CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ONCOLOGIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 12/18-19/97

QUESTIONS

QUESTIONS FOR THE ONCOLOGY DRUGS ADVISORY COMMITTEE

DROXIA NDA 16295 (S029)

DECEMBER 18, 1997

In the MSH Study Droxia appears to decrease the median annual sickle cell crisis rate by 46%, to decrease the number of patients transfused by approximately 30% and to decrease the number of transfusions by approximately 37%.

Although patients with 3 or more crises per year at baseline were eligible, most of the benefit in crisis reduction was restricted to the subgroups with 6 or more crises per year at baseline.

Considering the proposed patient population,

1. Does Droxia have a favorable risk/benefit ratio for the two year observation period in the MSH Study?

2. Does Droxia have a favorable risk/benefit ratio (especially regarding carcinogenicity) for adult life time use?

The Droxia capsules used in the MSH Study are a different formulation than the to be marketed Droxia capsules. The FDA will require verification of the relative bioavailability of the Droxia formulation used in the MSH Study and the to be marketed Droxia formulation. Providing this is satisfactorily accomplished,

3. Does the Committee recommend approval of this SNDA?

4. If so,

(a) Should the INDICATION be restricted to ▒ adult patients with sickle cell anemia with moderate to severe recurrent painful crises▒?

(b) Should the INDICATION be restricted to patients with ▒at least 3 crises during the last 12 months▒ (as per the MSH protocol eligibility requirement)? OR

(c) Should the INDICATION be restricted to patients with ▒at least 6 crises during the last 12 months▒ (as per the FDA subgroup analysis)?

5. Is the dosing regimen used in the MSH study appropriate for use in the labeling?

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ON ORIGINAL

Questions for the Oncology Drugs Advisory Committee Regarding NDA 20-798 DepoCyt

Carcinomatous meningitis is a late stage complication of solid tumors for which there is no consensus treatment. There are two currently approved medications for intrathecal use, methotrexate and cytarabine. This NDA presents data from 3 small trials of patients with carcinomatous meningitis; 61 patients in a Phase III randomized comparative study, 4 patients in a pharmacokinetic study, and 9 patients in a Phase I study. The efficacy results are summarized in the following tables.

SUMMARY OF RESPONSE IN SOLID TUMOR PATIENTS TREATED WITH DEPOCYT

Study	Total # of Solid Tumor Patients	# of DepoCyt Responders	% Response
Phase III	31	8	***26***
PK	4	2	***50***
Phase I	11	4	***36***
Total	44	14	***32***

EFFICACY DATA FROM RANDOMIZED TRIAL

	DepoCyt	Methotrexate	P value
Response Rate (cytologic response with no clinical progression)	26% (8/31)	20% (6/30)	***0.76***
Clinical Response Duration (median, days)	39	26	***0.49***
Cytologic Response Duration (median, days)	39	34	***0.95***
Clinical Time to Progression (median, days)	166.5	66.5	***0.03***
Cytologic Time to Progression (median, days)	50.5	84	***0.49***
Survival (median, days)	421	132.5	***0.19***

1. Can the trials that produced these data be considered adequate and well controlled studies?

2. In patients with carcinomatous meningitis from solid tumors is the cytological response of the CSF sample in the absence of clinical progression a surrogate endpoint that predicts clinical benefit?

3. The results show a longer Clinical Time to Progression for Depocyt , together with evidence of cytologic responses in the controlled and two other very small trials. Is the clinical endpoint, together with evidence of cytologic response, substantial evidence of the efficacy of DepoCyt?

4. The following table summarizes the incidence of adverse reactions observed in patients from all trials of Depocyt for treatment of carcinomatous meningitis:

Number (%) of Patients and Cycles	Patients n=59	Cycles n= 208
TOTAL CHEMICAL ARACHNOIDITIS	38 (64%)	59 (28%)
DEFINITE AND SERIOUS	8 (14%)	9 (4%)
POSSIBLE AND SERIOUS	3 (5%)	4 (2%)
DEFINITE	13 (22%)	20 (10%)
POSSIBLE	14 (24%)	26 (13%)

Given the incidence and severity of chemical arachnoiditis seen with the use of DepoCyt , and considering the efficacy demonstrated by Depocyt (questions 1-3), do you recommend that Depocyt be approved for the treatment of carcinomatous meningitis ?

Questions for # 97-0501; IL-2 in metastatic melanoma

1. This license application describes the results of eight studies, enrolling a total of 270 patients, treated with a comparable dose and schedule of IL-2. Approximately 70% of the study population had visceral disease and more than one site of metastatic disease, 74% of the patients had ECOG PS 0 at baseline and all met stringent entry criteria regarding cardiac and pulmonary function. The pooled data revealed an ORR of 16% and CR rate of 6%. The median duration of response for patients achieving a PR was 8.3 months; 10 of 17 complete responders remain in remission for over 2 years. The ORR for other single agents in this disease ranges from 5-25%, with CR rates of 1-4.5%. Median response durations for CR patients treated with other single agent therapies has been up to 15 months.

Please discuss: a) the type and quality of the responses observed and b) the population treated in this pooled dataset. Considering the rate, quality, and duration of response, can one conclude that IL-2 provides clinical benefit for patients with metastatic melanoma? If not, can one conclude that IL-2 has induced response which are reasonably likely to predict clinical benefit?

2. In these studies, 95% of the patients experienced grade 3 toxicity and 35% grade 4 toxicity. Treatment required hospitalization in an intensive care setting during the IL-2 administration and in the post-infusion period. The treatment related mortality, 6/270, was not dissimilar to the treatment related mortality of 11/259 observed in the renal cell studies. Mortality in the present dataset was disproportionately higher in patients with ECOG PS 1-2 (5/59) vs ECOG PS 0 (1/211). A logistic regression analysis indicated ECOG PS 0, lack of prior systemic therapy, and greater number of IL-2 courses administered correlated with a higher response rate. Current labeling for use in metastatic Renal Cell Cancer restricts use to intensive care facilities and to patients with normal cardiac and pulmonary function and notes that response rates were higher and mortality lower among patients with ECOG PS 0.

Please discuss the toxicities of IL-2. In view of the responses and the toxicities, should IL-2 be indicated for use in metastatic melanoma? If approved, should the label further restrict the use of IL-2 to specific populations, such as ECOG PS 0?

3. Under the accelerated approval mechanism, drugs and biologics that have been studied for serious and life threatening diseases and "that provide meaningful benefit to patients over existing treatments" may be approved based on a surrogate endpoint that is reasonably likely to predict benefit provided post marketing studies confirm net clinical benefit. Under standard approval, post marketing commitments can be required of the sponsor; e.g., for additional studies to optimize dosing regimen or the patient population.

If there is an accelerated approval, what studies would be appropriate to confirm clinical benefit? If there is a standard approval, what commitments for post marketing studies should be sought?

Questions for Oncologic Drugs Advisory Committee
NDA 20-806: Broxuridine

Two single-center, uncontrolled studies were submitted in support of using BUdR LI as an *in vivo* cell proliferation marker in patients with primary breast cancer. Protocol procedure involved the intravenous administration of a single dose of broxuridine during a period of 30 minutes in the hour before surgery to remove residual invasive breast cancer. Results in the table below were obtained from a Cox model with a single variable (dichotomized BUdR LI). The results show relative risk of death for patients with BUdR LI greater than, or less than, the breakpoint of 8.0.

Relative Risk of Death by Study

Study	n	Breakpoint	Relative Risk of Death (LI > 8.0 vs. ≤ 8.0)	p-value
T86-0217	163	8.0[1]	13.9	0.0004
CYL 93-02	28	NA[2]	NA[2]	

[1] - Based on median value of LI (163 patients in T86-0217
[2] - RR not obtainable from data set, model did not converge

1. The broxuridine labeling index (LI) breakpoint of 8.0 was based on the median value for 163 patients with primary breast cancer evaluated at a single institution (study T86-0217). There is no information in the NDA linking broxuridine LI with choice of therapy, nor is such information likely to be forthcoming. Does the broxuridine LI provide clinically meaningful information for physicians and breast cancer patients?

2. Is there sufficient evidence to conclude that a single, pre-surgical infusion of broxuridine at a dose of 200 mg/m^2 for *in vivo* tumor labeling is safe?

3. Do you recommend that broxuridine be approved as an infusion at surgery for LI determination to assign primary breast cancer patients to a higher versus a lower risk group? If not, what additional studies should be performed?

4. If approval for broxuridine is recommended, will a set of Kaplan-Meier survival plots for major prognostic groups (e.g., node-positive) be appropriate for presenting LI-related outcomes in product labeling?

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SLIDES

Regulatory Considerations Regarding the Carcinogenicity of Hydroxyurea

Paul A. Andrews, Ph.D.
Pharmacology Team Leader
Division of Oncology Drug Products

Hydroxyurea is Mutagenic

(causes alterations in the genetic code)

- bacteria (Ames test, etc.)
- protist (eucaryotic alga)
- fungi (yeast, *C. lagopus*)
- mammalian cells (TK locus, HGPRT locus, methotrexate resistance)

Hydroxyurea is Clastogenic

(causes structural alterations in DNA)

- In cultured cells
  - Chromosome aberrations
  - Chromosome losses
  - Chromosome breaks (hamsters, humans)
  - Sister chromatid exchanges
- In animals
  - Micronuclei in mouse erythrocytes

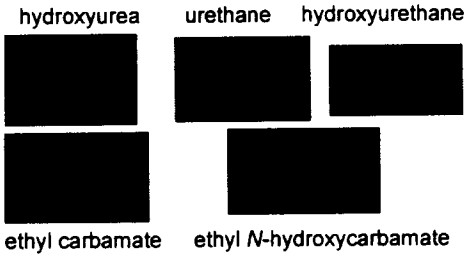
Hydroxyurea Induces Transformation

- in Syrian hamster embryo cells (SHE cells)
  - no HU data in paper (Europ. J. Cancer, 8:595, 1972)
- in mouse embryo cells
  - only in cells infected with ectromelia virus
- *SHE cell assay is 80-85% accurate for predicting rodent carcinogenicity (Crit. Rev. Oncogen., 6:251, 1995)*

Other Evidence of Genetic Toxicity of Hydroxyurea

- HU inhibits DNA repair
- HU promotes gene amplification

Structural Alert similar to known carcinogens



Published data is inadequate for assessing "carcinogenicity"

- Dosing is daily for up to 2 years
- 50 animals per sex per dose group
- For genotoxins the high dose is based on the MTD to assure a sufficient test
- All animals and tissues must be examined
- Survival should be ≥50% at 80-90 weeks

(See Fed. Reg., 50:10372, 1985 or Environ. Health Perspect., 67:201, 1986)

International Conference on Harmonization Guidance S1A

"Unequivocally genotoxic compounds, in the absence of other data, are presumed to be transspecies carcinogens, implying a hazard to humans. Such compounds need *not* be subjected to long-term carcinogenicity studies."

Evidence of Possible Carcinogenicity in Humans

- HU is clastogenic in humans (chromosome breaks & major aberrations)
  (Dis. Chest, 55:120, 1969)
- Reports of leukemia in polycythemia vera patients, and reports of skin cancer in patients with myeloproliferative disorders
  - direct association with hydroxyurea exposure can not be established based on current data

Conclusions

- HU is positive in all genotoxicity tests
- HU is positive in transformation assays
- HU is structurally similar to known carcinogens
- There is evidence that HU is clastogenic and possibly carcinogenic in humans
- HU is thus unequivocally genotoxic and a presumed transpecies carcinogen

Division's Position

1) The label should include a Warning stating the evidence that Droxia poses a carcinogenic risk to humans.

   The physician and patient must carefully consider the potential benefits of Droxia relative to the undefined risk of developing secondary malignancies.

Division's Position (cont.)

2) An animal study to unequivocally define the carcinogenic potential of hydroxyurea may be valuable. The study should preferably use an alternative model so that results will be quickly available.

ICH S1A: "However, if such a [unequivocal genotoxic] drug is intended to be administered chronically to humans, a chronic toxicity study (up to 1 year) may be necessary to detect early tumorigenic effects."

1

Droxia ®
(Hydrea, Hydroxyurea, HU)

New Drug Application (NDA) #: 16-295/SE1-029

Albert Lin, M.D., M.P.H.

ODAC PRESENTATION
December 18, 1997

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Acknowledgment

Review Team

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*: Team leader

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Proposed Indication

- Treatment of sickle cell anemia in adult patients to prevent painful crises and to reduce the need for blood transfusions

4

Outline

- Introduction
- Clinical Trial: Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)
- Patients
- Results
- Summary

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Regulatory History

Date	Events
1967	Approved for the treatment of melanoma, resistant chronic myelocytic leukemia, recurrent, metastatic, and inoperable ovarian cancer, and squamous cell carcinoma of head and neck
1990	Orphan drug designation for the treatment of sickle cell anemia
1995	Clinical Alert issued by the National Heart, Lung and Blood Institute, NIH, brought the Agency's attention to the new indication
1997, May 8	sNDA submission
1997, Sept 19	ODAC postponed at Applicant's request

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Pharmacokinetic Parameters for Hydroxyurea Following the Administration of a 2 g Oral Dose

Parameter	Johns Hopkins (Sickle Cell Patients*)			Study T91-0118 (Cancer Patients)		
	N	Mean	(SD)	N	Mean	(SD)
CMAX (μg/ml)	45	49.27	(16.04)	22	58.89	(18.98)
TMAX (hr)#	57	1.00	(0.50,6.00)	22	0.75	(0.5,5.92)
AUC (0-8) (μghr/min)	45	125.5	(30.5)	22	232.7	(68.6)
UR (%)	36	41	(19)	22	38	(9)

* Actual doses ranged from 1000 to 2000 mg; values for CMAX and AUC normalized to 2000mg before averaging;
# Median (min,max) reported

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Outline

- Introduction
- ➡ Clinical Trial
  - – Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)
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Primary Objective

- To determine if the treatment with HU will reduce more than 50% the frequency of acute vaso-occlusive (painful) crises (AVOC)

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Acute Vaso-occlusive Crises (AVOC)

- Visit to a health care facility lasting more than 4 hours for treatment of an acute painful event (including priapism) and requiring treatment with either
  - narcotics, parental or oral (if at a facility that does not use parental narcotics to treat sickle cell crisis); or,
  - an equi-analgesic dose of oral narcotics, or,
  - parental non-steroidal anti-inflammatory drugs (NSAIDs); or
- Chest syndrome or nepatic sequestration;
- Interval between events >24 hours

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Secondary Objective

- To establish the relationship of fetal hemoglobin levels and other patient or treatment characteristics to the occurrence of vaso-occlusive (painful) crises and
- To evaluate the effect of treatment on the quality of patients' lives

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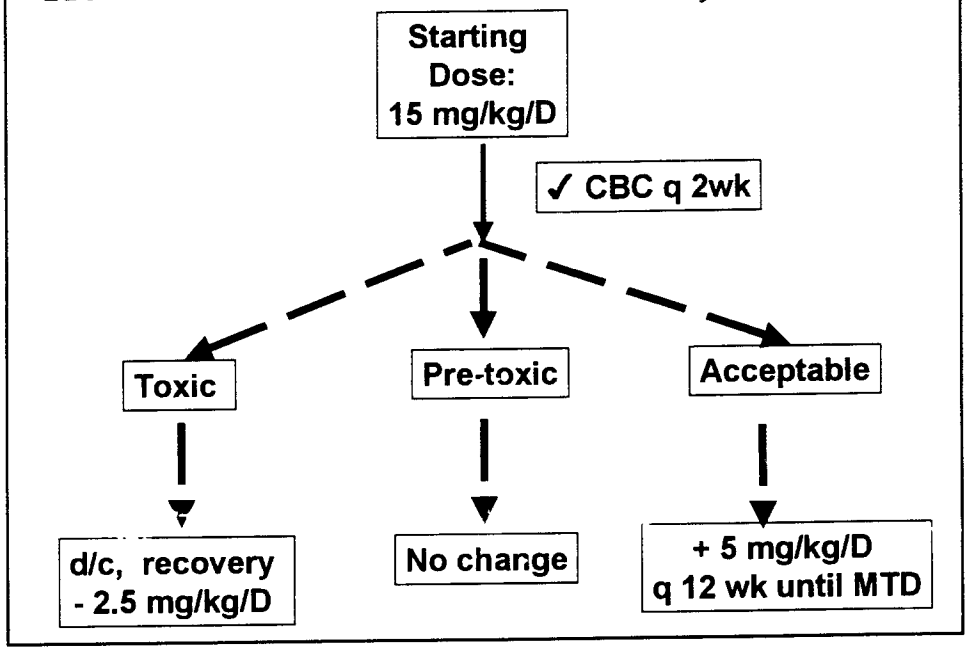
Treatment Administered & Dose Adjustment (1)



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Treatment Administered & Dose Adjustment (2)

	Toxic	Pretoxic	Acceptable
Neutrophil	< 2,000/mm^3	⟷	> 2,500/mm^3
Platelet	<80,000/mm^3		> = 95,000/mm^3
Reticulocyte	<80,000/mm^3 (if Hb <9gm/dL)		> = 95,000/mm^3
Hemoglobin	<4.5 g/dL		>5.3 g/dL

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Maximum Tolerated Dose (MTD)

- The highest dose
- No toxicity observed for 24 consecutive weeks
- Maximal allowed dose = 35 mg/kg/day

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Outline

- Introduction
- Clinical Trial - MSH
- ➡ Patients
- Results
  - –Efficacy Review
  - –Safety Review
  - –Other Issues
- Summary

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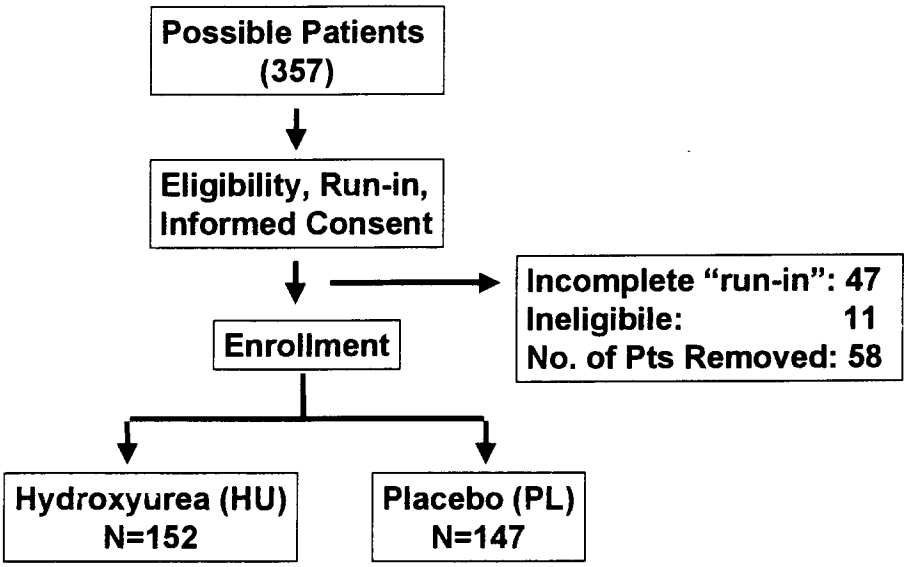
Patient Population



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Participating Clinical Centers (1)

MSH #	Clinical Centers	Enrollment	HU/PL
01	University of North Carolina	19	9/10
02	Duke University	16	9/7
03	Medical College of Georgia	15	8/7
04	Jefferson Medical College	21	10/11
05	University of Mississippi	19	10/9
06	University of Miami	12	7/5
07	University of California	6	3/3
08	University of Illinois	57	29/28
09	Howard University	20	10/10
10	University of Medicine and Dentistry of New Jersey	10	5/5
11	Emory University	14	7/7
13	St. Luke's - Roosevelt Hospital	18	9/9

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Participating Clinical Centers (2)

MSH #	Clinical Centers	Enrollment	HU/PL
14	Children's Hospital of Oakland	5	3/2
15	Medical College of Virginia	19	9/10
16	Case-Western Reserve University	5	2/3
17	The Hospital for Sick Children	6	2/4
18	Brigham and Womens Hospital	5	3/2
19	Interfath Medical Center	8	4/4
21	U. Alabama Birmingham	8	4/4
22	U. Pittsburgh	5	3/2
28	M. Reese Hospital	11	6/5
	Total	299	152/147

18 Baseline Characteristics: Demographics

Characteristics	HU (N=152) N (%)	PL (N=147) N (%)
Age (Yr)		
18-19	9(6)	12(8)
20-29	66(43)	66(45)
30-39	63(42)	52(36)
40-49	11(7)	15(10)
50	3(2)	2(1)
Sex		
Male	75(49)	71(48)
Female	77(51)	76(52)
Ethnic background		
Black	150(99)	142(97)
White	0(0)	2(1)
Other	2(1)	3(2)

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Baseline Characteristics: Annual Crisis Rates (crises/year)

Characteristics	HU N (%)	PL N (%)
3-5	67 (44.1)	64 (43.5)
6-10	50 (32.9)	44 (29.9)
11-15	28 (18.4)	32 (21.8)
>15	7 (4.6)	7 (4.8)

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Other Baseline Characteristics

- Patients assigned to either HU or PL arms have balanced distributions in:
  - Past Medical History
  - Concurrent Medications at Study Entry
  - Results of Physicial Examination
  - Laboratory Profiles, e.g.
    - Hematology (MCV, MCHC, retic counts, WBC, neutro, platelets, Hb, F retic, F cells)
    - Genotypeing
    - FCP Locus
    - Chemistry (BUN, Cr, total bili, AST, ALT, Alk-P, Uric acid)

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Outline

- Introduction
- Clinical Trial - MSH
- Patients
- ➡Results
  - –Efficacy Review
  - –Safety Review
  - –Other Issues
- Summary

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Efficacy Review

- Annual Crisis Rate
- Time-to-event Analysis
- Crisis Rate and Age

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Identification of Crisis and Crisis Rates

- No original records available
- Algorithm:
  - pain, and
  - duration > 4hr, and
  - parental narcotics, or
  - oral narcotics, where parental narcotics (-), or
  - parental NSAIDs.

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Annual Crisis Rate

	Applican't analysis		FDA reviewers' analysis	
	HU N=152	PL N=147	HU N=152	PL N=147
All crises				
Minimum	0.0	0.0	0.0	0.0
Median	2.5	4.6	2.3	4.5
Maximum	49.5	56.0	54.7	64.5
Mean ± SD	5.1± 7.3	7.9 ± 9.6	5.19±7.7	7.9±10.1
Van der Waerden 2-sample test, p-value	0.0010		0.0013	

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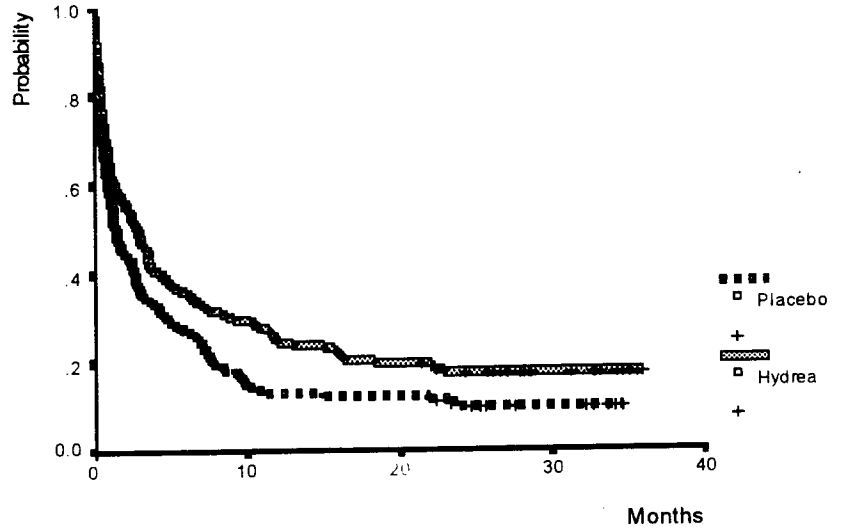
Time to the First Event

According to FDA's analysis of crisis



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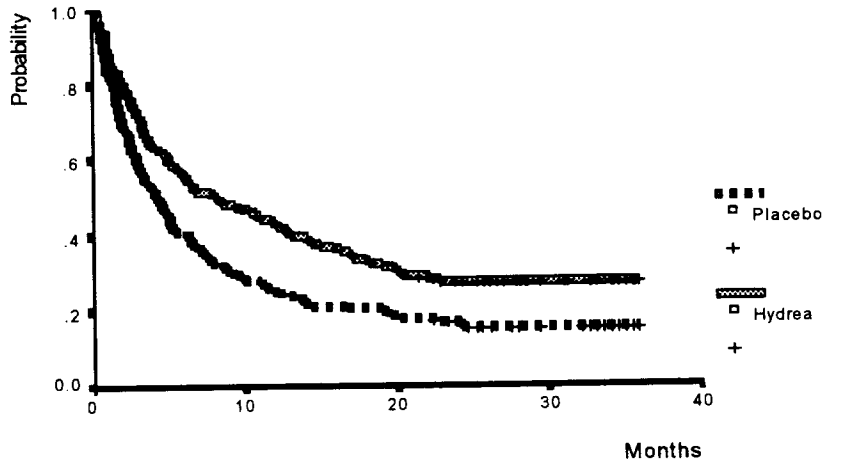
Time to the Second Event

According to FDA's analysis of crisis



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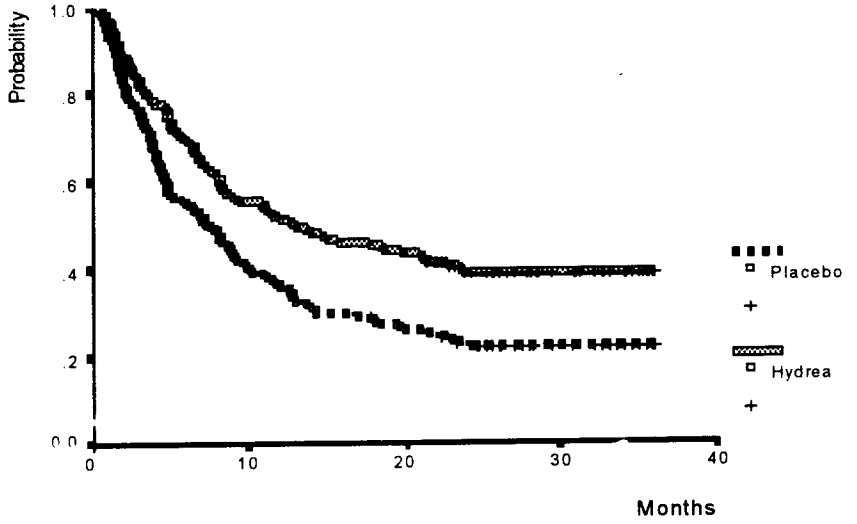
Time to the Third Event

According to FDA's analysis of crisis



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Annual Crisis Rates Before and After Treatment

	HU		PL	
	Before	After	Before	After
Mean	7.6	5.1	8.4	7.9
Median	6.0	2.5	6.0	4.6
Total	1160.0	776.3	1236.0	1158.2

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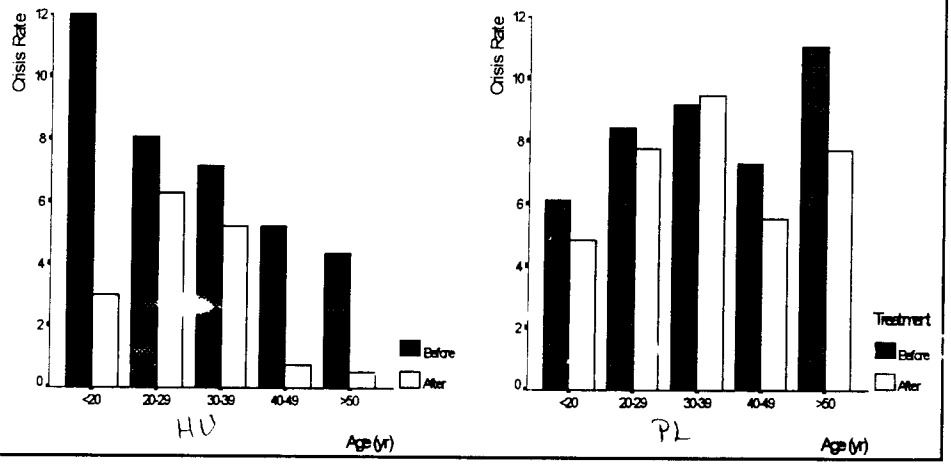
Annual Crisis Rates Before and After Treatment by Age Group: (A) Hydrea Group and (B) Placebo group



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Safety Review

- **Adverse Events**
  - Hematologic Toxicities
  - Non-hematologic Toxicites
  - Abnormal Laboratory Tests
- **Discontinuation of Medication**
- **Mortality**
- **Transfusion**
- **Pregnancy**
- **Drug-related Malignancy**

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Hematologic Toxicities

	HU (N=152) No. (%)	PL (N=147) No. (%)	p-value
Severe Myelotoxicity	120 (78.9)	54 (37)	<0.0001
Neutropenia	97 (63.8)	31 (21.1)	<0.001
Low reticulocyte count	70 (46.1)	28 (19.0)	<0.001
Anemia	4 (2.6)	8 (5.4)	0.25
Thrombocytopenia	9 (5.9)	2 (1.4)	0.06

neutrophils < 2,000 cells/mm^3, or platelets < 80,000/mm^3, or reticulocytes < 80,000/mm^3 and hemoglobin < 9.0 g/dL, or hemoglobin < 4.5 g/dL

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Clinical Toxicities: Symptoms*

	HU (N=152)		PL (N=147)		p-value
	Patients N(%)	Visits N	Patients N(%)	Visits N	
Hair loss	52 (34)	206	53 (36)	360	0.81
Skin rash	85 (56)	341	83 (56)	455	1.00
Fever	123 (81)	1002	127 (86)	1198	1.00
Febrile neutropenia	4 (3)	4	0 (0)	0	0.12
Nausea	126 (83)	1017	127 (86)	1265	0.42

Biweekly self-reported symptoms (Total no. of visits = 16, 818)

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Clinical Toxicities: Signs*

	HU (N=152)		PL (N=147)		p-value
	Patients N(%)	Visits N	Patients N(%)	Visits N	
Lymphadenopathy	61 (40)	102	67 (46)	133	0.35
New leg ulcer	14 (9)	27	13 (9)	14	1.00
Aseptic necrosis, femur	12 (8)	20	13 (9)	21	0.84
Aseptic necrosis, humerus	9 (6)	10	6 (4)	7	0.59
Bleeding tendency	10 (7)	13	4 (3)	5	0.17

New physical signs noted on semiannual medical review (Total no. of visits = 1,356)

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Laboratory Tests: Hematology (mean ± S.D.)

	Baseline		p-value	Two years		p-value
	HU	PL		HU	PL	
White blood cells (10^9/L)	12.6 ± 3.4	12.3 ± 3.2	0.46	9.9 ± 3.1	12.2 ± 2.8	0.0001
Neutrophils (10^9/L)	6.9 ± 2.4	6.7±3.2	0.51	4.9 ± 2.0	6.4 ± 2.0	0.0001
Platelets (10^9/L)	468 ± 147	457 ± 130	0.47	399 ± 124	423 ± 122	0.12
Hemoglobin (g/dL)	8.5 ± 1.4	8.5 ± 1.2	0.59	9.1 ±1.5	8.5 ± 1.3	0.0009
MCV (fl)	94 ± 9	93 ± 9	0.71	103 ± 14	93.9 ± 9	0.0001
Reticulocytes (10^9/L)	327 ± 98	325 ± 94	0.83	231 ± 100	300 ± 99	0.0001

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Laboratory Tests: Chemistry (mean ± S.D.)

	Baseline		p-value	Two years		p-value
	HU	PL		HU	PL	
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	0.20	1.0 ± 0.5	1.0 ± 0.5	0.64
Total bilirubin (mg/dL)	3.7 ± 2.4	3.7 ± 2.5	0.99	2.9 ± 2.5	4.2 ± 4.6	0.004
Direct bilirubin (mg/dL)	0.5 ± 0.3	0.5 ± 0.4	0.99	0.4 ± 0.3	0.7 ± 2.2	0.08
Aspartate aminotransferase	44 ± 23	41 ± 21	0.31	39 ± 20	43 ± 27	0.16
Alkaline phosphatase	120 ± 59	119 ± 67	0.84	117 ± 48	119 ± 71	0.71

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Permanent Discontinuation

Reasons	Hydrea N=20	Placebo N=19
Deceased	2	6
Chronic transfusion initiated	2	3
Pregnancy, patient	5	3
Pregnancy, partner	4	3
Overdose	2	0
Toxic at 2.5 mg/kg/day	3	2
Others	2	2

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Discontinuation due to Hematologic Toxicity

"Toxic" or 2-week stop

	HU N=152	PL N=147
No. of Patients	118	57
No. of Events	532	127

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Death on Study

Cause	HU N=2	Placebo N=6
Intracranial bleeding	1	0
Cardiorespiratory arrest	1	1
Acute renal failure	0	1
Crisis, Pulmonary congestion	0	2
Homicide	0	1
Sepsis/ Multiple organ failure	0	1

39

Post-Study Follow-up
(Nov. 15, 1997)

- Study close-out: Jan. 15, 1995
- Follow-up study initiated in Feb. 1996
- Enrolled and alive- 139
  To be enrolled- 125
  Deceased- 35

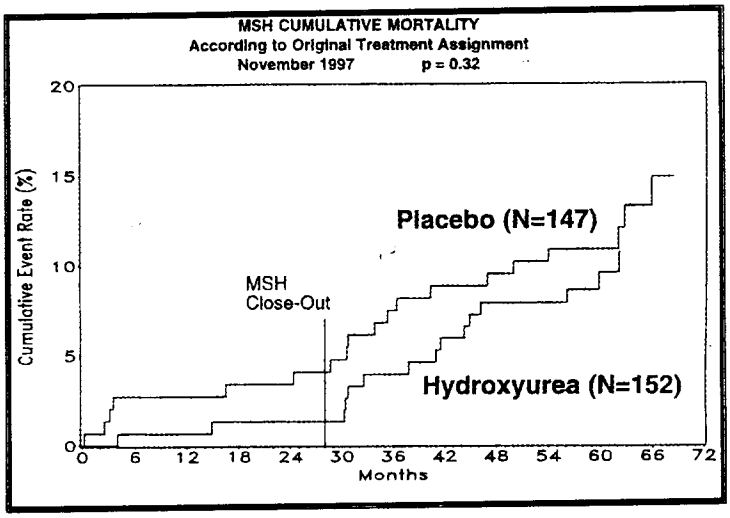
40

Cumulative Mortality
Safety Update (November 1997)

Cause of Death	Original Treatment Assignment	
	HU	PL
Sepsis	0	3
Renal disease	1	1
Hepatic disease	1	0
Gastrointestinal	1	0
Cerebrovascular	3	0
Cardiovascular	0	2
Pulmonary	6	11
Sudden death in crisis	1	1
Accident/Homicide	0	2
Indeterminate	1	0
Pending further information	1	0
TOTAL	15	20

41

Cumulative Mortality



42

Blood Transfusion

	HU N=152	PL N=147	p-value
No. of patients received transfusion	55	79	0.002*
Total units of transfusion	423	670	0.003**

* Chi-square test

** Van der Waerden rank test

43

Methods of Delivery

	HU N = 10	PL N = 6
Patient		
Normal full-term delivery	1	2
Elective termination	4	1
Partner		
Normal full-term delivery	4	3
Spontaneous abortion	1	0

44

Reproductive Events (November 1997)

Patient (Parent)	Reproductive Event	Original Treatment Assignment	
		HU	PL
Female	Live Birth	3	4
	Elective Termination	4	1
	Miscarriage/Fetal Death	0	3
Male	Live Birth	5	4
	Elective Termination	1	0
	Miscarriage/Fetal Death	2	1
TOTAL		15	13

45

Status at Birth and Development (November 1997)

MSH Patient (Parent)	No. of Live Offspring	
	Ever Taking HU	Never Taking HU
Female	5*	2
Male	5**	4

* One patient, who was originally assigned to PL and took HU six months after MSH and before becoming pregnant, delivered twins at 35 weeks: one was stillborn; the other was diagnosed with micr[illegible]phaly and blindness.

** One patient, who was originally assigned to HU, fathered a child born with supernumerary digits and mucocele.

46

Drug-related Malignancy

- Not observed during the study period in either the HU- assigned or PL-assigned patients
- Safety update (Nov. 1997):
  No. of cancer = 0
  (incomplete follow-up)

47 Incidence of Acute Leukemia in Patients Treated with Hydroxyurea for Polycythemia Vera (PV) or Essential Thrombocythemia (ET)

Author (Year)	The Study: Year , Location, Treatment, Duration of follow-up or treatment	Incidence of Acute Leukemia in % (No. of events/No. of patients)
Liozon et al. (1997)	1981-1995, France 58 patients with ET treated with HU as initial therapy; Mean follow-up: 73 months	5.2 (3/58)
Lofvenberg et al. (1990)	1981-1989, Sweden 81 consecutive patients, 35 PV, 32 ET, and 14 others, were treated with HU. Mean follow-up:3.8 years	6.2 (4/81) 9.4(3/32) - HU alone
Nand et al. (1996)	1993-1995, US 64 patients, 42 PV, 15 ET, and 7 others, received multiple regimens (phlebotomy, HU, ^{32}P, alkylating agent, interferon-α).	6.3 (4/64) 8.0 (2/25) -HU alone
PVSG-08 Fruchtman et al. (1997)	1977-1996, US 51 patients with PV were treated with HU Longest follow-up 15.3 year	9.8 (5/51) 5.9 (3/51)- HU alone

48 Incidence of Acute Leukemia in Patients Treated with Hydroxyurea for Polycythemia Vera (PV) or Essential Thrombocythemia (ET) (contd.)

Author (Year)	The Study: Year , Location, Treatment, Duration of follow-up or treatment	Incidence of Acute Leukemia in % (No. of events/No. of patients)
PSVG-12 Murphy et al. (1997)	1977-1992, US 91 patients with ET were enrolled and treated with different regimens. Median follow-up: 7.3 years	13.2 (12/91) 4.5 (1/22) - HU alone
Tatarsky and Sharon (1997)	May 1980 - Dec. 1995, Israel 71 patients with PV treated with HU; 33 of them had prior phlebotomy; Median follow-up: 10.9 years	5.6 (4/71)

49 Incidence of Acute Leukemia in Patients Treated with Hydroxyurea for Polycythemia Vera (PV) or Essential Thrombocythemia (ET) (contd.)

Author (Year)	The Study: Year , Location, Treatment, Duration of follow-up or treatment	Incidence of Acute Leukemia in % (No. of events/No. of patients)
Weinfeld (1994)	1976-1993, Sweden 50 consecutive patients, 30 PV, 10 ET, and 10 myelofibrosis, were entered HU prospective study. Medain follow-up:10 years	20 (10/50) 14.9 (7/47)- HU alone
West (1987)	1963-1983, US 100 consecutive PV patients were treated with phlebotomy and HU Mean treatment dur.: 64.9 months	2.0 (2/100) - HU alone

50 Comparative Incidence of Acute Leukemia from the Polycythemia Vera Study Group

Protocol	Total Patients	No. Events	%
	On-study		
HU (PVSG-08)	51	3	5.9
Phlebotomy (PVSG-01)	134	2	1.5
Wilcoxon X_1^2=1.305, p=.2532 Logrank X_1^2=1.791, p=.1808			
	On- & Off-Study		
HU (PVSG-08)	51	5	9.8
Phlebotomy (PVSG-01)	134	5	3.7
Wilcoxon X_1^2=2.749, p=.0973 Logrank X_1^2=2.344, p=.1258			

51

Other Issues

- Quality of Life
- Crisis Rates and HU Dose
- Blinding
- Compliance

APPEARS THIS WAY
ON ORIGINAL

52

?

Reduction in Crisis Rates $\approx$ Improvement in Quality of Life

APPEARS THIS WAY
ON ORIGINAL

53

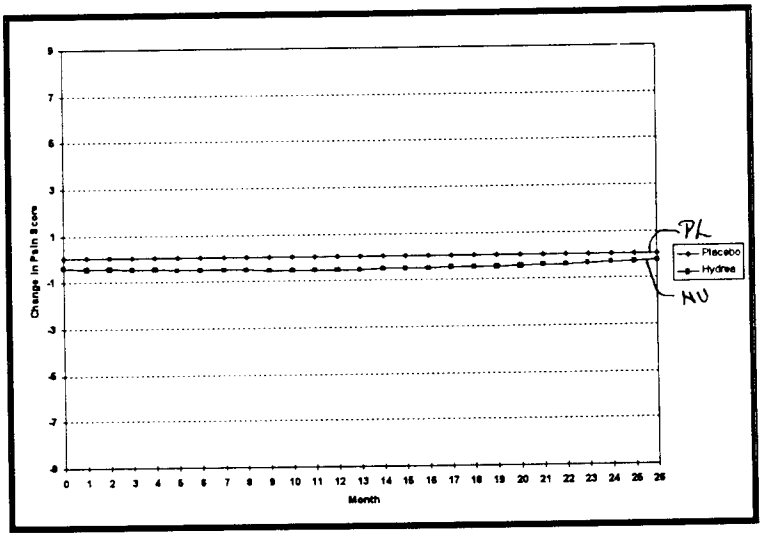
Growth Curve Analysis *

- To fit polynomial growth curves describing the mean value of change in pain score from the baseline over the study period
- To provides information on the temporal pattern of change
- (Robust estimates are employed.)

* FDA analysis by Dr. Masahiro Takeuchi

54

Change in Pain Score Over Study Period



* FDA analysis by Dr. Masahiro Takeuchi

55

Analysis of Correlation between Crisis Rates (Baseline and Two -Year) and Last Dose of HU

	cc	p
Baseline CR vs. 2-year CR	.3254	<.001
Baseline CR vs. Last Dose	.148	.069
2-year CR vs. Last Dose	.447	<.001

Note: cc, correlation coefficient, Spearman's rho; CR, crisis rates

56

Two-Year Crisis Rates (CR) by Basline CR*

Baseline CR	Hydroxyurea N=152		Placebo N=147		p value#
	N (%)	Median CR	N (%)	Median CR	
3-5	67(44)	2.0	64(44)	2.2	0.133
6-10	50(33)	4.0	44(30)	6.0	0.051
11+	35(23)	6.0	39(26)	10.0	0.007

Van der Waerden 2-sample test

* FDA analysis by Dr. Qing Liu

59

Compliance

- 15.3% of HU patients had non-detectable HU blood levels throughout the follow-up. The mean and median detectable rates per patient were 31% and 26%, respectively.
- N = no. of HU blood tests

	HU		PL		Combined	
	N	%	N	%	N	%
Positive	404	32.4	11	1	415	17
Negative	843	67.6	1203	99	2046	83
Total	1247	100.0	1214	100.0	2461	100.0

60

Outline

- Introduction
- Clinical Trial - MSH
- Patients
- Results
  - Efficacy Review
  - Safety Review
  - Other Issues
- ➡ Summary

61

- Study: Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)
- Design: Double-blind, randomized
- Primary endpoint: to determine if HU can reduce the frequency of AVOC approximately by 50%
- Enrollment: Jan. 28, 1992- April 27, 1993
- Patients: 152 HU vs. 147 PL

62

Benefits

- Reduction in annual crisis rates
- Delay in time-to- crises
- Reduction in the No. of patients requiring blood transfusion and the No. of units of blood transfused

63

Risks

- **Myelotoxicities**

APPEARS THIS WAY
ON ORIGINAL

64

Uncertainty (?)

- ? Optimal dose
- ? Carcinogenicity
- ? Teratogenicity
- ? Mutagenicity
- ? Validity of blinding in the MSH study
- ? Low HU compliance in the MSH study

DROXIA™ (hydroxyurea)

SLIDE MATERIALS
for presentation to the
ONCOLOGIC DRUGS ADVISORY
COMMITTEE

December 18, 1997

INTRODUCTION

Dr. Collier Smyth

- **A. Collier Smyth, M.D.**

  Vice President, Medical Affairs

  Bristol-Myers Squibb

  Oncology/ Immunology

  Princeton, NJ

- **DROXIA ™ (hydroxyurea capsules, USP)**

- **Treatment of sickle cell anemia in adult patients to prevent painful crises and to reduce the need for blood transfusions**

- **Currently, no FDA approved treatment for sickle cell anemia**

A2

- **1869 - First synthesized**
- **1928 - Leukopenia and anemia demonstrated in animal modes**
- **1958 - Antitumor activity in mammalian tumor systems**
- **1960 - Clinical trials for cancer treatment initiated**
- **1967 - FDA approval**

A3

- **Mechanism of Action**

  Ribonucleotide reductase inhibitor

- **Effects Relevant to Sickle Cell Anemia**

  Increases HbF and MCV

  Decreases neutrophils

- **Current Use**
  - **Myeloproliferative disorders**
    - **Polycythemia vera**
    - **Thrombocythemia**
  - **Psoriasis**
  - **Hypereosinophilic syndrome**
  - **Sickle cell anemia**
  - **Other hemoglobinopathies**

- **Orphan drug designation for Sickle Cell Anemia - October 1990**

- **Results of an open label dose-ranging trial (Charache, et al. Blood, 1992) resulted in increased HbF and MCV directly related to drug dose**

- **Subsequent double-blind placebo-controlled Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) initiated 1992**

MSH

- **299 adult patients studied in 21 clinics (United States and Canada)**

- **John Hopkins Medical Institutions**

  Administered Clinical Consortium

- **Maryland Medical Research Institute**

  Data Coordinating Center

- **National Heart, Lung and Blood Institute (NHLBI)**

  Study participation and DSMB monitoring

A7

- **MSH trial stopped in January 1995 before planned termination of study**

  Data and Safety Monitoring Board (DSMB) and Steering Committee recommendation due to beneficial effects of hydroxyurea

- **National Heart, Lung and Blood Institute issues clinical alert January, 1995**

- **SNDA filed August 21, 1997**

Presenters

- **Sickle Cell Disease**
  Martin H. Steinberg, M.D.
  Professor of Medicine
  University of Mississippi Medical Center
  Jackson, MS

- **Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)**
  Samuel Charache, M.D.
  Emeritus Professor of Medicine
  Johns Hopkins School of Medicine
  Baltimore, MD

- **MSH Follow-Up Study**
  Dr. Steinberg

- **Summary**
  Dr. Smyth

- **Michael L. Terrin, M.D., C.M., M.P.H.**
  Vice President
  Maryland Medical Research Institute
  Baltimore, MD

- **Franka Barton, M.S. (Hyg.)**
  Statistician
  Maryland Medical Research Institute
  Baltimore, MD

- **Duane R. Bonds, M.D.**
  Leader, Sickle Cell Disease Scientific Research Group
  National Heart, Lung and Blood Institute
  National Institutes of Health
  Bethesda, MD

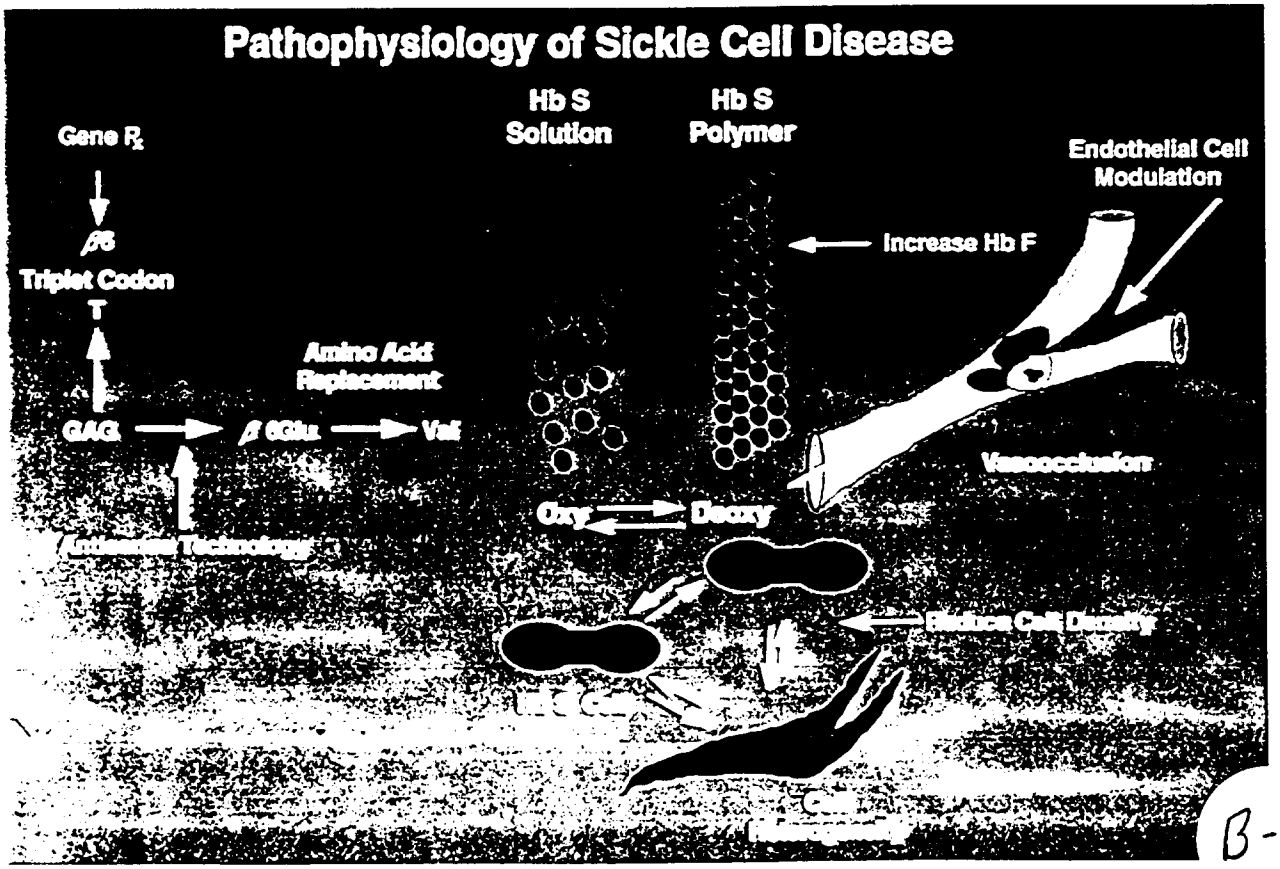
SICKLE CELL ANEMIA

Dr. Martin Steinberg

SICKLE CELL ANEMIA

- SICKLE CELL ANEMIA IS A GENETIC DISEASE OF HEMOGLOBIN
- ONE IN 350 AFRICAN-AMERICANS HAVE SOME TYPE OF SICKLE CELL DISEASE AND ONE IN 600 HAVE SICKLE CELL ANEMIA
- IN SICKLE CELL ANEMIA, THE MEDIAN AGE OF DEATH IS IN THE 5TH DECADE (NEJM, 330:1639, 1994)
- PAINFUL CRISES AND ACUTE CHEST SYNDROME ARE RISK FACTORS FOR EARLY DEATH

B-1



B-2

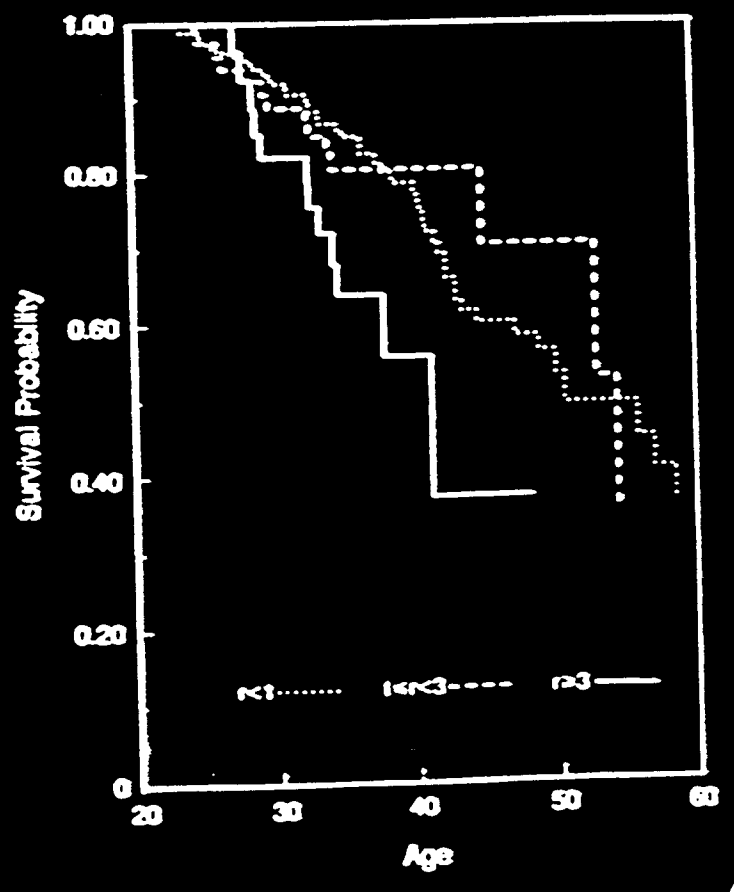
SICKLE CELL DISEASE

VASOOCCLUSIVE COMPLICATIONS

- PAINFUL EPISODES-MOST FREQUENT
- ACUTE CHEST SYNDROME-MOST DANGEROUS
- CVA-SCOURGE OF CHILDHOOD
- OSTEONECROSIS-CHRONICALLY PAINFUL

B-3

SURVIVAL PROBABILITY BY CRISIS FREQUENCY IN SICKLE CELL ANEMIA
(NEJM 325:11, 1991)



B-4

SICKLE CELL DISEASE

VASOOCCLUSIVE COMPLICATIONS

- PAINFUL EPISODES-MOST FREQUENT
- ACUTE CHEST SYNDROME-MOST DANGEROUS
- CVA-SCOURGE OF CHILDHOOD
- OSTEONECROSIS-CHRONICALLY PAINFUL

B-5
(B-3)

SICKLE CELL DISEASE

VASOOCCLUSIVE COMPLICATIONS

- LEG ULCERS-PAINFUL
- RETINOPATHY-Hb SC DISEASE
- PRIAPISM-IMPOTENCE
- SPLENIC SEQUESTRATION-DEATH IN CHILDHOOD

B-6

SICKLE CELL DISEASE

HEMOLYTIC COMPLICATIONS

- ANEMIA-USUALLY MODERATE
- CHOLELITHIASIS-50 % OF ADULTS
- ACUTE APLASTIC EPISODES-B 19 PARVOVIRUS
- RETICULOCYTOSIS-POSSIBLE ROLE IN VASOOCCLUSION

B-7

SICKLE CELL DISEASE

CHRONIC ORGAN DAMAGE

- SLOWLY PROGRESSIVE RENAL FAILURE-SEVERE ANEMIA
- SUBCLINICAL CORTICAL DAMAGE-COGNITIVE IMPAIRMENT
- CHRONIC LUNG DISEASE-COR PULMONALE
- PLACENTAL DAMAGE-MISCARRIAGE
- SPLENIC FIBROSIS-PNEUMOCOCCAL SEPSIS

B-8

Treatment of Sickle Cell Disease

- Analgesics
- Antibiotics
- Hydration
- Transfusion
- Transplantation

B-9

FETAL HEMOGLOBIN AND SICKLE CELL ANEMIA

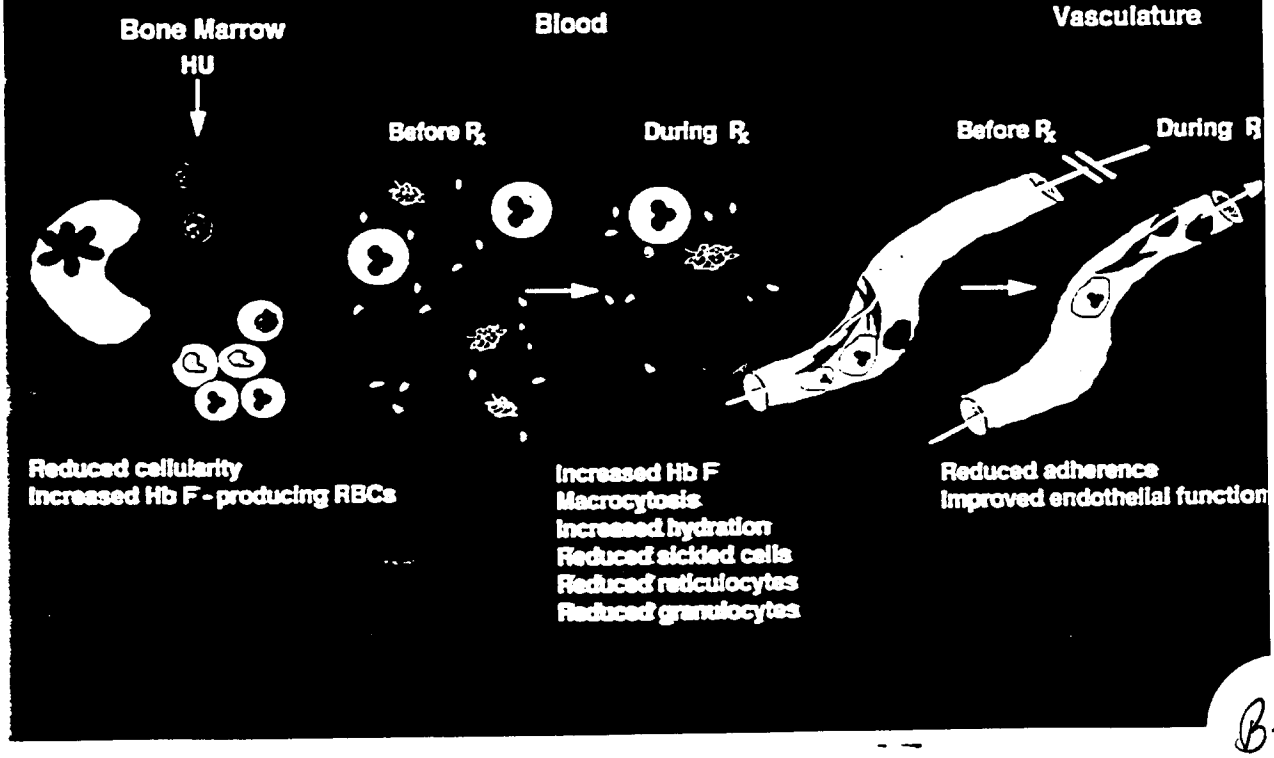
- NEWBORNS WITH SICKLE CELL ANEMIA ARE ASYMPTOMATIC
- PATIENTS WITH SICKLE CELL ANEMIA/HPFH ARE WELL
- FETAL HEMOGLOBIN INCREASES GELLING CONCENTRATION OF HB S
- γ-GLOBIN CHAINS INTERFERE WITH HB S POLYMERIZATION

B-10

HbF AND SURVIVAL IN HBSS

B-11

Effects of Hydroxyurea In Sickle Cell Disease



B-12

MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA

Dr. Samuel Charache

MAIN STUDY QUESTION

C-1

Can treatment with hydroxyurea substantially reduce the rate of acute vaso-occlusive crises in adult SS patients?

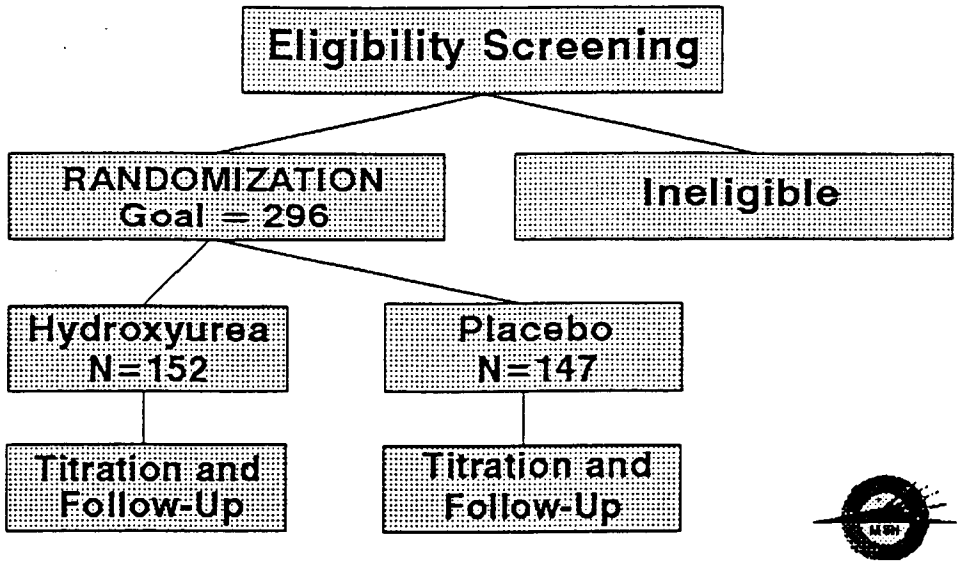
MSH ORGANIZATION

C-2

- Johns Hopkins University
  - Central Office
  - Core Laboratories
  - Treatments Distribution Center
  - Central Caller
  - Crisis Review Committee
- Maryland Medical Research Institute
  - Data Coordinating Center
- National Heart Lung and Blood Institute
  - Data and Safety Monitoring Board
  - Sickle Cell Disease Research Group

STUDY DESIGN AND RANDOMIZATION

C-3



INCLUSION CRITERIA

C-4

- Core Laboratory diagnosis of sickle cell anemia by electrophoresis
- 3 or more acute vaso-occlusive crises in year prior to enrollment
- 18 years of age or older
- Informed consent
- Pregnancy protection

EXCLUSION CRITERIA I

C-5

- > 30 oxycodone capsules / month
- Recent transfusion
- Active liver disease
- Elevated creatinine
- Contraindication to immunosuppressive therapy
- B-12, iron or folate deficiency

EXCLUSION CRITERIA II

C-6

- Previous hydroxyurea therapy
- Pregnant or breastfeeding
- S-beta thalassemia
- Anti-sickling agents
- Stroke within 4 years
- Congestive heart failure

DOSE TITRATION I
DEFINITION OF PRE-TOXICITY AND TOXICITY

C-7

	Pre-Toxic	Toxic
Neutrophils	< 2,500/cu mm	< 2,000/cu mm
Reticulocytes If Hb < 9 g/dL	< 95,000/cu mm	< 80,000/cu mm
Platelets	< 95,000/cu mm	< 80,000/cu mm
Hb		< 4.5 g/dL
If baseline Hb ≥ 7 g/dL and reticulocytes < 320 K/cu mm	5.1-5.3 g/dL	4.5-5.0 g/dL

DOSE TITRATION II
ESCALATION AND ADJUSTMENT

C-8

- Start at 15 mg/Kg daily
- Increase by 5 mg/Kg every 12 weeks
- If toxic (blood count depression)
  - Stop until blood counts recover
  - Resume at 2.5 mg/Kg lower
  - Adjust by 2.5 mg/Kg every 12 weeks
- If pre-toxic, do not increase

DOSE TITRATION III
MAXIMUM TOLERATED DOSE

C-9

- Highest dose which does not cause toxicity in 24 weeks, or
- 35 mg/Kg

APPEARS THIS WAY
ON ORIGINAL

C-10

NO BLOOD ...

... NO DRUG

APPEARS THIS WAY
ON ORIGINAL

ACUTE VASO-OCCLUSIVE CRISIS

C-11

- Visit to medical facility of 4+ hours duration
- Pain of sickle cell disease
- Specified treatment
- Included:
  - Chest syndrome
  - Hepatic sequestration
  - Priapism

CRISIS REVIEW COMMITTEE

C-12

- Independent hematologists & internists
- Not part of any clinical center
- Blind to treatment assignment
- Used classification rules developed a priori

APPEARS THIS WAY
ON ORIGINAL

11/97

CLASSIFICATION OF EVENTS

C-13

- Document medical contacts
- Crisis Review Committee (CRC)
  - ▸ Study definition of acute vaso-occlusive crisis
  - ▸ Two reviewers must agree

UNBLINDING

C-14

- Pregnancy
- Accidental ingestion or overdose
- Infection or bleeding with low blood counts
- Information critical for patient management

BASELINE CHARACTERISTICS (MEDICAL)

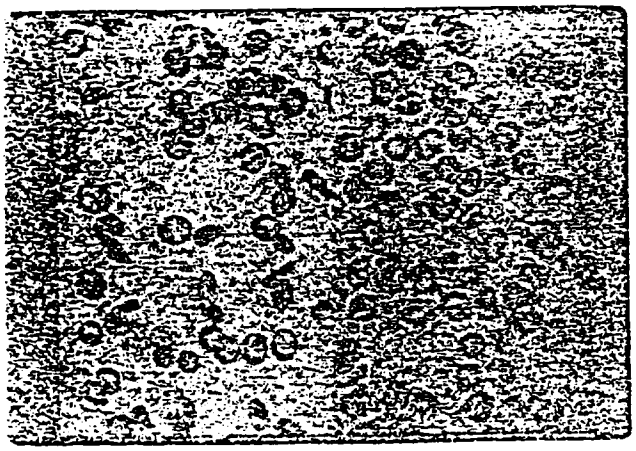
C-15

	Hydroxyurea (N=152)	Placebo (N=147)
History	%	%
Chest syndrome	68	67
Ankle ulcer	28	30
Aseptic necrosis	12	13
Crises in prior year		
3 - 5	44	44
6 - 10	33	30
>= 11	23	26

11/97

RBC's before/after 7 Hu

C-16



LABORATORY VALUES: BASELINE and 2-YEAR

C-17

	Baseline: HU	Baseline: PL	2-Year: HU	2-Year: PL
White Blood Cells (10^3/L)	12.6 (3.4)	12.3 (3.2)	9.9 (3.1)	12.2 (2.8)
Neutrophils (10^3/L)	6.9 (2.4)	6.7 (2.3)	4.9 (2.0)	6.4 (2.0)
Hemoglobin (g/dL)	8.5 (1.4)	8.5 (1.2)	9.1 (1.5)	8.5 (1.3)
Reticulocytes (10^3/L)	327 (98)	325 (94)	231 (100)	300 (99)
Hb-F (%)	5.0 (3.5)	5.2 (3.4)	8.6 (6.8)	4.7 (3.3)

11/97

PRIMARY END POINT

Annual Crisis Rate

C-18

	Hydroxyurea (N=152)	Placebo (N=147)
Minimum	0.0	0.0
25th percentile	0.7	2.0
Median	2.5	4.6
75th percentile	6.8	10.5
Maximum	49.5	56.0

11/97

p = 0.001

HOSPITALIZED VASO-OCCLUSIVE CRISIS
Annual Crisis Rate

C-19

	Hydroxyurea (N=152)	Placebo (N=147)
Minimum	0.0	0.0
25th percentile	0.0	0.5
Median	1.0	2.5
75th percentile	3.5	4.2
Maximum	16.5	52.2

11/97

p = 0.0027

TIME TO CRISIS

C-20

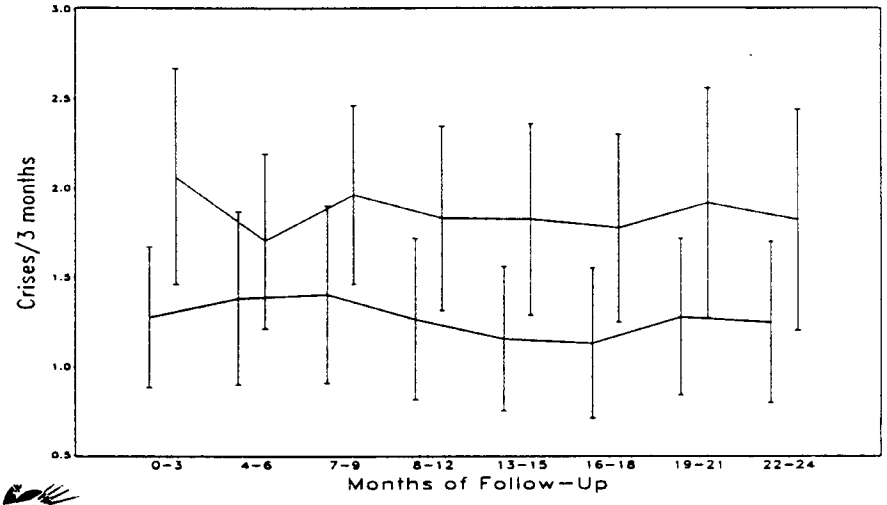
	Median Time (Months)[1]		
	Hydroxyurea	Placebo	p[2]
First crisis	2.76	1.35	0.014
Second crisis	6.58	4.13	0.0024
Third crisis	11.9	7.04	0.0002

[1] Kaplan-Meier estimates
[2] Cox proportional hazards model

11/97

C-21

CRISIS RATE BY QUARTER



11/97

DEATH, STROKE, CHEST SYNDROME AND HEPATIC SEQUESTRATION (2-YEAR) C-22

	Hydroxyurea (N=152)	Placebo (N=147)	p
	n	n	
Death	2	5	0.3
Stroke/chronic transfusion	2	3	0.64
Chest Syndrome	56	101	0.003
Hepatic Sequestration	2	3	0.55

11/97

TRANSFUSIONS

C-23

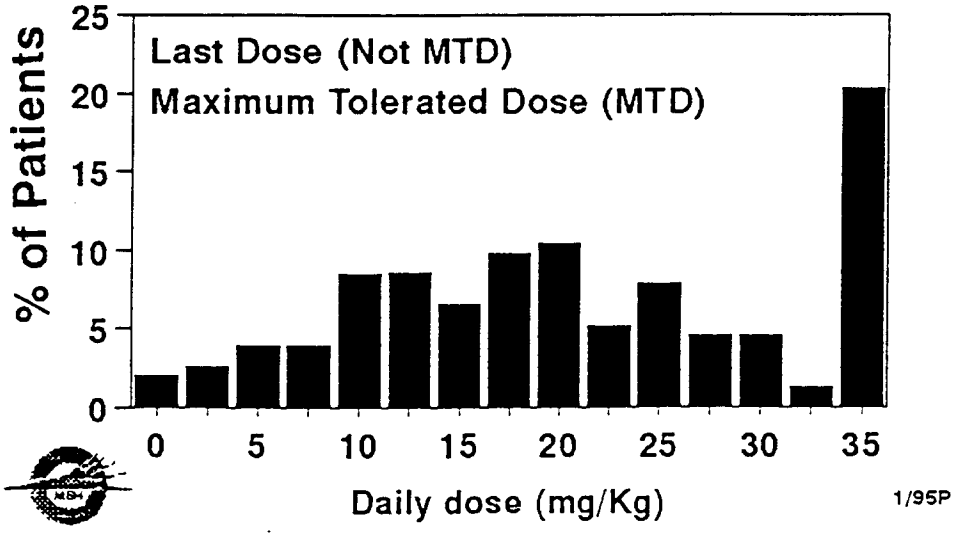
	Hydroxyurea (N=152)	Placebo (N=147)	
	n	n	p
Patients transfused	55	79	0.002
Units transfused	423	670	0.003

11/97

LAST PRESCRIBED DOSE

Hydroxyurea (N=152)

C-24



1/95P

PERMANENT TREATMENT STOP

C-25

	Hydroxyurea	Placebo
Total permanent treatment stops	19	13
Long-term transfusion therapy	2	3
Acute renal failure	1	0
Fulminant hepatitis	1	0
Myelotoxicity at 2.5 mg/Kg	3	2
Overdose by patient	2	0
Pregnancy	10	6
Elevated bilirubin/alkaline phosphatase	0	1
Personal physician decision	0	1

11/97

PREGNANCY (End of Study)

C-26

	Hydroxyurea	Placebo
Patients		
Normal full-term delivery	1	2
Elective termination	4	1
Partners of patients		
Normal full-term delivery	4	3
Spontaneous abortion	1	0

11/97

KNOWN SIDE EFFECTS OF HYDROXYUREA

C-27

	Hydroxyurea (N=152)	Placebo (N=147)
Symptoms (Ever)	%	%
Hair loss	34	36
Skin rash	56	56
Fever	81	86
GI disturbance	83	86

11/97

POSSIBLE ADVERSE EFFECTS NOT OBSERVED

C-28

- **Neoplasms**
- **Birth defects**
- **Deaths due to hydroxyurea**

SAFETY OF HYDROXYUREA
Careful Monitoring Required

C-29

- Blood counts
- Biochemistry
- Contraception

EFFICACY OF HYDROXYUREA
Reduction in

C-30

- Annual crisis rate
- Frequency of chest syndrome
- Frequency of transfusions

MSH FOLLOW-UP STUDY

Dr. Martin Steinberg

PURPOSE
MSH Patients' Follow-Up

- 5-Year observational study
- Evaluate mortality and health status
- Outcomes related to HU treatment
- According to:
- - original study treatment
- - original and susbsequent treatment

STUDY PLAN
MSH Patients' Follow-Up

- **Annual follow-up visits**
  - **Medical review and examination**
  - **Hydroxyurea usage summary**
  - **Laboratory determinations, chest X-ray, ECG**
  - **Offspring development review**
- **Ascertainment of events**
  - **Death**
  - **Stroke**
  - **Cancer**
  - **Renal, hepatic failure**
  - **Sepsis or serious infection**
  - **Reproductive events**

ENROLLMENT AND FOLLOW-UP
MSH Patients' Follow-Up

- 35 deceased (2 completed AV01)
- 139 alive, enrolled, completed AV01
- 125 yet to be seen in AV01

APPEARS THIS WAY
ON ORIGINAL

D-3
(Q117)

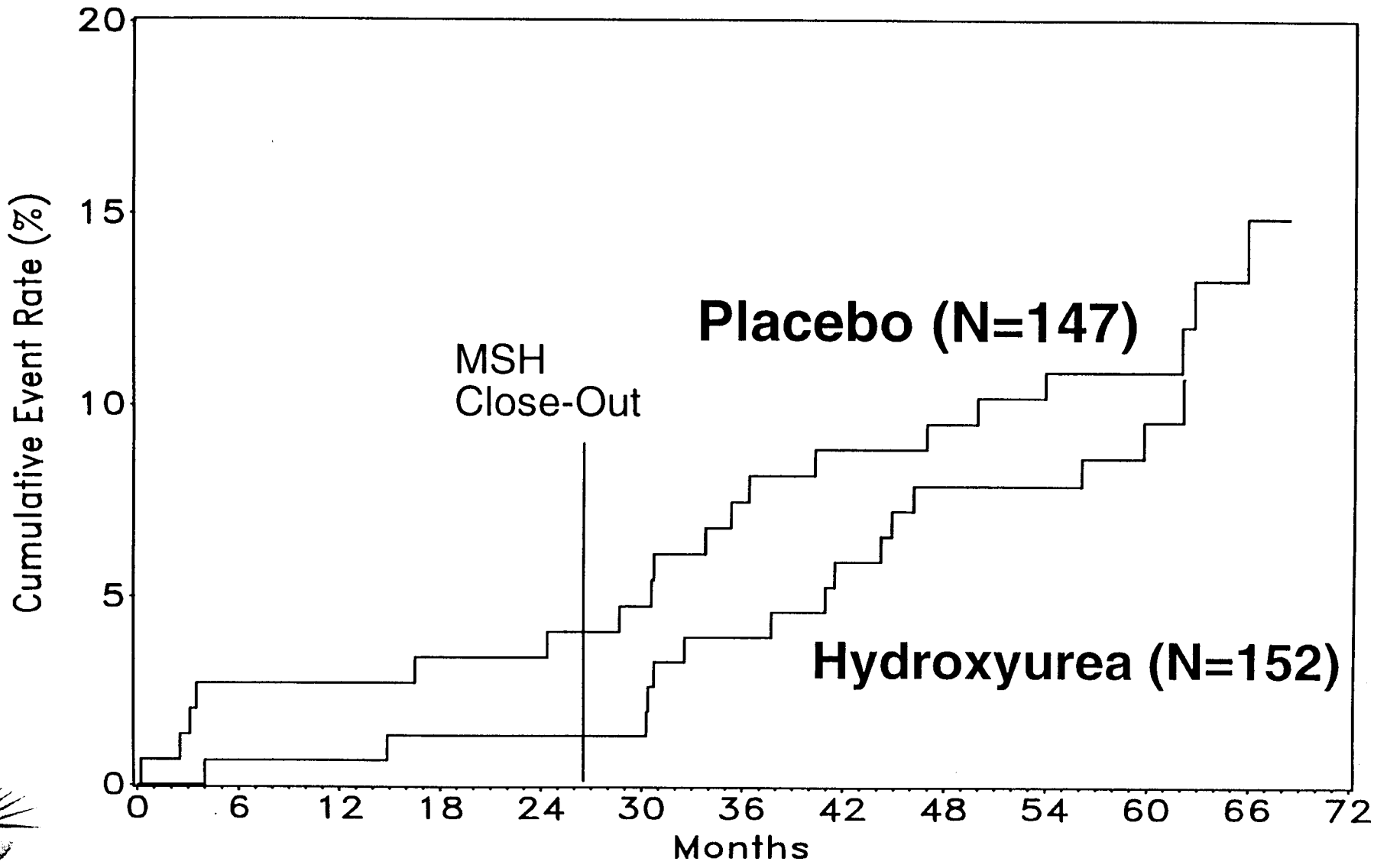
11/97

CUMULATIVE FATAL AND NON-FATAL EVENTS (November 1997)

	Hydroxyurea	Placebo
Patients with events	24	22
Death	15	20
Stroke	5	2
Renal failure	6	3
Hepatic failure	2	2
Cancer	0	0
Sepsis	2	4
Live birth	8	8
Other reproductive outcome	7	5

D-4

MSH CUMULATIVE MORTALITY
According to Original Treatment Assignment
November 1997 p = 0.32



D-5

CAUSE OF DEATH (November 1997)

Cause of death	Hydroxyurea	Placebo
Sepsis	0	3
Renal, Hepatic, GI	3	1
Cerebrovascular	3	0
Cardiovascular	0	2
Pulmonary	6	11
Sudden, in crisis	1	1
Other, Indeterminate	2	2
TOTAL	15	20

D-6

REPRODUCTIVE EVENTS (November 1997)

According to Original Treatment Assignment

Patient (Parent)	Reproductive event	Hydroxyurea	Placebo
Female	Live Birth	3	4
	Elective Termination	4	1
	Miscarriage/ Fetal Death	0	3
Male	Live Birth	5	4
	Elective Termination	1	0
	Miscarriage/ Fetal Death	2	1
TOTAL		15	13

D-7

LIVE OFFSPRING: BIRTH STATUS AND DEVELOPMENT
November 1997

MSH PATIENT (PARENT)	EVER TAKING HYDROXYUREA	NEVER TAKING HYDROXYUREA
Female	**5 live offspring** One patient, originally assigned to PL, took HU for six months after MSH and before pregnancy, delivered twins at 35 weeks; one was stillborn; the other has microcephaly and blindness.	**2 live offspring**
Male	**5 live offspring** One patient, originally assigned to HU, fathered a child born with polydactyly and mucocele of the lip.	**4 live offspring**

D-8

11/97

SUMMARY
MSH Patients' Follow-Up (Nov 1997)

- No evidence that hydroxyurea is associated with excess mortality or is protective with respect to mortality in sickle cell anemia
- No cancer or leukemia
- No adverse event attributable to hydroxyurea
- Many more patient-years of follow-up will be needed to detect any uncommon adverse events

D-9

SUMMARY

Dr. Collier Smyth

Summary

- **Thirty Year Clinical History for Hydroxyurea (1967-present)**

- **Benefits of Droxia ™ therapy for adult patients with sickle cell anemia outweigh potential risks.**

- **MSH :** **No deaths attributable to hydroxyurea**

  No patient developed neoplasia

  In patients experiencing myelosuppression, recovery was usually complete within two weeks

  Other toxicities comparable to placebo

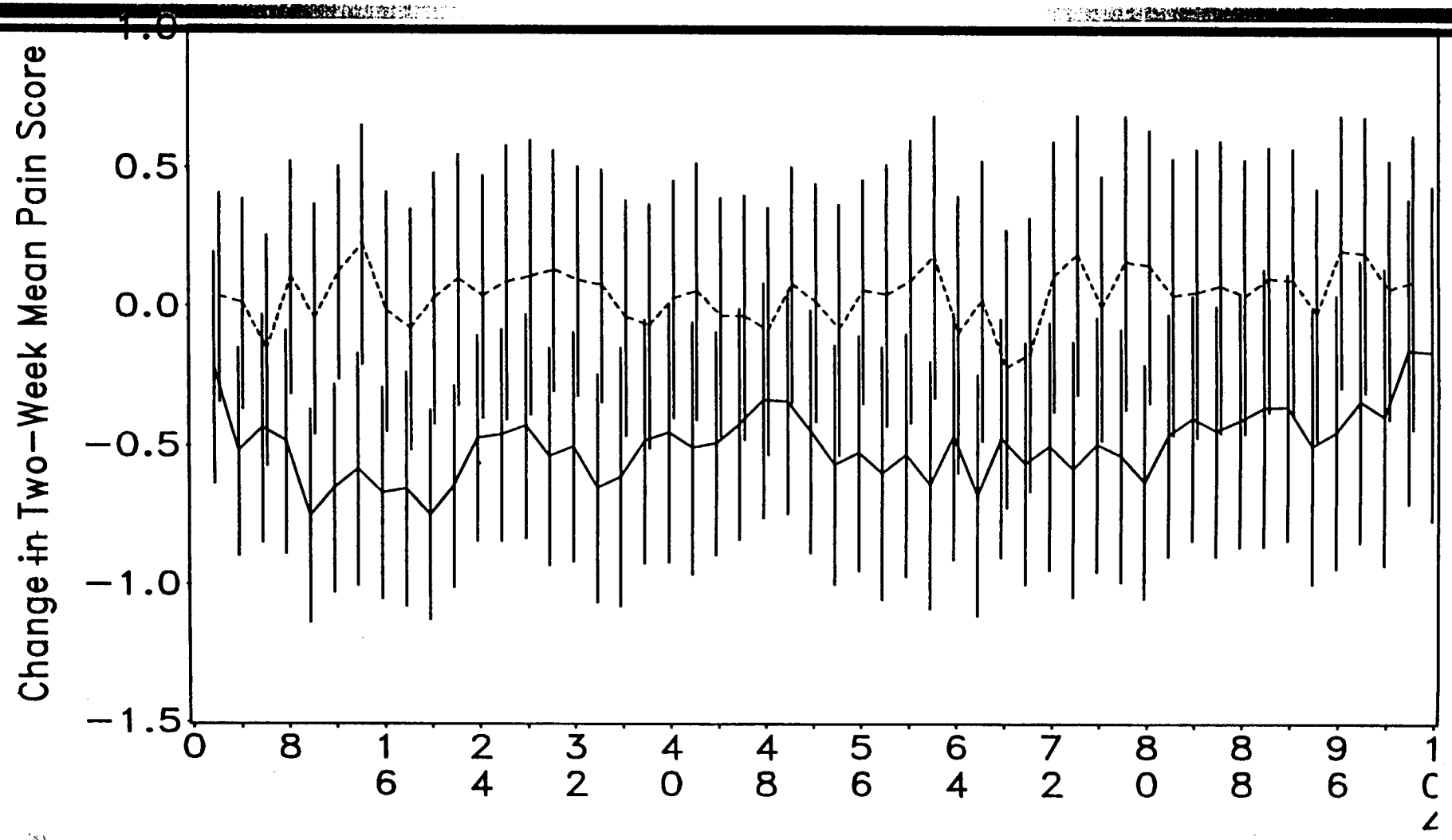
  Unknown long-term risks

- **The administration of Droxia ™ represents a safe and effective option for the treatment of sickle cell anemia in adult patients:**

  Prevention of painful crises

  Reduction in the need for blood transfusions

Mean (99%–CI) group change in daily average pain score from baseline



Q 105

Hydroxyurea (N=152) Placebo (N=147)

11/97

p = 0.0055

SF-36: Four-week Pain Recall

Mean (SD)

	Hydroxyurea (N = 152)	Placebo (N = 147)
Baseline	6.3 (2.3)	5.9 (2.5)
6 months	6.8 (2.2)	6.4 (2.5)
12 months	6.8 (2.3)	6.5 (2.5)
18 months	7.0 (2.3)	6.3 (2.4)
24 months	6.8 (2.4)	6.5 (2.3)

p=0.048

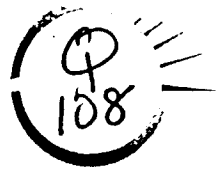
Ladder of Life

Mean (SD)

	Hydroxyurea (N = 152)	Placebo (N = 147)
Baseline	6.9 (2.0)	6.6 (2.1)
6 months	6.8 (2.1)	6.5 (2.1)
12 months	6.7 (2.0)	6.8 (2.2)
18 months	6.8 (2.0)	6.8 (2.0)
24 months	6.7 (1.9)	6.7 (2.1)

p=0.58

11/97



COMPLIANCE

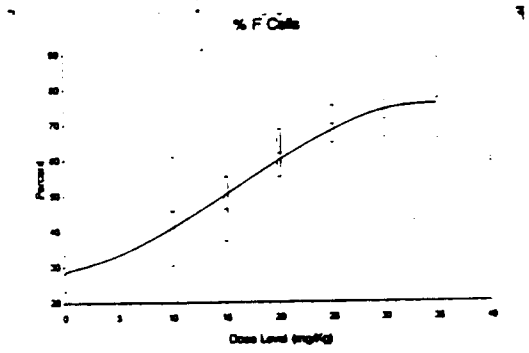
Group Mean (SD) of Percent for Each Patient

	Hydroxyurea (N=152)	Placebo (N=147)
% Follow-Up Visits Completed	90 (17)	90 (17)
% Capsules Taken	77 (25)	80 (21)
% Positive HU Assay	31 (25)	<1 (2)

TO BE REPLACED

I-4 ✓

% F cells vs dose



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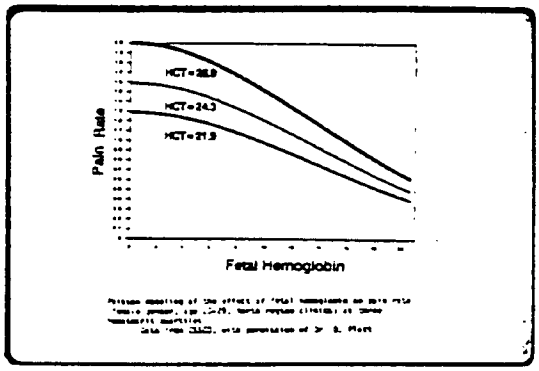
I-3

PATHOLOGY PHOTOGRAPHY

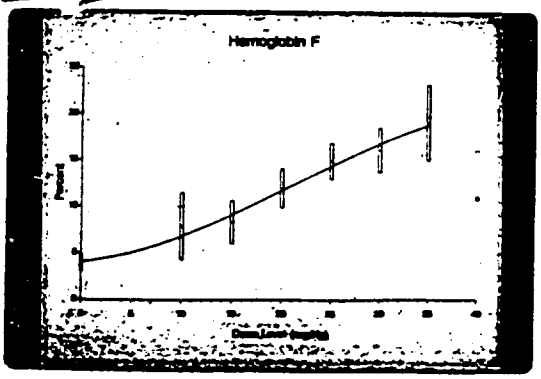


The Johns Hopkins Medical School

HC F vs dose

PATHOLOGY PHOTOGRAPHY

I-1



The Johns Hopkins Medical School

VIII-173

MCV vs F (alt)

PATHOLOGY PHOTOGRAPHY

I-5

The Johns Hopkins Medical School

VIII-135

BEST POSSIBLE COPY

COMPLIANCE

Group Mean (SD) of Percent for Each Patient

	Hydroxyurea (N=152)	Placebo (N=147)
% Follow-Up Visits Completed	90 (17)	90 (17)
% Capsules Taken	77 (25)	80 (21)
% Positive HU Assay	31 (25)	<1 (2)

QUARTILES OF 2-YEAR HB-F CHANGE

	Quartile 1 (n = 34)	Quartile 2 (n = 38)	Quartile 3 (n = 36)	Quartile 4 (n = 35)
Hb-F (2-yr change)	-1.5 (1.1)	+0.6 (2.4)	+5.1 (4.0)	+6.4 (3.8)
Neutrophils (2-yr change)	-0.3 (1.7)	-1.0 (2.0)	-2.2 (1.5)	-4.1 (2.3)
Toxic x2 (%)	47	58	86	94
≥50% Positive HU Assay	14	24	28	46
Crises/year mean (SD)	6.5 (5.9)	7.2 (10.1)	3.1 (5.2)	2.3 (4.5)

Blood 89:1078-1088 (1997)

Q151

TOTAL PARENTERAL NARCOTIC ANALGESIC
(2-Year Total Morphine Equivalent)
p=0.015 (Wilcoxon)

	Hydroxyurea (N=152)	Placebo (N=147)
Mean	5355	11943
StdErr	23058	72820
25th percentile	13	99
Median	345	741
75th percentile	2089	2989

Q 102

11/97

"AT-HOME" ORAL ANALGESIC
(2-Year Total Morphine Equivalent)
p=0.99 (Wilcoxon)

	Hydroxyurea (N=152)	Placebo (N=147)
Mean	6819	8504
StdDev	9723	18475
25th percentile	494	520
Median	2112	2157
75th percentile	11149	10150

Q 103 11

11/97

012/019

HYDROXYUREA TERATOGENESIS IN ANIMALS

Animal	Dose	Day	Findings
Hamster	50 mg	8	Central axis deformity, cranioschisis Spina bifida
Rat	185 mg/kg	9	Exencephaly, cleft palate, limb deformity
	750 mg/kg	12	Encephalocele, micrognathia

Others exhibiting teratogenicity: rabbits, dogs, cats, and rhesus monkeys.
Teratogenicity not clearly related to inhibition of DNA synthesis.
Integrated dose to fetus may be more relevant than dose to mother. **11/97**

G-1

HYDROXYUREA TERATOGENESIS IN HUMANS

Underlying Disease (n pregnancies)	Daily Dose	Outcome	Comment
ET (1)	1-2 gm	Normal	Stop Rx @ 6 wks
CML (9)	1.5-3 gm	8 normal 1 stillbirth	Follow-up 5-32 mos Mother eclamptic
CLL (1)	1.5 gm	Normal	Stop Rx 3-9 mos
AML (2)	Combination Chemotherapy	1 abortion	Normal children p Rx
ALL (2)	Combination Chemotherapy	Normal	1 child in 5th %ile

HYDROXYUREA THERAPY IN CHILDREN WITH SICKLE CELL DISEASE

No Leukemia or Developmental Abnormality in Any Series[1]

Author	Patients (N)	Dose (mg/kg/day)	Follow-Up
Scott	13	10-35	Median 24 months
de Montalembert	35	33 ± 7[2,3]	Mean 32 months
	57	20 ± 6[2,4]	Mean 32 months
Ferster	22	<20-25	6-month cross-over
Vichinsky	17	MTD	12+ months
Rogers	16	25-30	Median 20 months
Jayabose	9	20-35	Median 23 months
HUG-KIDS	84	MTD	1 year at MTD

[1] No linear growth in 5/15 older patients; all patients gained weight

[2] HU given 4 days/week

[3] Secondary amenorrhea in one 18-yo girl

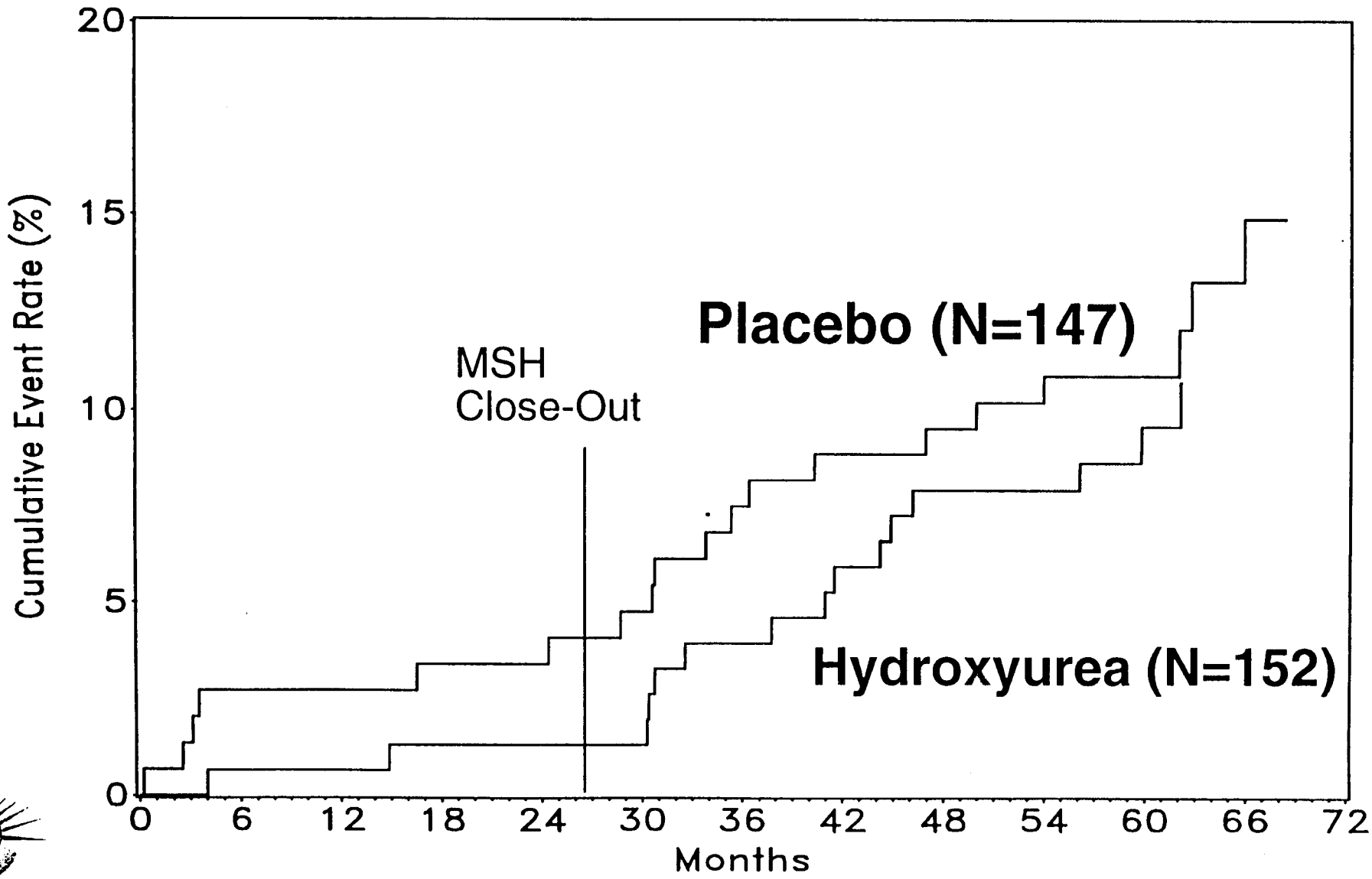
[4] 10-yo girl: acute lymph. leukemia >2 months Rx

11/97

H-1

(F-7)

MSH CUMULATIVE MORTALITY
According to Original Treatment Assignment
November 1997 p = 0.32



D-5

TRANSFUSIONS

(Q 35)
C-23

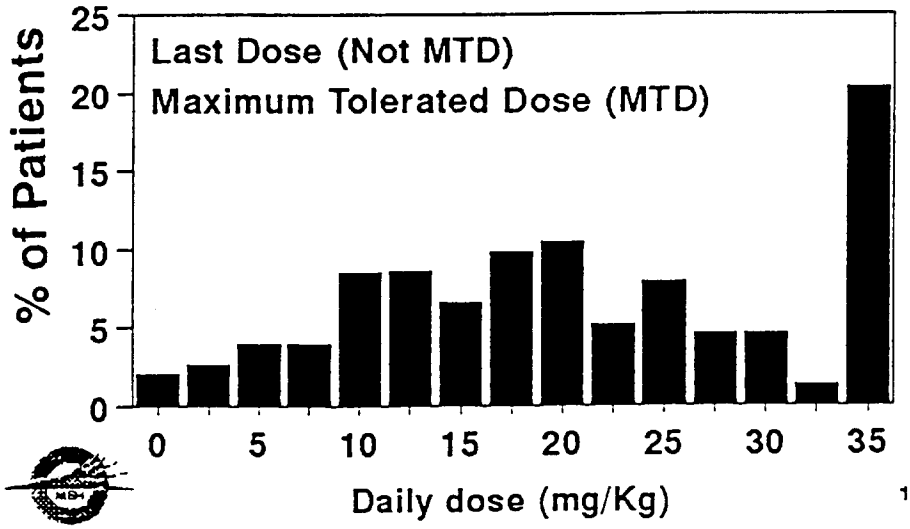
	Hydroxyurea (N=152)	Placebo (N=147)	
	n	n	p
Patients transfused	55	79	0.002
Units transfused	423	670	0.003

11/97

LAST PRESCRIBED DOSE

Hydroxyurea (N=152)

(Q 45)
C-24



1/95P

PROLEUKIN® (ALDESLEUKIN) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA

Oncologic Drug Advisory Committee Meeting

December 19, 1997
Chiron Corporation

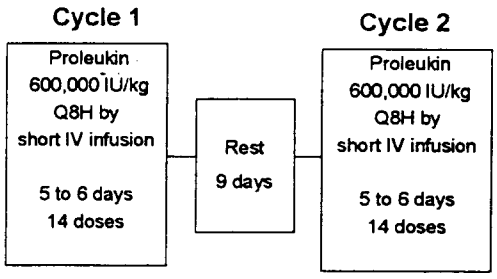
Introduction: Slide 1

PROLEUKIN MILESTONES

- 1983 Cloned
- 1984 First clinical trials initiated
- 1989 European approval
  - Metastatic Renal Cell Cancer
- 1992 FDA issues license

Introduction: Slide 2

COURSE OF THERAPY



Introduction: Slide 3

METASTATIC RENAL CELL CANCER

- Efficacy based on response rate and durability
- Post licensure commitment to follow responders
- Follow-up data shows durability of responses

Introduction: Slide 4

METASTATIC RENAL CELL CANCER

	Patient # (%)	Duration of Response	
		Median (months)	Range (months)
CR + PR	37 (15%)	54	3 to 107+
PR	20 (8%)	20	3 to 97+
CR	17 (7%)	*	7 to 107+

* Not yet observed, >54 months (Fall 1996)

Introduction: Slide 5

METASTATIC RENAL CELL CANCER
COMPLETE RESPONDERS

Patient ID	Duration (months)
2376155	7
061166518	11
4438	16
191LW	17
019HF	23+
01	49+
2381291	49+
1509376	50+
017FT	54+
1501780	55+
055621471	58+
2310053	58+
659JM	81+
001GS	83+
198HO	85+
205CS	86+
197AC	107+

Introduction: Slide 6

METASTATIC MELANOMA

- 270 patients treated with single-agent Proleukin
- Eight protocols
- Supplemental Biologic License Application submitted

Introduction: Slide 7

PROLEUKIN® (ALDESLEUKIN) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA

Indication: Adult patients with metastatic melanoma

Dosage: 600,000 IU/kg
Q8H, 15-minute IV infusion
Following 9 days rest, repeat cycle

Introduction: Slide 8

PROLEUKIN® (ALDESLEUKIN) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA

AGENDA

Introduction	Mary O'Hara, Chiron Corporation
Metastatic Melanoma- A Disease Overview	Michael Atkins, MD, Beth Israel Deaconness Medical Center
Efficacy and Safety of Proleukin in Patients with Metastatic Melanoma	Lori Kunkel, MD, Chiron Corporation
Conclusions	Mary O'Hara

Introduction: Slide 9

METASTATIC MELANOMA: NATURAL HISTORY AND RESULTS OF CONVENTIONAL THERAPY

MICHAEL B. ATKINS, M.D.
Beth Israel Deaconess Medical Center
Harvard Medical School

Introduction: Slide 10

APPEARS THIS WAY
ON ORIGINAL

METASTATIC MELANOMA

"Metastatic Melanoma is the disease that gives cancer a bad name"
Canellos

- Young patients (median age ~46)
- Suboptimal therapy
- Median survival 6-9 months
- 2-3% of patients survive

Disease: Slide 1

MELANOMA: U.S. 1997

- Incidence
  - 40,300 new cases; 7,500 deaths
  - 3% of all cancers; 1.5% of all cancer deaths
  - 10 fold increase since 1935
- Lifetime risk:
  - approximately 1 in 90
  - approximately 1 in 75 by year 2000

Disease: Slide 2

STAGE IV MELANOMA

- More than one LN station involved
- Lymph Node >5 cm, fixed
- In transit metastases ≥5 in number
- Involvement of skin or soft tissue beyond site of primary tumor
- Visceral metastases

Disease: Slide 3

Stage Survival Curves

Slide Not to be Shown

Disease: Slide 4

PROGNOSTIC FACTORS FOR SURVIVAL IN METASTATIC MELANOMA SINGLE FACTOR ANALYSIS

Factor	P Value
# of metastatic sites	<0.000001
Site of metastases	0.0001
Primary melanoma site	0.209
Remission duration	0.245
Ulceration	0.356
Tumor Thickness	0.428
Level of invasion	0.642
Lymphocyte infiltration	0.642
Age	0.760
Gender	0.975

Balch et al J Clin Oncol 1:126, 1983

Disease: Slide 5

of Metastatic Sites Survival Curve

Disease: Slide 6

Visceral vs Non-visceral Survival Curve

Disease: Slide 7

PROGNOSTIC FACTORS FOR SURVIVAL IN METASTATIC MELANOMA MULTIFACTORIAL ANALYSIS

Factor	P Value
Number of metastatic sites	<0.00001
Remission duration	0.0186
Site of metastases	0.0192

Balch et al J Clin Oncol 1:126, 1983

Disease: Slide 8

ADVERSE PROGNOSTIC FACTORS FOR SURVIVAL

Source	n	Prognostic Factors
Univ. of Alabama (Balch)	200	>1 metastatic site Organ sites of metastisis (Visceral) Remission duration <12 months
John Wayne (Barth)	1521	Organ sites of metastases (Visceral) >1 metastatic site Short disease free interval
SWOG (Flaherty)	649	Performance status >0 >1 metastatic site Liver metastases Short disease free interval
ECOG (Ryan)	635	Performance Status >0 >1 metastatic site Liver/CNS metastases Short disease free interval Male gender

Disease: Slide 9

SERIES REVIEW

	UAB (Balch) n=200	ECOG (Ryan) n=635	SWOG (Flaherty) n=649	John Wayne (Barth) n=1521
>1 metastatic site	51%	NR	70	14%
Visceral involvement	79%	NR	83	75%
Disease free interval				
Median (months)	NR	NR	12-24	33.8
<1 year	37%	NR	NR	NR
Median Survival (months)	8	6	5.5	7.5
5 year overall survival	4-5%	1.6%	2%	6%

NR = Not reported

Disease: Slide 10

TREATMENT OPTIONS

- Surgery
- Chemotherapy
- Immunotherapy
  - Interferons
  - Interleukins
  - Vaccines
  - Monoclonal Antibodies
- Combinations of the above

Disease: Slide 11

SURGICAL SERIES

	Karakousis (n=495)	Roses (n=147)	Wong (n=1250)
Resected	23%	33%	11%
5 year survival of resected patients	22%	13%	16%

Disease: Slide 12

BIASES WITH SURGICAL DATABASES

- Patients with single site, limited lesion (more surgically resectable) disease
- Includes local recurrence, in transit mets or multiple nodal sites
- Patients receive other therapies

Disease: Slide 13

SINGLE AGENT CHEMOTHERAPY

Agent	n	Response Rate	95% CI
DTIC	1936	20%	18-22
BCNU	122	18%	11-32
CCNU	270	13%	9-17
CDDP	188	23%	17-29
Vincristine	52	12%	3-20
Vinblastine	62	13%	5-21
Paclitaxel	65	18%	9-28

Disease: Slide 14

SINGLE AGENT DTIC

	CR	OR
Response Rate	5%	19%
Median Duration of Response (months)	13.5	4

- 6 year overall survival of all patients is 1-2%

Hill et al. Cancer 53:1299-1305, 1984 (n=580)
Houghton et al "Chemotherapy for Metastatic Melanoma Balch:1992 Cutaneous Melanoma 2nd edition (n=967)

Disease: Slide 15

NEW CYTOTOXIC AGENTS

Agent	Response Rate	Median Survival (Months)	2 Year Survival
Temozolomide	21%	5.5	8%
Fotemustine	24%	NR	NR
Carboplatin	11-19%	4.7	3%
Vindesine	20%	NR	NR
Docetaxel	15%	NR	NR

Disease: Slide 16

CYTOKINE THERAPY

Agent	Response Rate	5 Year Survival
Interferon alpha	10-17%	NR
Interleukin-2*	16%	14%
Interleukin-4	<5%	NR
Interleukin-6	<5%	NR
Interleukin-12	NR	NR

*Proleukin

Disease: Slide 17

INTERFERON ALPHA THERAPY

- Indicated in adjuvant setting
- Response rate in metastatic melanoma approximately 16%
  - CR approximately 4%
  - Response rate higher with small tumor burden ($\leq$ 1.5 cm)
  - Response rate lower with liver or bone mets

Disease: Slide 18

COMBINATION CHEMOTHERAPY

Regimen	Response Rate
BHD	27-31%
BOLD	20-40%
CDDP/DTIC	20-53%
CVD	20-40%
CDBT "Dartmouth"	15-55%

- 5 year survival not reported

Disease: Slide 19

DARTMOUTH REGIMEN SWOG EXPERIENCE

Regimen	n	OR	CR	OR Duration (months)
BCNU/DTIC/DDP + TAM	79	15%	6%	8

Margolin et al. Proc. ASCO, 1997

Disease: Slide 20

COMBINATION CHEMOTHERAPY VS DTIC

Institution	Regimen	n	OR	CR	Median Survival (months)
SWOG	BHD	256	29%	11%	11*
(Costanza)	DTIC + BCG	130	18%	7%	7
MDACC	CVD	46	24%	0%	6
(Buzaid)	DTIC	46	11%	0%	6

- ECOG Dartmouth vs. DTIC just completed

*No significant difference

Disease: Slide 21

COMBINATION CHEMOTHERAPY AND TAMOXIFEN

Institution	Regimen	Outcome
Ital. Oncology (Cocconi)	DTIC + /- TAM	Significant Difference in RR and Median Survival
NCI (Rusthoven)	CBD + /- TAM	No Difference
MDACC (Legha)	CVD/IFN + /- TAM	No Difference
Pittsburgh (Ferri)	Carb/DTIC + /-TAM	No Difference
ECOG 3690 (Falkson)	DTIC +/- TAM DTIC/IFN +/- TAM	No Difference

Disease: Slide 22

COMBINATION DTIC AND IFN

Institution	Regimen	n	OR	CR	OR Duration (months)
U. of Pretoria	DTIC	30	20%	8%	2.5
(Falkson)	DTIC + IFN	30	53%	40%	9

Three other randomized trials showed no difference
Kirkwood 1990, Thomson 1993 and Bajetta 1994

Disease: Slide 23

ECOG 3690

Regimen	n	OR	CR	TTF (months)	Median Survival (months)
IFN-	128	16%	3%	2.1	8.4
*IFN+	122	20%	7%	2.7	9.4

*Includes 62 patients entered on DTIC + IFN + TAM arm

Disease: Slide 24

ECOG 3690

Regimen	n	OR	CR	TTF (months)	Median Survival (months)
TAM-	126	18%	6%	2.6	9.5
*TAM+	124	19%	4%	2.5	8.4

*Includes 62 patients entered on DTIC + IFN + TAM arm

Disease: Slide 25

SUMMARY

- Metastatic pattern associated with poor clinical outcome defined
  - Multiple sites
  - Visceral disease
- Surgery produces 5 year disease free survival in approximately 5% of all patients
  - Single sites
  - Single lesion metastases involving skin, lymph node and lung

Disease: Slide 26

SUMMARY (CONTINUED)

- Single agent chemotherapy produces 5 year survival of 1-2%
- IFN produces responses in about 16% of patients
  - Responses in small volume disease
- Combination chemotherapy or addition of Tamoxifen or Interferon to chemotherapy not yet proven superior to DTIC alone

Disease: Slide 27

CONCLUSIONS

- Metastatic melanoma is a "bad" disease
- Responses to conventional therapy are usually short and 5 year survival is rare
- Additional therapeutic options are necessary

Disease: Slide 28

EFFICACY AND SAFETY OF PROLEUKIN IN PATIENTS WITH METASTATIC MELANOMA

LORI A. KUNKEL, M.D.
Associate Director
Chiron Corporation

HALLMARK OF PROLEUKIN THERAPY IS DURABLE RESPONSES

Efficacy & Safety: Slide 1

METASTATIC MELANOMA

- Study criteria prospectively defined
- Cohort
  - Patients with metastatic melanoma
  - Proleukin as a high-dose Q8H regimen
  - 1985 through 1993 enrollment
- Retrospective review

Efficacy & Safety: Slide 2

EFFICACY PROTOCOLS

- 7 NCI sponsored protocols
  - 4 Intramural
  - 3 Extramural
- 1 Chiron sponsored protocol
- 22 Investigational sites
- Median follow-up for responders: 62 months (Fall 1996)

Efficacy & Safety: Slide 3

STUDY OBJECTIVES

- Efficacy of Proleukin
  - Response rates
  - Response duration
  - Progression free survival
  - Survival
- Safety profile

Efficacy & Safety: Slide 4

PATIENT COHORT

- Assigned or randomized and treated with single agent Proleukin
- Measurable disease
- ECOG PS: 0-2
- Informed consent

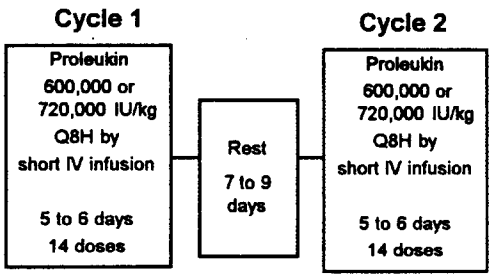
Efficacy & Safety: Slide 5

STUDY CRITERIA

- Cardiac and pulmonary function screening
- Liver, kidney and hematologic parameters
- No CNS metastasis
- No active infections
- No concomitant steroid therapy

Efficacy & Safety: Slide 6

COURSE OF THERAPY



Efficacy & Safety: Slide 7

EFFICACY PROTOCOLS

Protocol #	Indication (Phase)	Melanoma Patients
Intramural: (n=147)		
T94-0634	Metastatic Cancer (I)	28
T95-0097	Advanced Cancer (II)	84
T90-0053	Renal Cell Carcinoma or Melanoma (II)	32
92C-0084	Cancer/AIDS/Skin Disease (IV)	3
Extramural: (n=118)		
T96-0063	Melanoma (I)	9
T96-0170 (Cytokine Working Group)	Unresectable Melanoma (II)	64
C97-0002 (Modified Group C)	Metastatic or Unresectable Malignant Melanoma (II)	45
Chiron: (n=5)		
CS-L291-06	Solid Tumor Carcinoma (I)	5

Efficacy & Safety: Slide 8

EFFICACY PROTOCOLS

	Intramural n=147	Extramural n=118	Chiron n=5
Dose (IU/kg) in Course 1	720,000	600,000	360,000 or 540,000
Median Doses	15.0	21.0	20.5
Median Cumulative Dose (MIU/kg)	10.8	12.6	9.5

Efficacy & Safety: Slide 9

DEMOGRAPHICS

- 270 Patients
- Median age: 42 years (18-71 years)
- Males: 64%, Females: 36%
- Performance Status
  ECOG 0: 71%
  ECOG 1: 27%
  ECOG 2: 2%

Efficacy & Safety: Slide 10

PRIOR SYSTEMIC THERAPY

	Patients # (%)
Chemotherapy Only	37 (14%)
Immunotherapy Only	51 (19%)
Hormonal Only	2 (1%)
Multiple Modalities	32 (12%)
Any Systemic	123 (46%)

Efficacy & Safety: Slide 11

ORGAN SITES OF DISEASE

Number of Sites	Patients # (%)	
1	79 (29%)	
2	110 (41%)	71%
3	47 (17%)	
≥ 4	34 (13%)	

- 69% of patients had at least one site of visceral involvement

Efficacy & Safety: Slide 12

CLINICAL ENDPOINTS

- Response Rate
- Response Duration
- Progression Free Survival
- Survival

Efficacy & Safety: Slide 13

RESPONSE RATE

	CR # (%)	PR # (%)	CR + PR # (%)
Intramural (n=147)	10 (7%)	13 (9%)	23 (16%)
Extramural (n=123)	7 (6%)	13 (11%)	20 (16%)
Total (n=270)	17 (6%)	26 (10%)	43 (16%)*

*95% CI: 12%, 21%

Efficacy & Safety: Slide 14

DURATION OF BEST RESPONSE

	n	Median (months)	Range (months)
CR + PR	43	8.9	
CR	17	*	
PR	26	5.9	

*Not yet observed, >40 months (Fall 1996)

Efficacy & Safety: Slide 15

DURABLE RESPONSES

Patient ID	Duration (months)
IL610	24.1+
IL595	40.5+
IL592	41.2+
009KB*	54.9+
IL451	59.1+
IL392	61.9+
IL321	65.3+
IL277	72.3+
H9	86.3+
C076*	91.5+
IL006	102.7+
C016	106.2+

*Patients classified as partial responders

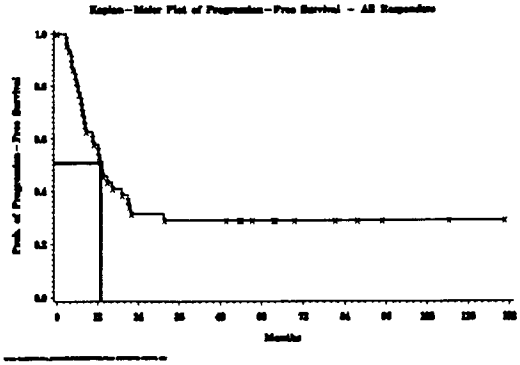
Efficacy & Safety: Slide 16

PROGRESSION FREE SURVIVAL

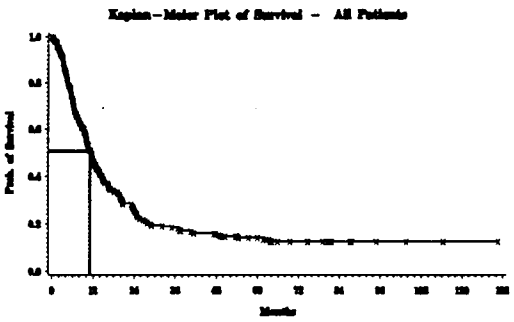
	n	Median (months)	Range (months)
CR + PR	43	13.1	
CR	17	*	
PR	26	8.3	

*Not yet observed, >54 months (Fall 1996)

Efficacy & Safety: Slide 17



Efficacy & Safety: Slide 18



Efficacy & Safety: Slide 19

FOLLOW-UP OF COMPLETE RESPONDERS

- 10/17 ongoing CRs without further therapy
  - All responses >24 months
- 7 CRs relapsed
  - 2 were durable survivors

Efficacy & Safety: Slide 20

PRE-TREATMENT/POST-TREATMENT SCAN

- Patient Scan

Efficacy & Safety: Slide 21

FOLLOW-UP OF PARTIAL RESPONDERS

- 2 ongoing at 54.9+ and 91.5+ months
- 24 subsequently progressed
  - 6 are surviving

Efficacy & Safety: Slide 22

PRE-TREATMENT/POST-TREATMENT SCAN

- C082
  - Subcutaneous

Efficacy & Safety: Slide 23

PRE-TREATMENT/POST-TREATMENT SCAN

- 009KB
  - Lung

Efficacy & Safety: Slide 24

PRE-TREATMENT/POST-TREATMENT SCAN

- 009KB
  - Liver

Efficacy & Safety: Slide 25

PRE-TREATMENT/POST-TREATMENT SCAN

- IL470
  - Lung/Adrenal

Efficacy & Safety: Slide 26

FIVE YEAR CLINICAL OUTCOME (KAPLAN-MEIER)

	CR	PR	All Responding Patients
Response duration >5 years	59%	8%	29%

Efficacy & Safety: Slide 27

FIVE YEAR CLINICAL OUTCOME (KAPLAN-MEIER)

	CR	PR	All Responding Patients
Survival >5 years	76%	35%	51%
# of Patients	9	8	17

Efficacy & Safety: Slide 28

PROGNOSTIC FACTORS

- Associated with response:
  - Performance status
  - Prior systemic therapy

Efficacy & Safety: Slide 29

PERFORMANCE STATUS

ECOG PS	n	CR # (%)	PR # (%)	CR + PR # (%)
0	191	14 (7%)	22 (12%)	36 (19%)
≥1	79	3 (4%)	4 (5%)	7 (9%)

- Performance status is associated with response, odds ratio (PS ≥1 vs 0) is 0.42 (95% CI: 0.16, 0.93)

Efficacy & Safety: Slide 30

PRIOR SYSTEMIC THERAPY

Systemic Therapy	n	CR # (%)	PR # (%)	CR + PR # (%)
No	147	15 (10%)	16 (11%)	31 (21%)
Yes	123	2 (2%)	10 (8%)	12 (10%)

- Patients without prior systemic therapy were more likely to have a response, odds ratio (yes vs no) is 0.41 (95% CI: 0.19, 0.81)

Efficacy & Safety: Slide 31

NUMBER OF ORGAN SITES OF DISEASE

Organ Sites #	n	CR # (%)	PR # (%)	CR + PR # (%)
1	79	5 (6%)	5 (6%)	10 (13%)
≥2	191	12 (6%)	21 (11%)	33 (17%)

- Patients with multiple sites of disease are responsive to Proleukin, odds ratio (≥2 vs 1) is 1.44 (95% CI: 0.69, 3.23)

Efficacy & Safety: Slide 32

VISCERAL INVOLVEMENT

Visceral Involvement	n	CR # (%)	PR # (%)	CR + PR # (%)
No	84	6 (7%)	11 (13%)	17 (20%)
Yes	186	11 (6%)	15 (8%)	26 (14%)

- Patients with visceral involvement are responsive to Proleukin, odds ratio (yes vs no) is 0.64 (95% CI: 0.33, 1.28)

Efficacy & Safety: Slide 33

EFFICACY SUMMARY

- 16% of patients respond to Proleukin
- Durable complete responses
  - 59% are cancer free at 5 years

Efficacy & Safety: Slide 34

REVIEW OF SAFETY

- Toxicities are well characterized
- Safety in current package insert
- 102 patients with metastatic melanoma
  - These melanoma patients included in protocol

TOXICITY CHARACTERISTICS

- Capillary leak syndrome
- Neurologic toxicity
- Sepsis

TREATMENT GUIDELINES

- Screening: Adequate organ function
- Supportive measures: Concomitant medications
  Prophylactic antibiotics

ADVERSE EVENTS (≥ 20%), ANY GRADE

Body as a Whole
- Chills
- Malaise
- Fever
- Reaction unevaluable

Cardiovascular
- Hypotension

Digestive System
- Vomiting
- Diarrhea
- Nausea

Hemic and Lymphatic
- Thrombocytopenia
- Anemia
- Leukopenia

Metabolic/Nutritional Disorders
- Bilirubinemia
- SGOT increase
- Creatinine increase
- Peripheral edema

Nervous
- Confusion

Respiratory
- Dyspnea

Skin and Appendages
- Rash

Urogenital
- Oliguria

ALL GRADE 4 ADVERSE EVENTS

Body as a Whole	# (%)
Infection	6 (2%)
Fever	4 (1%)
Sepsis	3 (1%)
Reaction unevaluable	2 (1%)
Cardiovascular	
Cardiovascular Disorder	7 (3%)
Hypotension	3 (1%)
Myocardial Infarction	2 (1%)
Atrial Arrythmia	1 (<1%)
Ventricular Tachycardia	2 (1%)
AV Block (second degree)	1 (<1%)
Myocardial Ischemia	1 (<1%)
Digestive System	
Vomiting	7 (3%)
Diarrhea	9 (3%)
Nausea and Vomiting	1 (<1%)
Pancreatitis	1 (<1%)
Stomatitis	1 (<1%)
Hemic and Lymphatic	
Thrombocytopenia	4 (1%)
Anemia	1 (<1%)
Leukopenia	1 (<1%)

Metabolic and Nutritional Disorders	# (%)
Bilirubinemia	5 (2%)
SGOT increase	3 (1%)
Hypocalcemia	1 (<1%)
Nonprotein nitrogen increase	1 (<1%)
Alkaline phosphatase increase	1 (<1%)
Nervous	
Psychosis	5 (2%)
Neuropathy	2 (1%)
Coma	2 (1%)
Stupor	1 (<1%)
Respiratory	
Respiratory disorder	12 (4%)
Dyspnea	2 (1%)
Lung Edema	1 (<1%)
Pneumothorax	1 (<1%)
Urogenital	
Oliguria	23 (8%)
Anuria	21 (8%)
Acute Kidney Failure	1 (<1%)

EARLY TERMINATORS
n =22

Event	Number	Long term effects
Acute		
Cardiac	5	cardiac dysfunction (1)
Respiratory	4	none
Sepsis	2	ischemic necrosis (1)
Metabolic (acidosis)	1	none
Neurologic	1	none
Hepatic insufficiency	1	none
Chronic		
Hepatitis B	1	chronic Hepatitis B
Paresthesias	1	persistent neuropathy
Other		
Refusal	5	none
Alternate treatment	1	none

DRUG-RELATED DEATHS

Cause	Date of Death
Sepsis	6/26/87
Sepsis	4/4/88
Sepsis	5/28/88
Sepsis	3/8/89
Sepsis	5/1/89
Sepsis	6/22/90

- Overall incidence of on-study drug-related deaths was 2%

Efficacy & Safety: Slide 41

SAFETY SUMMARY

- Toxicities are common
  - Predictable/reversible
  - Most not chronic or cumulative
- Treatment guidelines incorporated

Efficacy & Safety: Slide 42

COMPARATIVE OBSERVATION

Metastatic Renal Cell
- 255 Patients
  - 37 (15%) Responding patients
    - 17 CR patients
    - 20 PR patients

Metastatic Melanoma
- 270 Patients
  - 43 (16%) Responding patients
    - 17 CR patients
    - 26 PR patients

Efficacy & Safety: Slide 43

COMPARATIVE OBSERVATION

Metastatic Renal Cell
- 255 Patients
  - 37 (15%) Responding patients
    - 17 CR patients
    - 20 PR patients
- **Median duration of CR >54 months**

Metastatic Melanoma
- 270 Patients
  - 43 (16%) Responding patients
    - 17 CR patients
    - 26 PR patients
- **Median duration of CR >40 months**

Efficacy & Safety: Slide 44

COMPARATIVE OBSERVATION

Metastatic Renal Cell
- 255 Patients
  - 37 (15%) Responding patients
    - 17 CR patients
    - 20 PR patients
- Median duration of CR >54 months
- **11 (4%) drug-related on-study deaths**

Metastatic Melanoma
- 270 Patients
  - 43 (16%) Responding patients
    - 17 CR patients
    - 26 PR patients
- Median duration of CR >40 months
- **6 (2%) drug-related on-study deaths**

Efficacy & Safety: Slide 45

PROLEUKIN® (ALDESLEUKIN) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA

- Favorable risk-benefit
- Toxicity predictable, manageable, reversible
- Durable responses

Efficacy & Safety: Slide 46

CONCLUSION

Proleukin is an important therapeutic option for patients with metastatic melanoma

Efficacy & Safety: Slide 47

PROLEUKIN® (ALDESLEUKIN) FOR THE TREATMENT OF PATIENTS WITH METASTATIC MELANOMA

Indication: Adult patients with metastatic melanoma

Dosage: 600,000 IU/kg
Q8H, 15-minute IV infusion
Following 9 days rest, repeat cycle

Efficacy & Safety: Slide 48

Interleukin-2, Aldesleukin® for metastatic melanoma

Chiron Corporation

Oncologic Drugs Advisory Committee

BLA 97-0501

December 19,1997

Interleukin-2, Aldesleukin® for metastic melanoma

CBER Review Committee

- Medical Reviewers: **Stephen D. Litwin**, MD
  Rebecca Dachman, MD
- Statistician: **Terry Neeman**, PhD
- Regulatory Coord: **Mrunal Chapekar,** PhD
- Bioresearch: **Pat Holobaugh**
- Pharm. Review**:** **Anne Pilaro,** PhD
- Post-marketing **:** **Fred Varicchio,** MD,PhD

Interleukin-2, Aldesleukin®

TIMEPOINTS

- **1985-1992** -Studies IL-2 treatment of solid tumors using bolus/short IV infusion q8h
- **7/30/90** BRMAC -IL-2 for RCC discussed
- **1/17/92** BRMAC -IL-2 for RCC-favorable recommendation
- **5/6/92** FDA licensed IL-2 for RCC
- **4/10/97** Application -IL-2 for MM

Interleukin-2, Aldesleukin®

TIMEPOINTS

- **1985-1992** -Studies IL-2 treatment of solid tumors using bolus/short IV infusion q8h
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Interleukin-2, Aldesleukin®

APPROVED INDICATION FOR RENAL CELL CARCINOMA

- IL-2 induces durable CR or PR in subset of RCC patients
  - careful patient selection
  - cardiac and pulmonary function testing
- Basis of approval
  - durable remissions
  - regression of >90% tumor burden
  - bulky disease responds

PROPOSED INDICATION FOR METASTATIC MELANOMA

- Aldesleukin is indicated for the treatment of adults with metastatic melanoma
- Same dose, and route of administration for RCC & metastatic melanoma
  - 600,000 IU/kg IL-2 IV q8h for 5d [cycle 1]- 6-10 d rest- repeat 5 d cycle for course of 28 doses

Interleukin-2, Aldesleukin for metastatic melanoma

EXPERIMENTAL DESIGN

- Eight studies integrated into a single-arm database (n= 270) after auditing
- Doses 600,000 (n=118) IU/kg IL-2
  & 720,000 (n=147) IU/kg IL-2
- Dose withheld for AE grade 3 or 4
- Patient disposition
  - 291 patients registered-21 were ineligible
  - 270 evaluable, 22 dc'd prematurely

Interleukin-2, Aldesleukin for metastatic melanoma

STUDY POPULATION

- **Eligibility**
  - –metastatic melanoma patients who failed standard therapy
  - –measurable lesions

Interleukin-2, Aldesleukin for metastatic melanoma

STUDY POPULATION

ELIGIBILITY

Study	n=	Included / ***added***
• 0054, 0097, 0053	144	Platelets, WBC, Bilirubin, creatinine
• 0063	9	***/ FEV 2 liters or 75% of predicted***
• 0170	64	***/ Stress treadmill & NE heart disease***
• 70002	45	***/ Thallium stress test***

Interleukin-2, Aldesleukin for metastatic melanoma

STUDY POPULATION

- Stage of disease not specified
- Patients enrolled seriatim? selected?

Interleukin-2, Aldesleukin for metastatic melanoma

OUTCOMES

	OR	CR	PR
Response rate	**16%** (43/270)	**6%** (17/270)	**10%** (26/270)
Duration response (range)	**8.9mos** (2,106+)	**NR** (3,106+)	**5.9mos** (2,92+)

Interleukin-2, Aldesleukin for metastatic melanoma

Study Comparability

	0054 n=28	0097 n=84	0053 n=32	70003 n=45	0170 n=64
Visceral disease	61%	85%	69%	53%	69%
2 or > sites	71%	60%	79%	64%	72%
total IL-2	12.6	14.1	13.7	13.8	13.2
CR,PR %	7,7	7,10	6.4,9.6	2,11	8,9

Interleukin-2, Aldesleukin for metastatic melanoma

SAFETY

- ADVERSE EVENTS
  - GRADE 3 -95%, GRADE 4-35%
- DOSES WITHHELD > 90% patients
- EARLY TERMINATIONS n= 22
  - toxicity 16, pt refused 5, alternative 1
- DEATHS -6 of 8 who died on-study were IL-2 related (death rate 2%)

Interleukin-2, Aldesleukin for metastatic melanoma

SAFETY

Cumulative experience RCC + MM patients, grades 1-4 (n=525)

- **Cardiovascular**
  - Hypotension 71%,
  - Arrhythmia 10%, CV disorders 11%
- **Pulmonary:** Dyspnea 43%, lung disorders 24%
- **Renal:** Oliguria 63%

Interleukin-2, Aldesleukin for metastatic melanoma

SAFETY

Cumulative experience RCC + MM patients, grades 1-4 (n=525)

- Bilirubinemia 40%, incr creatinine 33%, incr. SGOT 23%, edema 28%
- Nausea 35%,vomiting 50%, diarrhea 67%
- Confusion 34%, somnolence 22%
- Rash 42%, thrombocytopenia 37%
- ***Infections 13%***

Interleukin-2, Aldesleukin for metastatic melanoma

SAFETY

6 MM IL-2-related Deaths

- Anuria/oliguria, Pulm. failure, Recurrent melanoma
- ***Sepsis***, Pulm. failure
- ***Sepsis,*** Hepatic & renal failure
- ***Sepsis,*** Hepatic failure
- ***Pulm. failure & pneumonia***, Oliguria
- ***Sepsis,*** Hypotension

Interleukin-2, Aldesleukin for metastatic melanoma

SAFETY

11 RCC IL-2-related Deaths

- Myocardial infarction n=2
- Cardiac tamponade n=1
- Sepsis n=2
- Bowel performation and sepsis n=1
- GI bleeding n=1
- Pulmonary complications n=3
- Unknown n=1

Interleukin-2, Aldesleukin for metastatic melanoma

REVIEW ISSUES

- Consistency of 8 studies
- Definition of patient population
- Durability / tumor regression
- Analysis of variables/factors related to prognosis

Interleukin-2, Aldesleukin for metastatic melanoma

DEFINITION STUDY POPULATION

• Age	median	43.5 yr
• Gender	M/F	174/96
• ECOG	PS 0,1,2	71,27,2%
• Visceral involvement		69%
• 2 or > sites disease		71%

- Stage of disease not specified
- Limited information on prior therapy
- Limited information non-responders

Interleukin-2, Aldesleukin for metastatic melanoma

REVIEW ISSUES

- Consistency of 8 studies
- Definition of patient population
- Durability and tumor regression
- Analysis of variables/factors related to prognosis

Interleukin-2, Aldesleukin for metastatic melanoma

DURABILITY COMPLETE REPONSES

	Response duration in months
Ongoing complete responses n=10	106+, 103+, 86+. 72+, 65+, 62+, 59+, 41+, 41+, 24+
Relapsed complete responses n=7	3, 6, 6, 8, 9, 13, 18

Interleukin-2, Aldesleukin for metastatic melanoma

DURABILITY PARTIAL RESPONSES

	Response duration in months
Ongoing partial responses n= 3	92+, 55+, 6.4*
Relapsed partial responses n=23	29, 18, 17, 14, 13, 10, 8, 7, 7, 6, 6, 4, 4, 4, 4, 3, 3, 3, 2, 2, 2, 2, 2, 1

Interleukin-2, Aldesleukin for metastatic melanoma

DEGREE OF REGRESSION OF TUMOR IN PR PATIENTS

% tumor shrinkage	# patients/# PR
• 90% or >	7/25
• 80-89 %	5/25
• 70-79 %	4/25
• 60-69 %	6/25
• 50-59 %	3/25

One patient lacked baseline values and was not evaluable

Interleukin-2, Aldesleukin for metastatic melanoma

FURTHER ANALYSIS PRs

Patient	*Response duration*	*Tumor burden*
CO76	92+ mos	30 cm^2
009kb	55+ mos	49 cm^2
3140	29 mos	25 cm^2
6923	18 mos	1 cm^2
6207	17 mos	7 cm^2
431	14 mos	100 cm^2
CO82	13 mos	26 cm^2

Interleukin-2, Aldesleukin for metastatic melanoma

FURTHER ANALYSIS PRs

Patient	*IL-2 to OR*	*IL-2 post OR*
CO76	106 d	21 d
009kb	73 d	190 d
3140	63 d	none
6923	79 d	4 yrs
6207	75 d	19 d
431	241 d	none
CO82	37 d	70 d

Interleukin-2, Aldesleukin for metastatic melanoma

PARTIAL RESPONSE PATIENTS

- Long duration of response, 7pts > 1yr
- Substantial tumor burden
- Bulky tumors can respond to IL-2
- Response duration not related to tumor burden
- Responses occured after 1st course of IL-2 and were ongoing
- 20/26 Partial responders rc'd IL-2 after OR

Interleukin-2, Aldesleukin for metastatic melanoma

REVIEW ISSUES

- Consistency of 8 studies
- Definition of patient population
- Durability and tumor regression
- Analysis of variables/factors related to prognosis

Interleukin-2, Aldesleukin for metastatic melanoma

FACTORS NOT ASSOCIATED WITH RESPONSE

Variable

- –Age
- –Gender-M vs F
- –Visceral involvement- yes or no
- –Number of metastatic sites

Interleukin-2, Aldesleukin for metastatic melanoma

FACTORS ASSOCIATED WITH RESPONSE

Variable	Comparison	RR	Odds Ratio (95% CI)
ECOG	PS 1	9%(7/79)	0.42‡
	PS 0	19%(36/191)	(0.16,0.93)
Prior systemic therapy	Yes	10%(12/123)	0.41‡
	No	21%(31/147)	(0.19,0.81)

‡-significant

Interleukin-2, Aldesleukin for metastatic melanoma

FACTORS ASSOCIATED WITH RESPONSE-ECOG status

	ECOG PS 0	ECOG PS 1 or 2	total
n (%)	191 (71%)	79 (29%)	270
ORR #	36	7	43
%	19%	***9%***	16%
Deaths #	1	5	6
%	<1%	***6%***	2.%

Interleukin-2, Aldesleukin for metastatic melanoma

ALTERNATIVE TREATMENTS FOR MM

Therapy	ORR	CR	CR-MD
DTIC	14% (84/580)	4.5% (26/580)	58wk
Fotemustine	25% (57/226)	3% (7/226)	
Cisplatin	10-26%		
BOLD	45%	15%	3-15mos
Dartmouth	55%	20%	
BCNU/HU/DTIC*	27% (48/178)	(55/384)	

Interleukin-2, Aldesleukin for metastatic melanoma

ALTERNATIVE TREATMENTS FOR MM

Other therapies

- Various combination therapies
  - with or without Tamoxifen 4 studies
  - with or without IFN-alpha 4 studies
    - ***No difference in ORR or survival***
- Biochemotherapy- report high ORR and substantial toxicity

Interleukin-2, Aldesleukin for metastatic melanoma

SUMMARY -1

- *Issues regarding study population:*
  - –varying dose
  - –patient selection
  - –staging
  - –lack NR, prior therapy, prospective endpoint data

Interleukin-2, Aldesleukin for metastatic melanoma

SUMMARY -2

- *Issues regarding safety*:
  - impact of changes in management of in fluids, antibiotic prophylaxis and patient selection not known
  - ECOG 1 & 2 patients have higher toxicity and lower response
  - risk of infections, & of cardiovascular AE not fully known

Interleukin-2, Aldesleukin for metastatic melanoma

SUMMARY -3

- ***Issues regarding efficacy***:
  - –majority PRs are short
  - –limited tumor regression
  - –continuing therapy after OR
- Major clinical value is in the limited number of durable CR, PR and IL-2 as alternative therapy

Questions for # 97-0501; IL-2 in metastatic melanoma

1. This license application describes the results of eight studies, enrolling a total of 270 patients, treated with a comparable dose and schedule of IL-2. Approximately 70% of the study population had visceral disease and more than one site of metastatic disease, 74% of the patients had ECOG PS 0 at baseline and all met stringent entry criteria regarding cardiac and pulmonary function. The pooled data revealed an ORR of 16% and CR rate of 6%. The median duration of response for patients achieving a PR was 8.3 months; 10 of 17 complete responders remain in remission for over 2 years. The ORR for other single agents in this disease ranges from 5-25%, with CR rates of 1-4.5%. Median response durations for CR patients treated with other single agent therapies has been up to 15 months.

- **Please discuss: a) the type and quality of the responses observed and b) the population treated in this pooled dataset. Considering the rate, quality, and duration of response, can one conclude that IL-2 provides clinical benefit for patients with metastatic melanoma? If not, can one conclude that IL-2 has induced response which are reasonably likely to predict clinical benefit?**

Questions for # 97-0501; IL-2 in metastatic melanoma

2. In these studies, 95% of the patients experienced grade 3 toxicity and 35% grade 4 toxicity. Treatment required hospitalization in an intensive care setting during the IL-2 administration and in the post-infusion period. The treatment related mortality, 6/270, was not dissimilar to the treatment related mortality of 11/259 observed in the renal cell studies. Mortality in the present dataset was disproportionately higher in patients with ECOG PS 1-2 (5/59) vs ECOG PS 0 (1/211). A logistic regression analysis indicated ECOG PS 0, lack of prior systemic therapy, and greater number of IL-2 courses administered correlated with a higher response rate. Current labeling for use in metastatic Renal Cell Cancer restricts use to intensive care facilities and to patients with normal cardiac and pulmonary function and notes that response rates were higher and mortality lower among patients with ECOG PS 0.

Questions for # 97-0501; IL-2 in metastatic melanoma

- Please discuss the toxicities of IL-2. In view of the responses and the toxicities, should IL-2 be indicated for use in metastatic melanoma? If approved, should the label further restrict the use of IL-2 to specific populations, such as ECOG PS 0?

Questions for # 97-0501; IL-2 in metastatic melanoma

- 3.Under the accelerated approval mechanism, drugs and biologics that have been studied for serious and life threatening diseases and "that provide meaningful benefit to patients over existing treatments" may be approved based on a surrogate endpoint that is reasonably likely to predict benefit provided post marketing studies confirm net clinical benefit. Under standard approval, post marketing commitments can be required of the sponsor; e.g., for additional studies to optimize dosing regimen or the patient population.

- **If there is an accelerated approval, what studies would be appropriate to confirm clinical benefit? If there is a standard approval, what commitments for post marketing studies should be sought?**