overall survival results consistently better in almost all subgroups

Clinical Perspective

Hilary Calvert, MD

Professor, Medical Oncology

Director, Cancer Research Unit
Northern Centre for Cancer Treatment

Newcastle, UK

Chairman, Cancer Research Campaign,

Phase I/II Committee, UK

CRC Phase II Temozolomide Melanoma Trials

- Population: Stage IV melanoma, CNS mets permitted
- Regimen: 200 mg/m^2/day x 5 q 28 d
- Study 020, 60 pts. (JCO April 1995)
  - Overall RR — 21% (95% CI = 10 - 32%)
  - Median response duration — 5 mos. (2.7-64.5+)
- Study 028, 61 pts. (BJC September 1998)
  - Overall RR — 13%
  - Median response duration — 6.4 mos. (3.9-45.5+)

Management of Metastatic Melanoma (NCCT, UK)

- 30 - 40 patients per year
- First line dacarbazine or investigational agent
- Significant responses seen with dacarbazine in some patients
- Spontaneous remissions - 3 observed in 18 years

Study I95-018: Appropriate Design?

- A 50% improvement in survival was in retrospect too ambitious
  - Survival benefits are seldom seen with drugs with a 20% response rate
  - Temozolomide is a more efficient prodrug than dacarbazine for MTIC, not a qualitatively different agent
  - Equivalence would have been a realistic goal
  - Noteworthy that trends to superiority seen in all endpoints

Temozolomide and Dacarbazine Patient Convenience

- Both drugs showed a very similar incidence of adverse events
- Dacarbazine requires venous access (IV line, or 5 daily infusions), office visits, and potent antiemetics
- Temozolomide is an oral agent and only requires clinic visits for assessment

Temozolomide in Melanoma: Conclusions

- Clinically meaningful improvement in treatment
- Easy drug for physician administration and patient convenience
- Basis for future improvements in therapy

Discussion

Dr. Robert Spiegel
Schering-Plough Research Institute

Conclusions

Consistent evidence of effectiveness

- All point estimates demonstrate effectiveness of temozolomide
    - Obective responses
    - Longer response duration
    - More responders alive at 12, 18, and 24 months
    - PFS favors temozolomide
    - Overall survival favors temozolomide, supporting demonstration of equivalence to dacarbazine
- Temozolomide delivers higher MTIC concentrations at equitoxic doses to dacarbazine
- Temozolomide is a convenient, well tolerated oral drug