NDA 21-051 Advanced, Metastatic Melanoma
FDA Review Team

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NDA 21-051 Administrative History

FDA-SPRI TMZ Meetings	Actions re NDA
11/17/94	No Discussion
10/8/96	No Discussion
8/7/97	No Discussion
6/18/98 (Pre NDA)	Trial results presented
8/13/98	NDA Submitted
3/23/99	ODAC

DTIC in Advanced, Metastatic Melanoma

Regulatory History

- Evaluated in 450 patients enrolled in NCI sponsored cooperative group trials.
- FDA approval in May 1975.
- Approval based on response rate; 23% overall, 6% CR's.
- No data indicating that DTIC prolongs Overall or Progression Free Survival.

NDA # 21-051 Metastatic Melanoma

Pivotal Trial I95-018

TMZ/DTIC

34 Sites/0 USA

I95-018: Pertinent Design Features

- Different Treatment schedules
  - Temozolomide PO every 4 weeks
  - Dacarbazine IV every 3 weeks
- No Blinding

I95-018- FDA Study Analysis

- Response and Progression - From actual tumor measurements (site reviewer primary data).

- All other information from tables compiled by the sponsor.

I95-018 - FDA Study Analysis

- Delayed (> 1 month) evaluations indicating progression

  Censored at last evaluation - FDA

- Death without documented progression or clinical deterioration

  Censored at last evaluation - FDA

Melanoma Data Set - SPRI

- ITT Population (305 Pts)

- Eligible Population (292 Pts)
  - Protocol Specified Diagnosis
  - No Prior Treatment
  - No Brain Metastases

- Treated Eligible Population (280 Pts)

Primary Efficacy Endpoint

Overall Survival

With 210 deaths a 3 month median survival difference (6 mos for DTIC vs 9 mos for TMZ) would be detectable with 80% power at an overall 5% level of significance

244 deaths occurred (124 TMZ, 120 DTIC)

Melanoma-Secondary Efficacy Endpoints

Progression Free Survival
Objective Response Rates
Quality of Life
Pharmacokinetics

Regulatory Issue
Overall & Progression Free Survival

DTIC is not known to prolong overall- or progression free survival of patients with metastatic melanoma.

Thus TMZ must be superior to DTIC; Equivalence is not sufficient.

Patient Characteristics

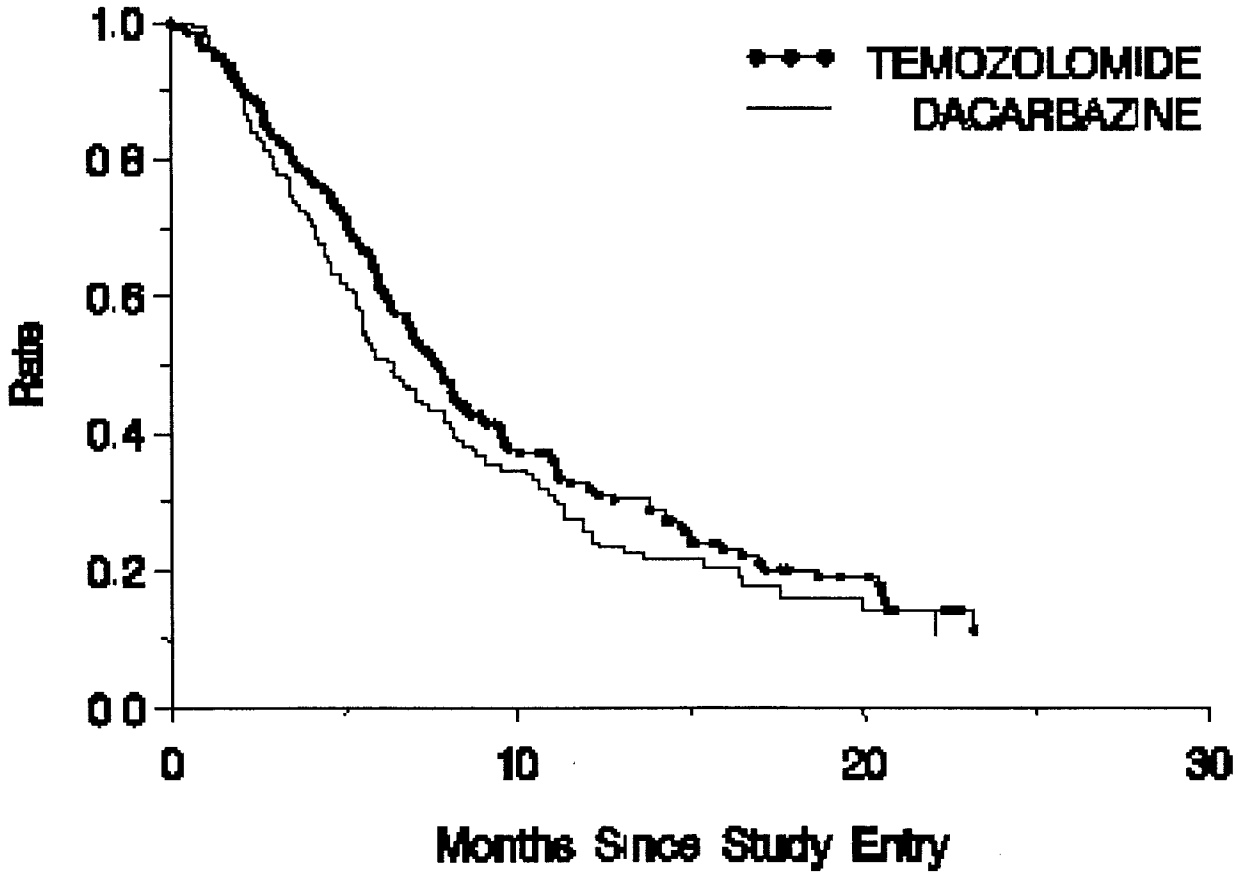
TMZ & DTIC Patients Comparable For:

- Age
- Sex
- Race
- P.S.
- Initial Disease Stage
- Time-Dx to metastasis
- Time-Metastasis to Rx
- Sites of Metastases
- Prior Therapies
- Hgb, Albumin, LDH

Overall Survival - ITT Population

Treat-ment	# of Pts/ # Dead	Median Survival (mo)	p-value	Hazard Ratio	HR 95% CI
TMZ	156/124	7.7	0.20	1.18	0.92, 1.52
DTIC	149/120	6.4			

Overall Survival - ITT Population



Survival-Eligible & Treated Eligible-SPRI

Group	Rx	n	Median Surv (mo)	p	H.R.	HR 95% CI
Elig	TMZ	149	7.9	0.06	1.28	0.99, 1.65
	DTIC	143	5.9			
Rx Elig	TMZ	144	7.9	0.054	1.29	0.99, 1.70
	DTIC	136	5.7			

6-Month Survival Rate-SPRI

ITT Population	6-Month Survival Rate	95% CI	p
TMZ (n=156)	61%	53-69%	0.063*
DTIC (n=149)	51%	43-59%	
* chi-square test			

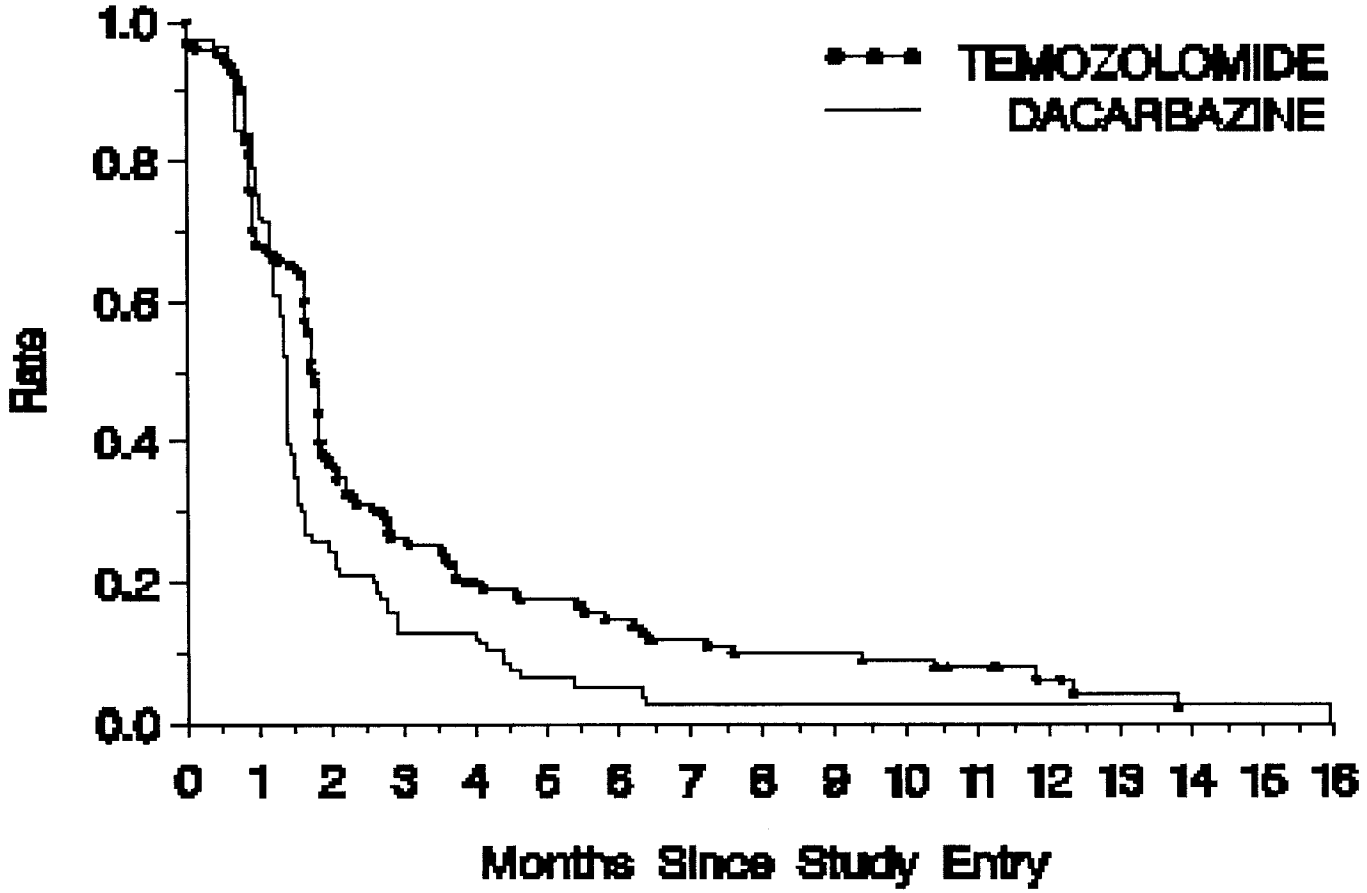
Progression Free Survival - FDA

ITT # Pts/ # Progressed	Median PFS mos.	Log-rank p	Hazard Ratio	95% CI for HR
TMZ 156/140	1.74 (1.64-1.84)	0.002§	1.49	1.15-1.92
DTIC 149/128	1.38* (1.32-1.41)			

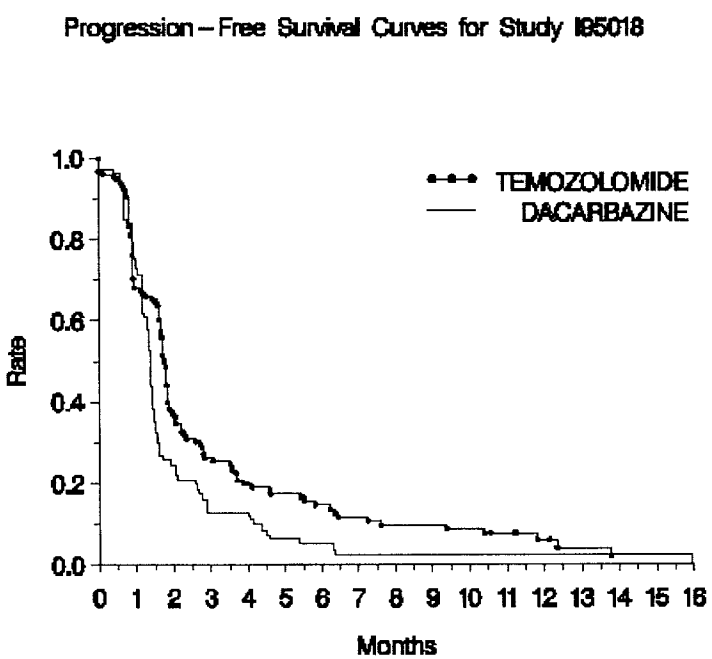
* Difference = 0.36 mo. or about 11 days

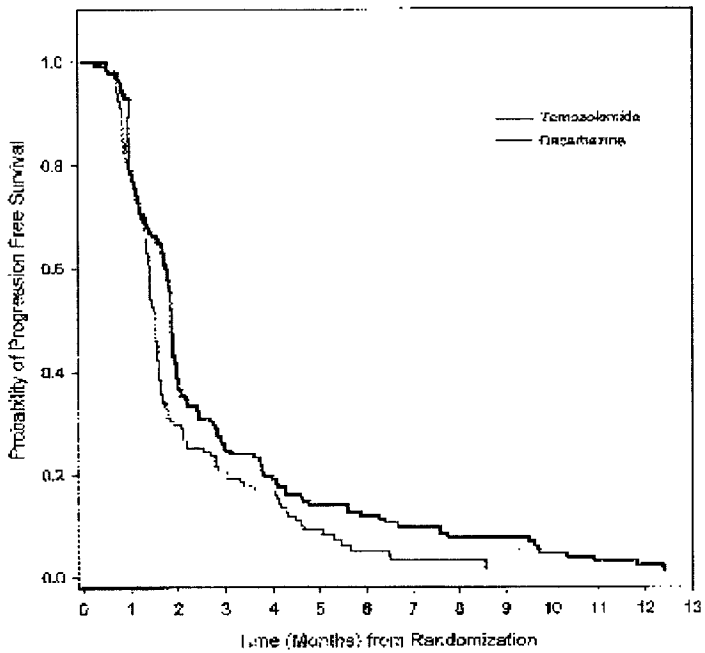
§ Sponsor's p-value 0.012 (1.9 vs 1.5 mo)

Progression Free Survival -ITT Population-FDA



PFS per FDA and Sponsor





Response Rate per Sponsor

	TMZ – 156 pts		DTIC – 149 pts	
	n	%	n	%
CR	4	2.6	4	2.7
PR	17	10.9	14	9.4
CR+PR	21	13.5	18	12.1
$\chi\theta$Test	P=0.7			

Response Rate per FDA

	TMZ 156 pts		DTIC 149 pts	
	n	%	n	%
CR	4	2.6	4	2.7
PR	15	9.6	10	6.7
CR + PR	19	12.2 (7.07-17.3)	14	9.4 (4.7-14.1)
$\chi\theta$Test	p=0.43			

Objective Responders
Sites of Disease

Disease Sites	Number of Responders		
	TMZ	DTIC	Total
Cutaneous or Nodes or Both	7	7	14
Lung ± Cutaneous ± Nodes	6	4	10
Liver ± Other	3	2	5
Other Visceral or Bone	3	1	4

Complete Responders
Sites of Disease

	Number of Patients	
	TMZ	DTIC
Cutaneous, Nodes, Both	2	4
Bone	1	0
Liver	1	0

Mean Baseline Tumor Area

Responders vs All Patients

	Mean Tumor Area (cm^2)	Range (cm^2)
Responders	3.7	0.05-99.0
All Patients	10.8	0.04-304.0

Response Duration

	No. of responders	Median response duration (m)	95% CI
TMZ	19	5.53	4.3-8.7
DTIC	14	3.22	2.4-4.1

Chemotherapy After Progression

No. of Cycles	No. of Patients	TMZ	DTIC
1	217	109	108
2	162	84	78
3	122	64	58
4	97	51	46
5	73	38	35
6	48	26	22
>6	8	3	5

Chemotherapy After Progressive Disease

Drug	TMZ Treated	DTIC Treated	Total
DTIC	28	29	57
Cisplatin	28	31	59
Nitrosourea	21	21	42
Vinblastine/ Vindesine	16	18	34

Survival After Progressive Disease

	n	Median (mo)	95% CI	p	HR (95%CI)
TMZ	122	4.7	3.5-5.2	0.27	1.15 (0.9-1.5)
DTIC	119	3.8	2.8-4.6		

HQL Evaluation

Protocol: Longitudinal & QTwiST Analyses

Actually Performed:

- Q-TwiST analysis
- HQL at weeks 12 and 24 compared to baseline
- Improvement or maintenance of good functional level
- HQL changes in clinical responders

Conclusion: All analyses subject to heavy censoring
No statistically significant differences

Mean Pharmacokinetic Parameters

	Mean (%CV)			
	TMZ 200 mg/m2	DTIC 250 mg/m2	MTIC (T)	MTIC (D)
Cmax	11.2 (27)	10.2 (44)	0.31 (56)	0.29 (41)
Tmax	1.06 (58)	0.5 (25)	1.05 (55)	0.62 (28)
t½	1.77 (9)	1.63 (36)	1.76 (22)	1.42 (36)
AUC µg·hr/ml	34.4 (13)	16.0 (69)	0.86 (39)	0.47 (28)

Hematologic Toxicity - FDA

	TMZ (n=156)		DTIC (n=149)	
	Pts with data	Gr 3 or 4 toxicity No. (%)	Pts with data	Gr 3 or 4 toxicity No. (%)
Hgb	155	10 (6)	149	10 (7)
Neutrophils	154	24 (16)	149	19 (13)
Platelets	155	31 (20)	149	19 (13)

Hematologic Toxicity Duration- FDA
% of Blood Counts with Gr 3/4 Toxicity

	% (range) of all CBC's with Gr 3/4 Toxicity	
	TMZ	DTIC
Neutrophils	17 (3-33)	25 (3-52)
Platelets	23 (4-63)	25 (4-67)

Hematology: Time From Nadir to Recovery - SPRI

	Median Time to Recovery (Days)	
	TMZ	DTIC
Neutrophils	7.0	11.5
Platelets	7.0	10.0

? TMZ Related Hypercoagulability

	TMZ	DTIC
Thrombosis	2	2
Phlebitis	0	1
Suspected Pul-monary Embolus	0	2

FDA Concerns with Study Population

ITT Population 305 Pts
SPRI Eligible 292 Pts

FDA Analysis

- Ineligible (minimum) 53 pts
- Non-Evaluable (Response & PFS) 25 pts

Reasons for Study Ineligibility- FDA

	TMZ # pts	DTIC # pts
Brain scan abnormal	3	4
No measurable tumor	3	2
Inclusion criteria not met	2	3
Exclusion criteria met	3	3
Biologic Rx within 28 days	4	4
Radiation Rx within 14 days	1	1
Baseline Hgb <10g/dl	8	5
Other cancer	1	0
Stage 4 at Dx >3m to 1st Rx	6	0
Total	31	22

Reasons for Non-Evaluability - FDA

Response or Progression

	TMZ	DTIC	Total
No baseline tumor measurement	2	4	6
No tumor measurement after baseline	9	10	19
Total	11	14	25

Overall & 6 Month Survival - SPRI

Popul-ation	Drug	# of Pts	Median (mos)	p	H.R	95% CI
ITT	TMZ	156	7.7	0.20	1.18	0.92, 1.52
	DTIC	149	6.4			
Eligible	TMZ	149	7.9	0.06		
	DTIC	143	5.9			
Treated Eligible	TMZ	144	7.9	0.054		
	DTIC	136	5.7			
6 Month Survival ITT	TMZ	156	61%	0.063		
	DTIC	149	51%			

FDA Concerns With Survival Analyses

- FDA-Equivalence of survival is insufficient since DTIC has never been shown to prolong survival.

- FDA-Disagrees with eligible patient population.

- FDA-Notes that 6-month survival analysis was:
  - not pre-specified in the protocol.
  - not used by FDA as a basis for marketing approval.
  - only a snapshot and does not consider what came before or after.

FDA Concerns With PFS

Despite p=0.002 Favoring Temozolomide

- Median PFS difference is about 11 days
- DTIC patients were evaluated more frequently for progression.
- Study was not blinded.

FDA Concerns with Response Rate

Response Rates

TMZ 12.2% (7.07, 17.3) (p=0.43)

DTIC 9.4% (4.7, 14.1)

- Odds ratio for tumor response 1.337 (0.664, 2.775)
  - TMZ response rate (rr) could be 34% < DTIC rr.

- Difference in response rates 0.028 (-0.056, 0.119)
  - TMZ response rate could be 5.6% < DTIC rr.

Response Duration

	No. of responders	Median response duration (m)	95% CI
TMZ	19	5.53	4.3, 8.7
DTIC	14	3.22	2.4, 4.1

FDA Concerns with Other Secondary Endpoints

Quality of Life

- All Analyses subject to Heavy Censoring
- No Statistically Significant Differences

Pharmacokinetics

Mean AUC for parent drug and MTIC was twice as high in the temozolomide treatment group. ? Equivalent drug doses.

Safety

FDA Agrees With Sponsor

- Temozolomide has an acceptable safety profile.
- Most adverse events are mild to moderate in severity.
- Grade 4 Adverse events were primarily thrombo-cytopenia (5%) or neutropenia (2%).