

Maxim Pharmaceuticals, Inc.

Histamine Dihydrochloride

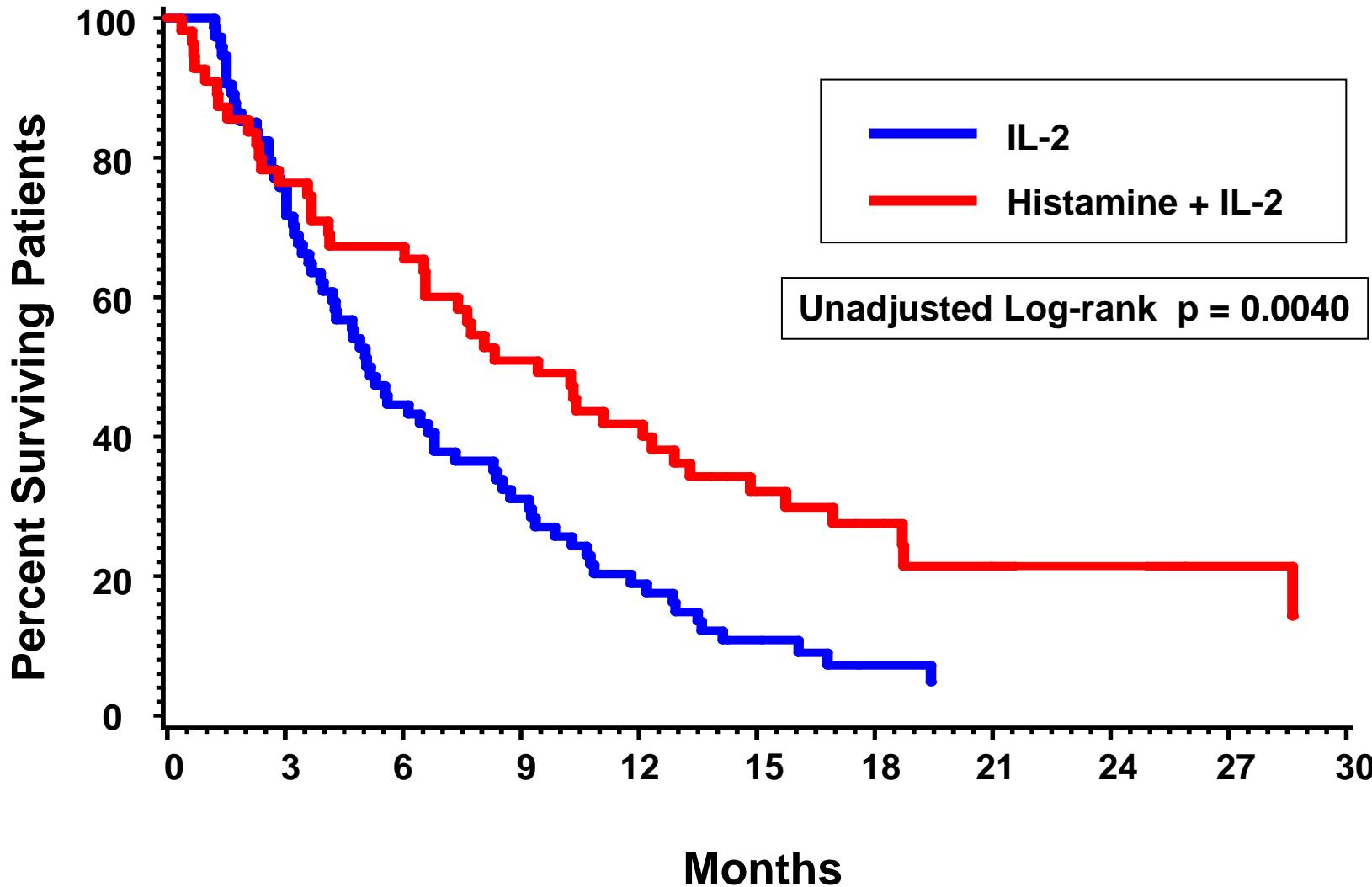
NDA 21-240

**Combination Therapy for Patients with
Advanced Metastatic Melanoma**

Oncology Drugs Advisory Committee
December 13, 2000

Survival

Patients with Baseline Liver Metastases (ITT- LM)



Presentation Agenda

- ◆ **Background - Metastatic Melanoma
(Dr. Michael Atkins)**
- ◆ **Rationale for Combination Therapy**
- ◆ **Clinical Experience**
- ◆ **Phase 3 Randomized Clinical Trial**
- ◆ **Supportive Single-arm Phase 2 Trial**
- ◆ **Eighteen Month Efficacy Update**
- ◆ **Summary and Conclusions**
- ◆ **Discussion**

Prognosis and Management of Stage IV Melanoma

Michael B. Atkins, MD

Beth Israel Deaconess Medical Center
Harvard Medical School

Melanoma Epidemiology: 2000

- ◆ Incidence: 44,700 cases
7,700 deaths
3% of all cancers
1% of all cancer deaths
- ◆ Lifetime risk: 1 in 74 Americans

Stage IV “Metastatic” Melanoma

Definition

- ◆ Involvement of skin or soft tissue beyond the region of the primary tumor
- ◆ Involvement of distant nodal sites
- ◆ Visceral metastases

Metastatic Melanoma: Prognosis

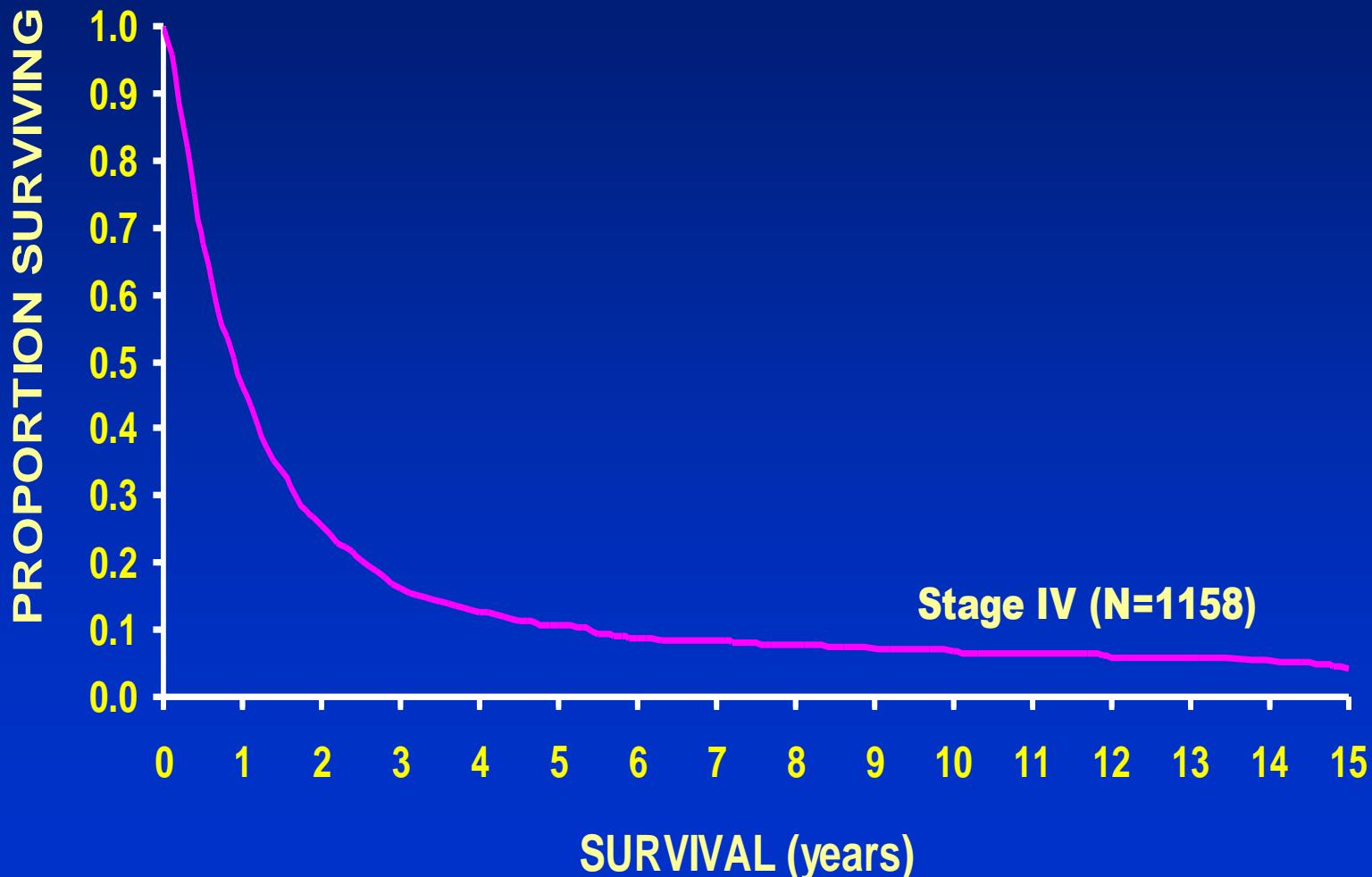
“Metastatic melanoma is a bad disease.”

- ◆ Median age: 45-50
- ◆ Median Survival: 6-10 months
- ◆ 5 -year survival: < 5%

Few if any effective therapies

AJCC MELANOMA STAGING DATABASE

Survival Curve for Proposed STAGE IV



Multifactorial Analysis of Prognostic Factors for Survival in Stage IV Melanoma*

<u>Factor</u>	<u>P value</u>
Number of metastatic sites	<0.00001
Remission duration	0.0186
Site of metastases	0.0192

*Balch et al J Clin Oncol 1:126, 1983

Prognostic Factors Stage IV Melanoma: Impact of Site on Survival

<u>Site(s) (proportion)</u>		% Survival		
		<u>1 yr</u>	<u>2yr</u>	<u>5yr</u>
non-visceral	(20%)	35	20	10*
visceral	(40%)	15	3	<2
both	(39%)	9	1	0

*significantly better

Balch et al JCO1:126 1983

Prognostic Factors In Stage IV Melanoma

Metastases to the liver carries a particularly poor prognosis

Survival Based on First Site of distant metastases

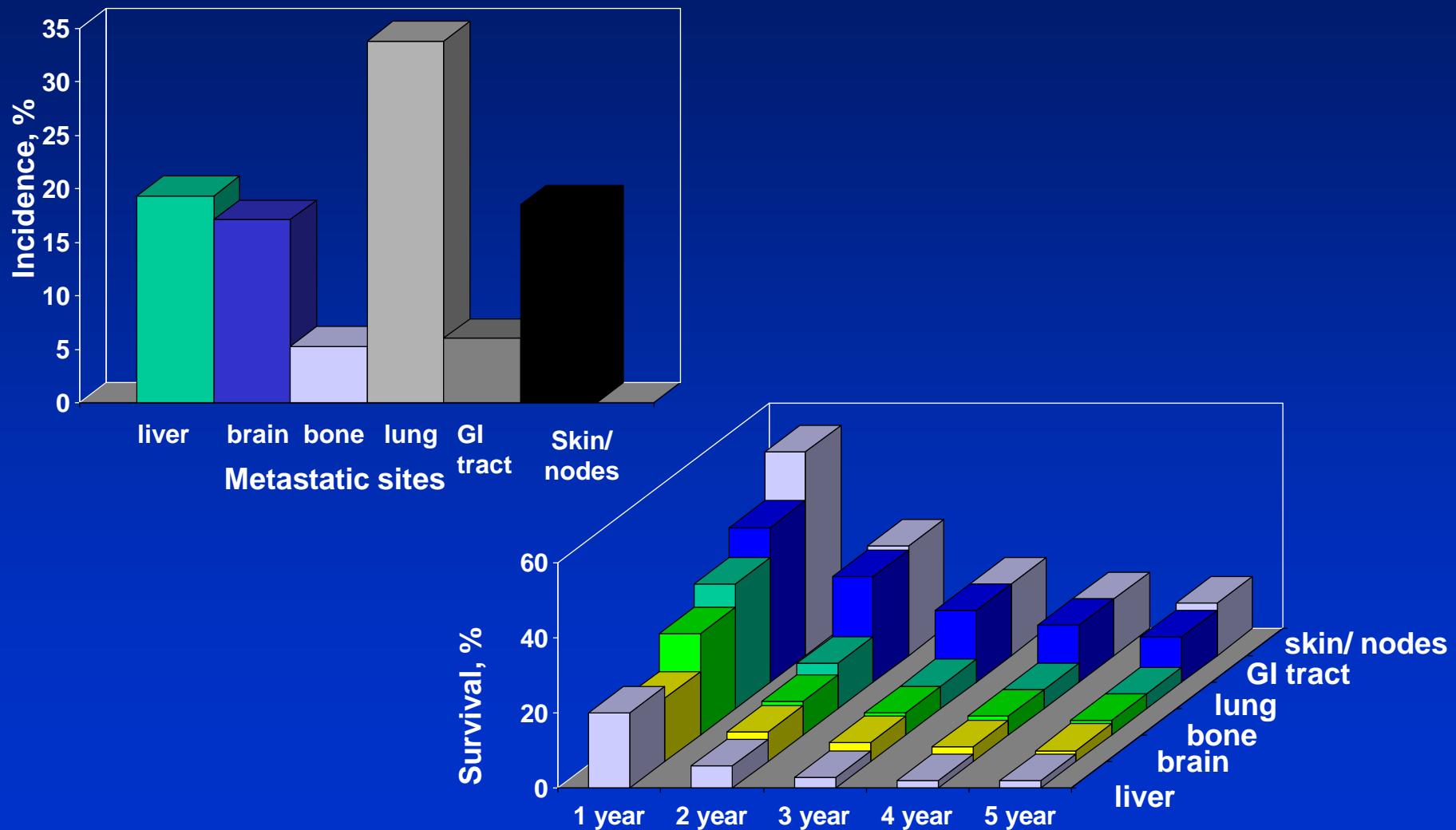
Site	Overall (%)	Incidence (%)	Site Alone	Plus Other Sites	
			Median Survival (months)	Incidence (%)	Median Survival (months)
Skin, subcutaneous tissues, and distant lymph nodes	59	23	7.2	36	5.0
Lung	36	11	11.4	25	4.0
Brain	20	8	5.0	12	1.4
Liver	20	3	2.4	17	2.0
Bone	17	3	6.0	14	4.0
Other	12	2	2.2	10	2.0
Widespread	4		2.4		2.4

SURVIVAL PATIENTS WITH STAGE IV MELANOMA (UCLA / JW) 1521 PTS

<u>Site</u>	<u>1y</u>	<u>3y</u>	<u>5y</u>	<u>median</u>
Skin, LN	54%	19%	14%	15 mos
GI	41%	19%	12%	11 mos
Lung	33%	12%	4%	8 mos
Bone	27%	6%	4%	6 mos
Liver	20%	3%	2%	4 mos
Brain	17%	5%	3%	4 mos
All sites	32%	8%	6%	7.5 mos

Barth et al, J Am Co Surg 181:193; 1995

Survival According to Metastatic Site in 1,521 Patients with AJCC Stage IV Melanoma



Prognostic Factors For Survival: SWOG Database*

<u>Factor</u>	<u>P value</u>
Performance Status	<<0.01
Number of metastatic sites	<<0.01
Liver metastases	0.01
Disease Free Interval	0.03

649 consecutive patients on 11 trials involving chemotherapy

5 year survival: 2%

*Flaherty et al. Proc ASCO, 1996

Prognostic Factors for Survival: ECOG Pooled Analysis*

<u>Factor</u>	<u>RR</u>	<u>P-value</u>
PS ≥ 1	1.49	0.0001
GI tract mets	1.49	0.0008
Liver mets	1.44	0.0001
Weight loss	1.23	0.004
Lung mets	1.19	0.006
No of met sites	1.12	0.0001
Gender	0.87	0.02
Prior Immune RX	0.84	0.047

*8 studies - 1362 patients - 25 years
Manola et al, J Clin Oncol Nov, 2000;

Prognostic Factors: Liver Metastases

Why is prognosis so poor for patients with liver metastases?

No clear answer; however, liver mets appear to be an indicator of more aggressive disease and/or impaired host defenses rather than simply increased tumor burden.

Prognostic Factors In Stage IV Melanoma

*Elevated serum LDH
is also strong
negative prognostic
factor*

Prognostic Factors: MD ANDERSON SERIES

Site	%	Median Survival	p value
high LDH	61%	6 mo.	0.001
>1 visceral site	39%	6 mo.	0.01
males	64%	7 mo.	0.02
low albumin	11%	3 mo.	0.03
	(Eton et al; JCO, 1998)		

318 STAGE IV Patients

Prognostic Factors: ECOG Pooled Analysis*

<u>Factor</u>	<u>RR</u>	<u>P-value</u>
Abnl LDH	1.89	0.0001
Abnl Alk Phos	1.76	0.0001
GI tract mets	1.66	0.02
Abnl Platelets	1.63	0.001
No of met sites	1.30	0.0001

3 studies (with lab parameters) - 362 patients

***Manola et al, J Clin Oncol 11/2000**

Prognostic Factors for Stage IV Melanoma - Summary

- ◆ 5 studies found either number of sites or visceral mets to be most predictive of poor survival
 - One metastatic site better than multiple sites
 - Skin, SC and distant lymph nodes have best prognosis
 - Lung (?GI) metastases are intermediate
 - Liver, brain and other visceral sites have 4 - 6 months median survival
- ◆ Performance Status ≥ 1 = poor prognosis
- ◆ Elevated serum LDH may be as important as above factors

Proposed New AJCC Staging System: Stage IV Melanoma

M Status	Site	Serum LDH
M1a	Distant skin, SC, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral mets Or any distant met	Normal Elevated

Prognostic Factors: ECOG Pooled Analysis*

Survival By AJCC Staging Category

	<u>N</u>	<u>Med</u>	<u>%2yr</u>	<u>%5yr</u>
Skin / SC / Nodes	217	10.6	15.3	6.1
Lung	284	8.7	10.7	1.2
Other	809	5.0	5.9	2.2

8 studies - 1362 patients

*Manola et al J Clin Oncol November, 2000

Prognostic Factors: ECOG Pooled Analysis*

Survival By AJCC Staging Category (Includes LDH)

	<u>N</u>	<u>Med</u>	<u>%2yr</u>	<u>%5yr</u>
Skin / SC / Nodes	38	12.8	29	22.6
Lung	47	11.8	21.3	5.5
Other + LDH	277	7.8	11.6	5.0

3 studies - 362 patients

*Manola et al J Clin Oncol November, 2000

METASTATIC MELANOMA

SYSTEMIC TREATMENT OPTIONS

- ◆ Cytotoxic chemotherapy
- ◆ Immunotherapy
 - Cytokines
 - Vaccines
 - MoAbs
- ◆ Combinations of the above

Metastatic Melanoma: Therapy - 2000

Approved Therapies Date

DTIC	1970's
High-dose interleukin-2	1998

*No reproducible survival benefit
established to date*

Metastatic Melanoma: Therapy - 2000

Single Agent DTIC Activity*

- ◆ Response Rate 19%
- ◆ Median Response Duration 4 mos
- ◆ Median Survival 6-9 mos
- ◆ 6 year survival < 2%

* Hill et al Cancer 53:1299; 1984 (n=580)

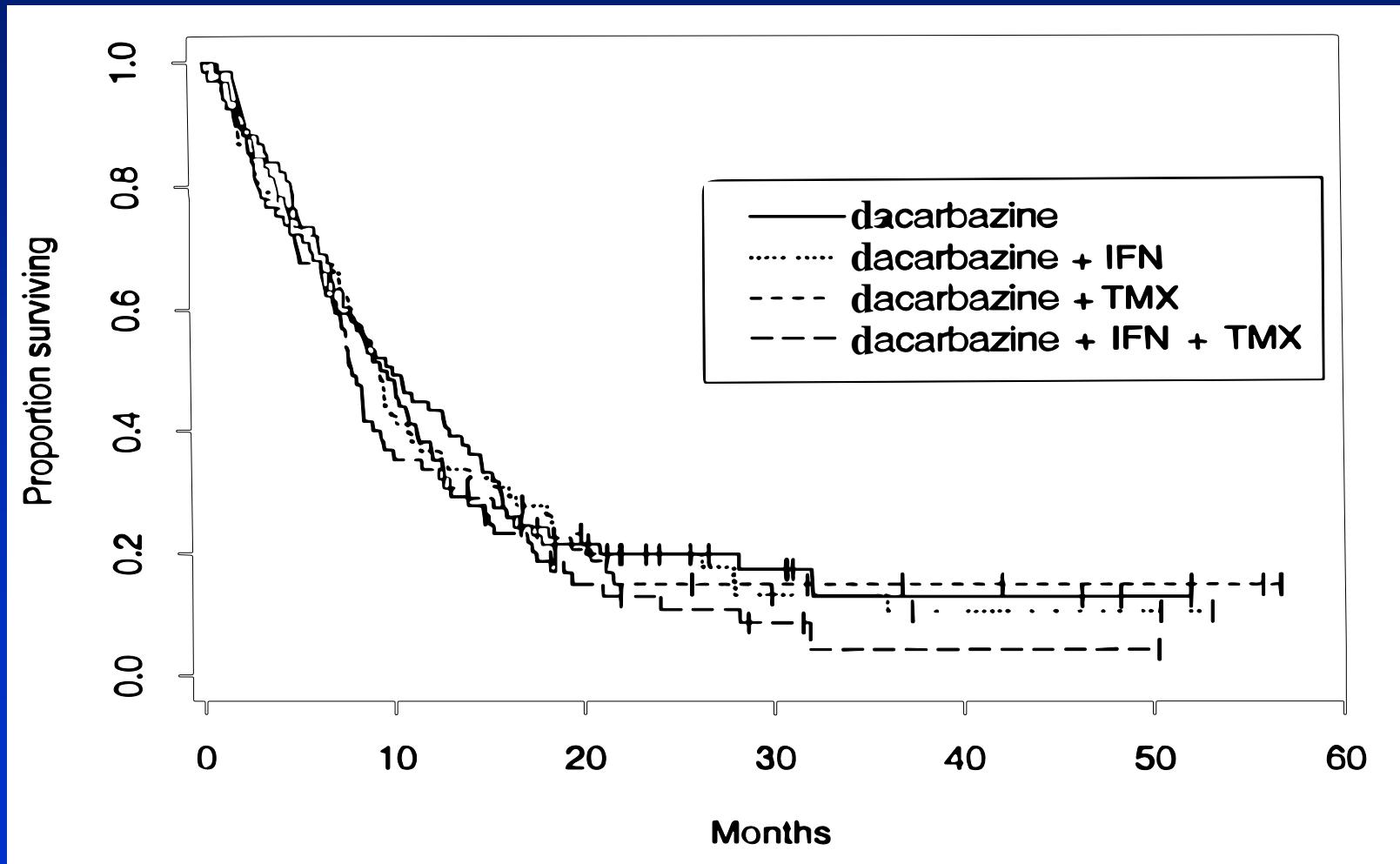
Metastatic Melanoma: Promising Phase II / III Approaches

<u>Regimen</u>	<u>RR</u>	<u>Author</u>
DTIC + Tam*	28%	Cocconi
DTIC + IFN*	53%	Falkson
CVD	40%	Legha
CDBT “Dartmouth”	55%	McClay

*Small phase III trials vs. DTIC alone

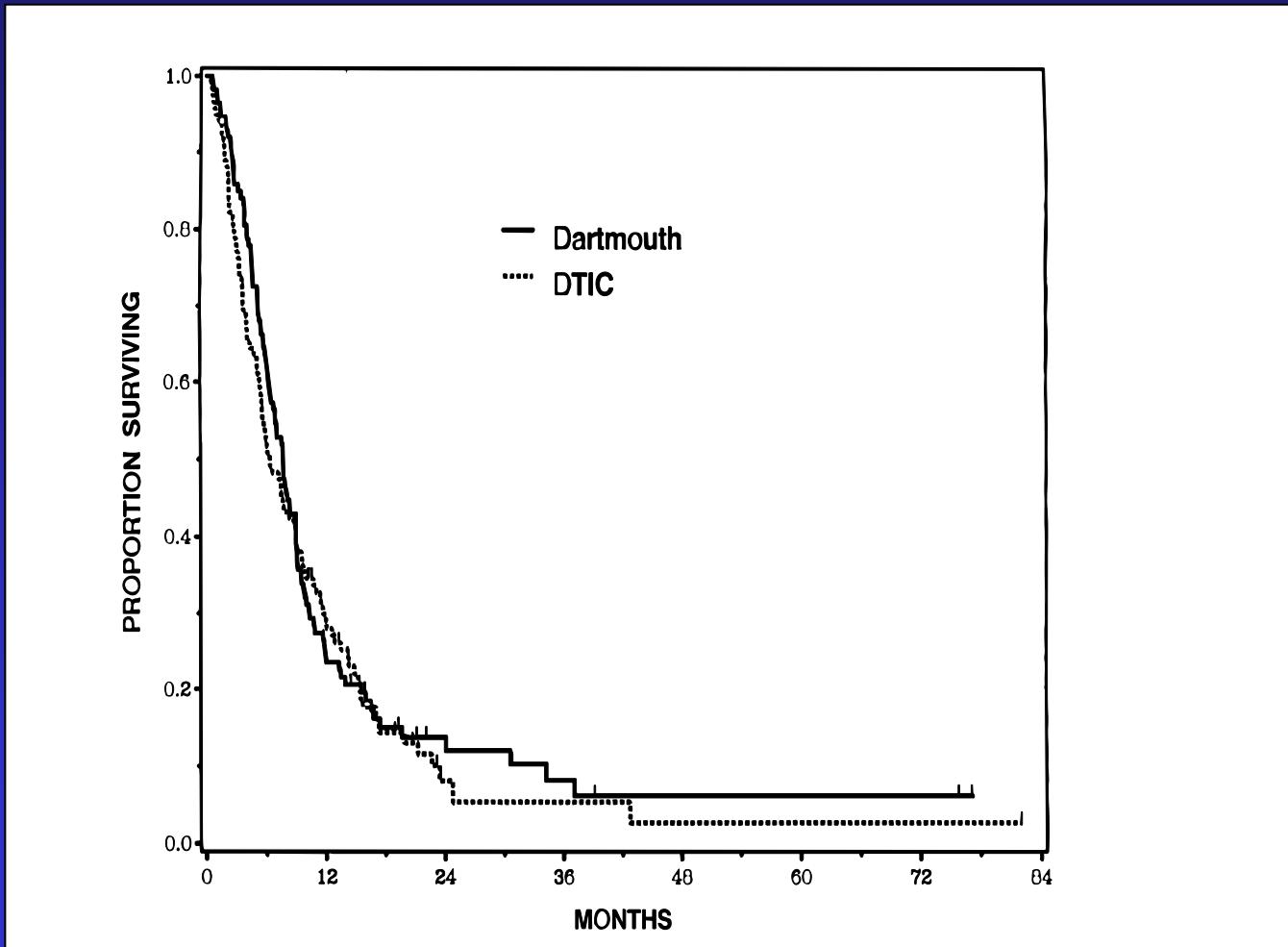
Metastatic Melanoma: Recent Phase III Trials

DTIC +/- IFN +/- Tam



Metastatic Melanoma: Recent Phase III Trials

DTIC vs Dartmouth



HD IL-2: TREATMENT REGIMEN

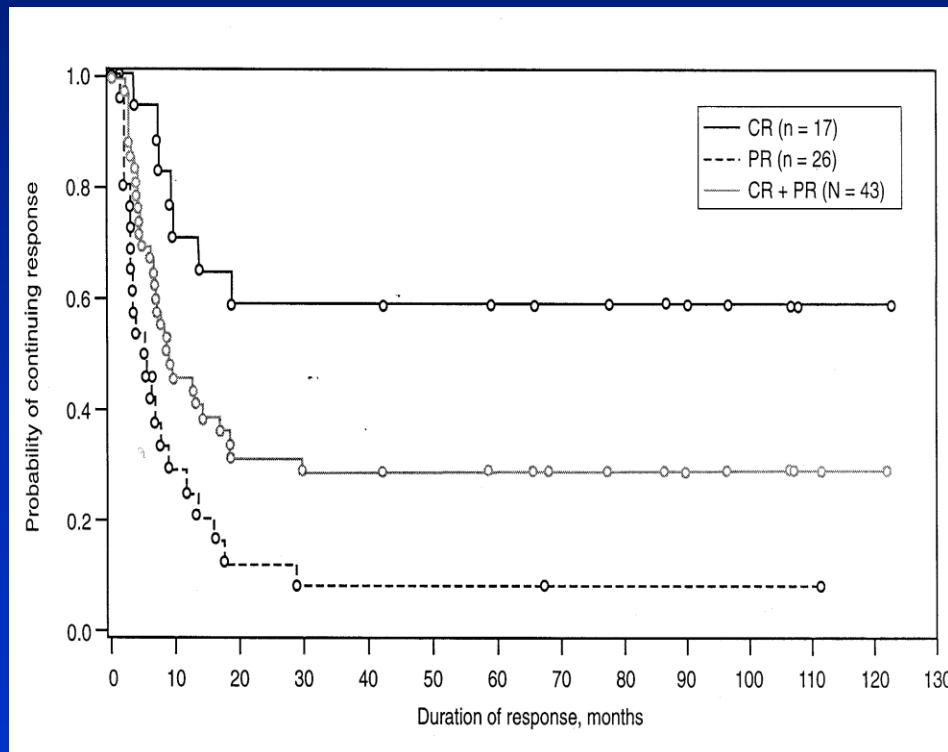


Repeat at 8-12 weeks if responding

Maximum 2-5 courses

Metastatic Melanoma: High Dose IL-2 Therapy*

Durable Responses (Median 8.9 mos; CR not reached)



RR: 16% (43 / 270)

- ◆ Highly toxic
- ◆ Inpatient
- ◆ Expensive
- ◆ Impractical
- ◆ Use limited to selected pts and Rx centers

*Atkins et al JCO, 1999 (N=270)

RESPONSE CHARACTERISTICS (1)

<u>Prognostic factor</u>	<u>Odds Ratio</u>	<u>95% CI</u>
ECOG PS	0.42	0.16-0.93
Prior systemic Rx	0.41	0.19-0.81
Visceral disease	0.64	0.33-1.28
No. of organ sites	1.44	0.69-3.23
Dose intensity (course 1)	1.36	0.71-2.69
Gender	0.82	0.42-1.62
Age	0.86	0.44-1.65

RESPONDER CHARACTERISTICS(2)

- ◆ Response by PS:

ECOG	0	19%
	≥ 1	9%

- ◆ Response by Prior Rx:

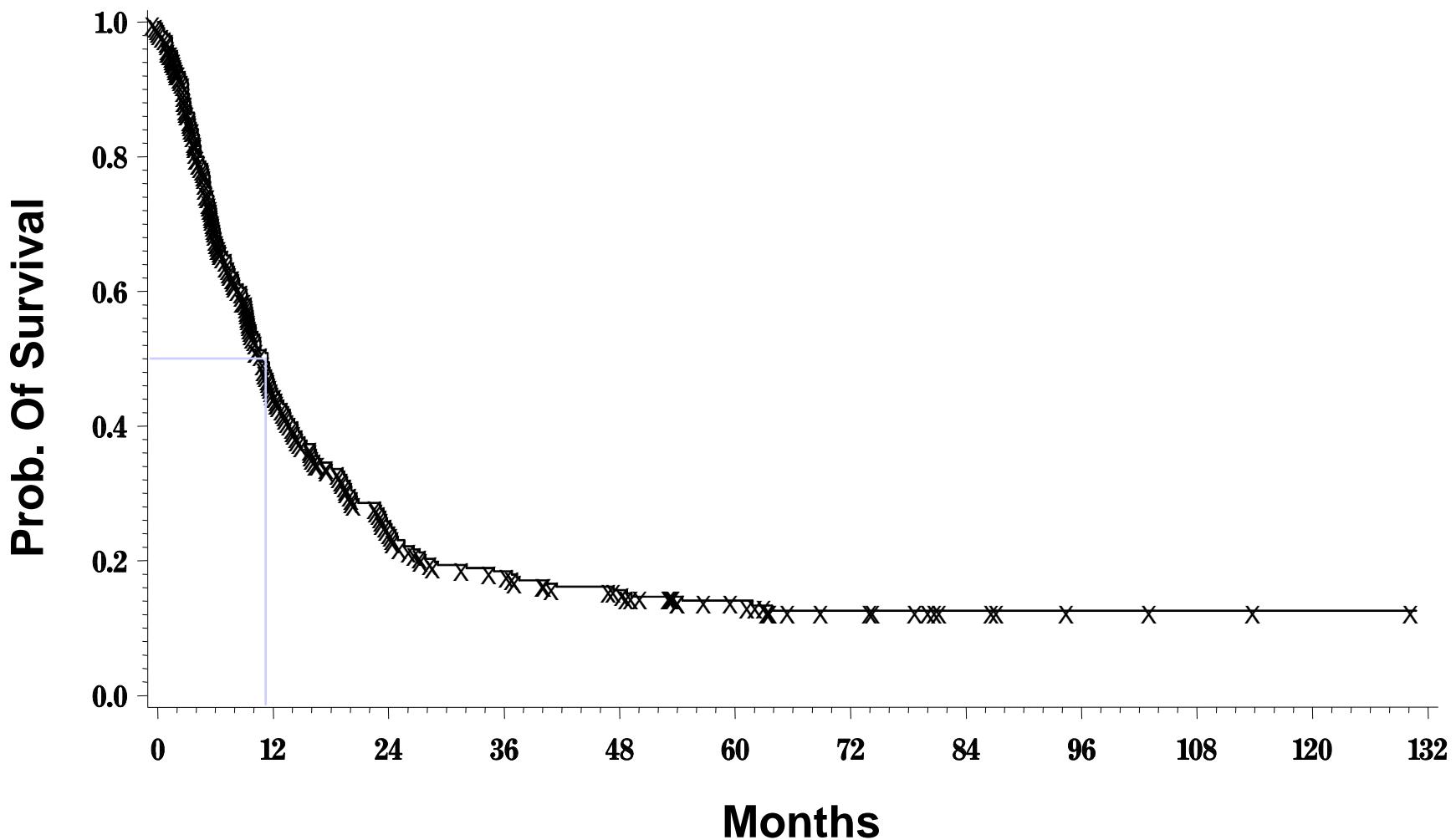
no	24%
yes	6%

HD IL-2: SURVIVAL

	<u>median (mos)</u>	<u>range</u>
overall	12.0	0.3 - 150+

*11% (30/270) remain alive at
minimum 5 year f/up*

Kaplan-Meier Plot of Survival - All Patients



High Dose IL-2: TOXICITY

Incidence

> 50%

Toxicity

hypotension, diarrhea, n / v
hyperbilirubinemia

25-50%

chills, malaise, anemia, plts,
wt gain, dyspnea, skin, CNS
or renal dysfunction

Death: 6 (2.2%) -- all related to infection in
the era before routine antibiotic
prophylaxis

IL-2-based Therapy For Stage IV Melanoma

Low dose IL-2 has limited activity in Stage IV melanoma

IL-2 in Melanoma: Continuous Infusion and Low-dose Regimens

<u>IL-2 Regimen</u>	<u>N</u>	<u>CR+PR</u>	<u>RR (%)</u>
HD Cont Infusion	219	40	18
“Hybrid”	18	4	22
“Low dose”	95	1	1

Adapted from Atkins, Shet, Sosman in Devita, Hellman, Rosenberg Principles and Practice of the Biologic Therapy of Cancer 3rd Edition

Melanoma Biochemotherapy: Early Inpatient Phase II Studies

Results Summary

<u>Invest</u>	N	CR/PR (%)	Dur	Surv
Richards	83	12/34(55)	8+	11
Legha	100	15/34(49)	NA	12
Khayat	127	13/49(49)	6-14	11
Atkins	65	6/20(40)	5-6	11
Totals	375	46/137	48%	(45-51%)

Biochemotherapy: Meta-analyses

Response Rates

<u>Treatment</u>	*Keilholz et al (n=631)	**Allen et al (n=3285)
IL-2	14.9%	14.3%
IL-2 +IFN	23.0%	15.8%
IL-2+CT	20.8%	22.2%
IL-2+IFN+CT	44.9%	41.2%

P < 0.001

* JCO 16:1752; 1998

** Ca Therapeutics 1:168, 1998

Biochemotherapy: MD Anderson Phase III Trial Results*

	<u>Eval</u>	<u>RR</u>	<u>TTP</u>	<u>Survival</u>
CVD-Bio	91	48%	4.9 mos	11.9 mos
CVD	92	25%	2.4 mos	9.2 mos

Comments: Significant diff in RR and TTP
Borderline survival diff
(P=0.079)

* Eton et al, Proc ASCO 2000

Biochemotherapy: MD Anderson Phase III Trial - Problems

- ◆ Inpatient and intensive
- ◆ Highly toxic
- ◆ Few durable responses
- ◆ Borderline survival benefit
- ◆ No confirmatory trials

Other Phase III Trials of Biochemotherapy

- ◆ EORTC: IL-2 / IFN +/- CDDP (Keilholz)
 - improved RR, no survival benefit
- ◆ NCI SB: CDDP/DTIC +/- HD IL-2/ IFN (Rosenberg)
 - improved RR, no survival benefit
- ◆ EORTC: CDDP/DTIC / IFN +/- IL-2 (Keilholz)
 - no RR or survival difference
- ◆ Intergroup: CVD +/- IL-2/ IFN (Atkins)
 - nearing completion

Metastatic Melanoma: Summary (1)

- ◆ Specific features associated with poor outcome
 - PS ≥ 1
 - visceral disease (particularly liver mets)
 - multiple sites
 - elevated LDH
- ◆ Single agent chemotherapy produces 5 year survival in 1-2% of patients
- ◆ Combination chemotherapy or the addition of tamoxifen or IFN α have not proven superior to DTIC alone

Metastatic Melanoma: Summary (2)

- ◆ HD IL-2 produces durable responses in a small percentage of patients; mostly previously untreated, PS 0 patients
- ◆ Low dose IL-2 alone has limited effectiveness
- ◆ Biochemotherapy increases response rate and toxicity; effect on survival uncertain
- ◆ Improved tumor response rate does not necessarily correlate with improved median survival

Metastatic Melanoma: Conclusions

- ◆ Metastatic melanoma is a bad disease
- ◆ Patients with liver metastases comprise a group with especially poor prognosis
- ◆ No treatment as yet has an established survival advantage

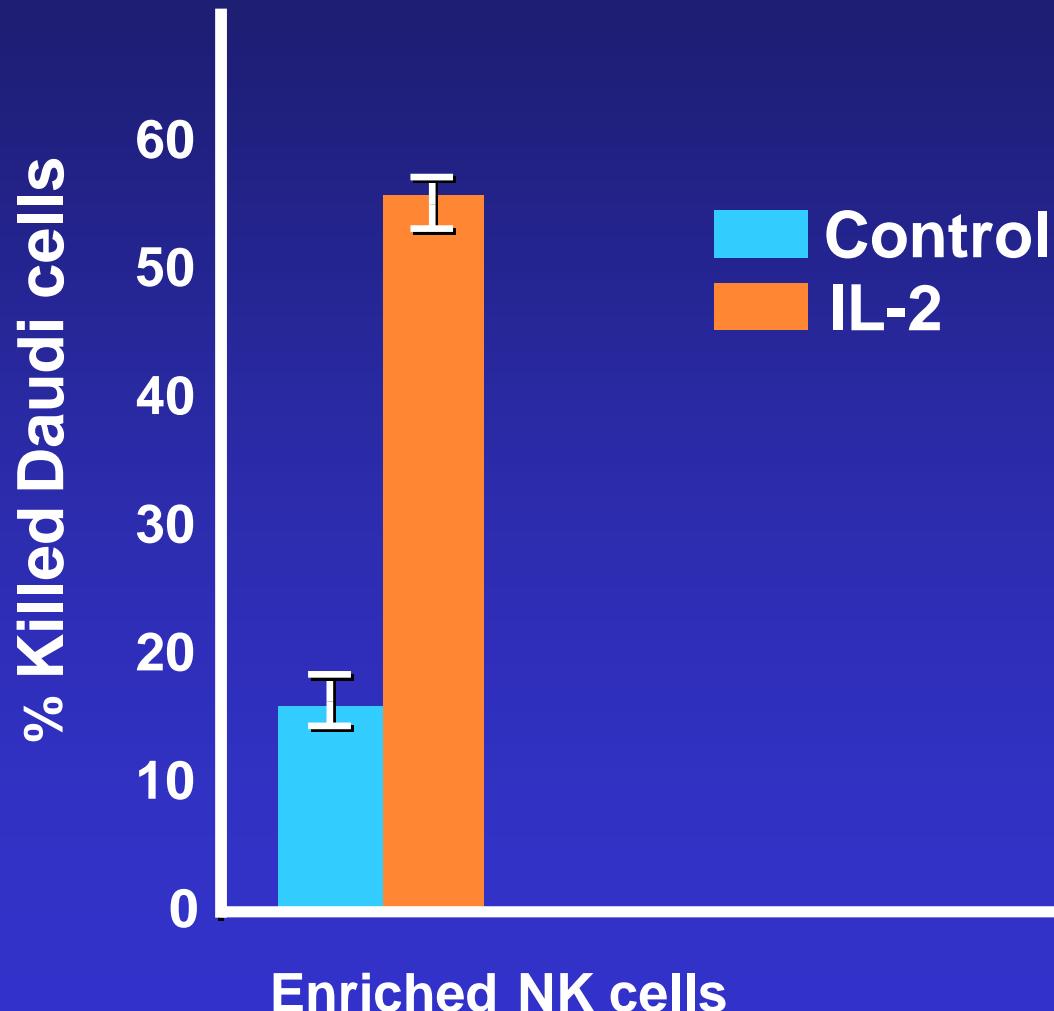
Rationale

Combination Therapy:
Histamine Dihydrochloride and
Interleukin-2

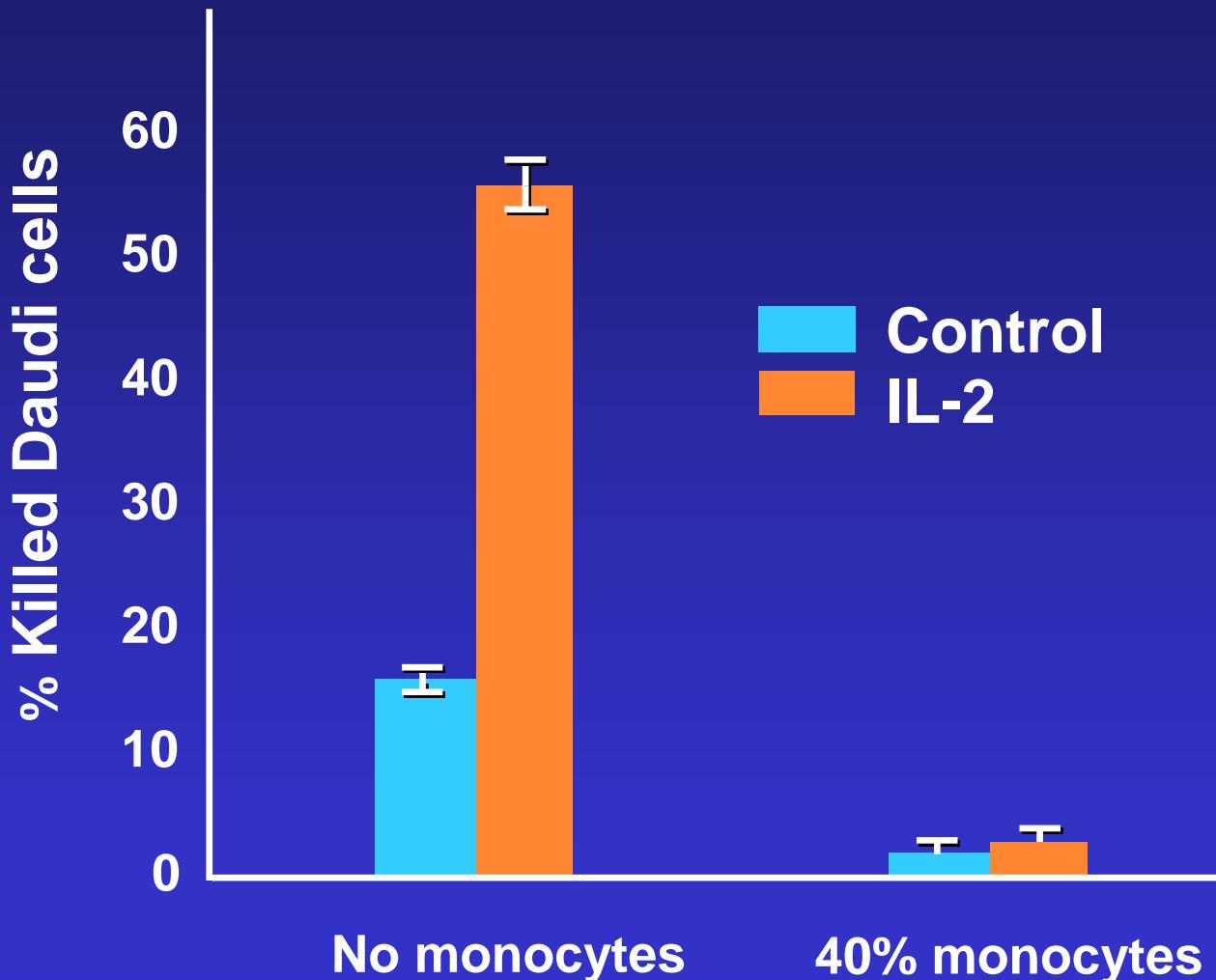
Immunosuppression: Role of Monocytes and Macrophages

- ◆ Monocytes/Macrophages (MO) Inhibit IL-2-induced Activation of Human Lymphocyte Functions
 - Natural killer (NK) cell-mediated tumor cell lysis
 - NK cell proliferation and activation
 - NK cell cytokine production
 - T cell proliferation and activation
- ◆ Histamine developed to protect NK and T cells from MO-induced inhibition and restore responsiveness to IL-2

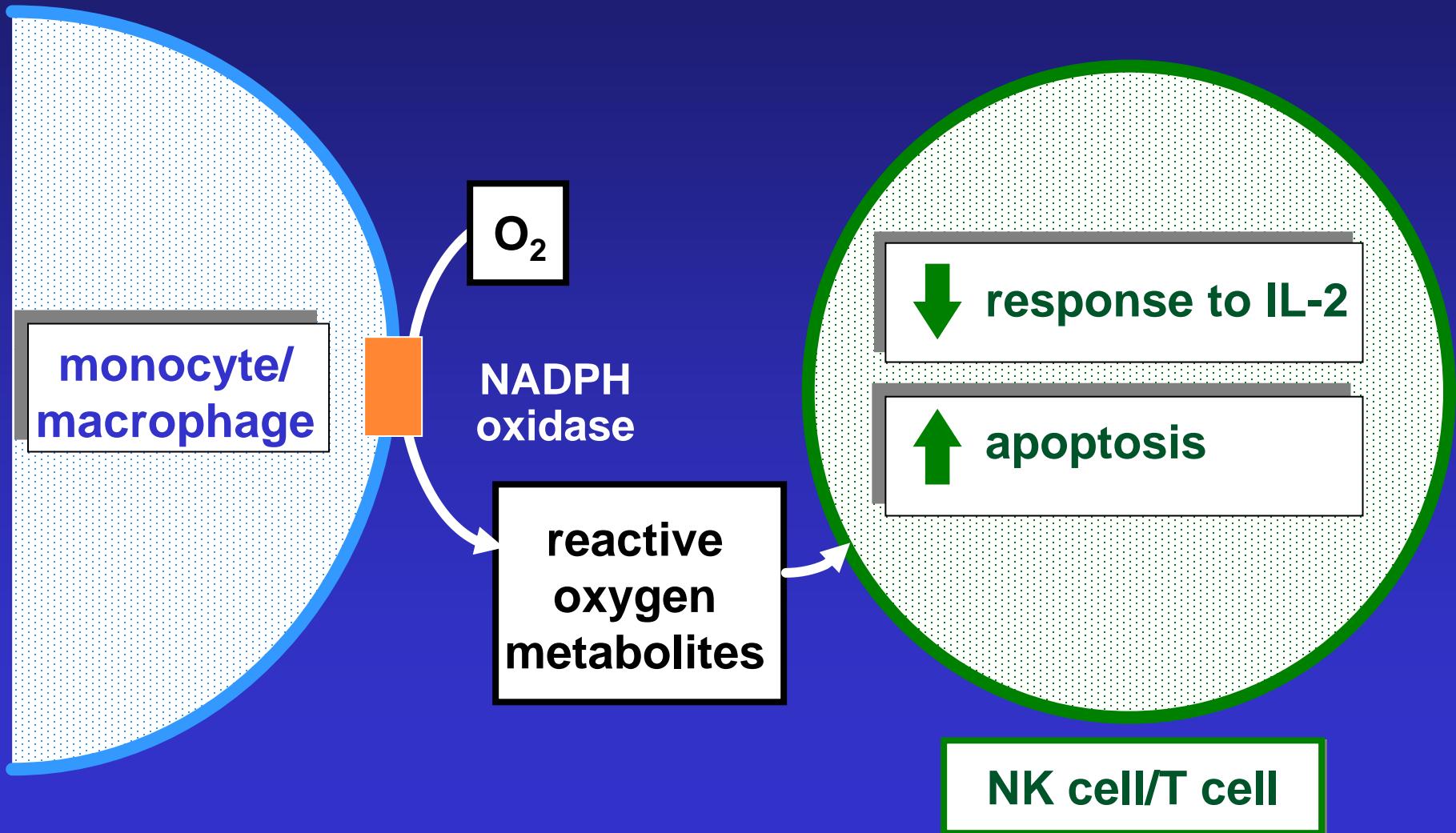
NK cell Function: Activation by IL-2



NK cell Function: Inhibition by Monocytes

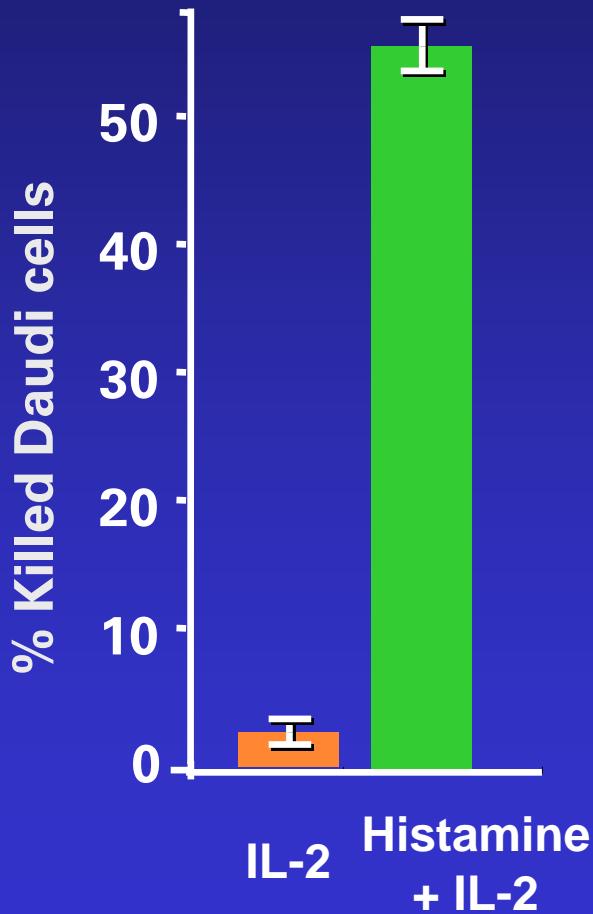


Mechanism of MO-induced Inhibition



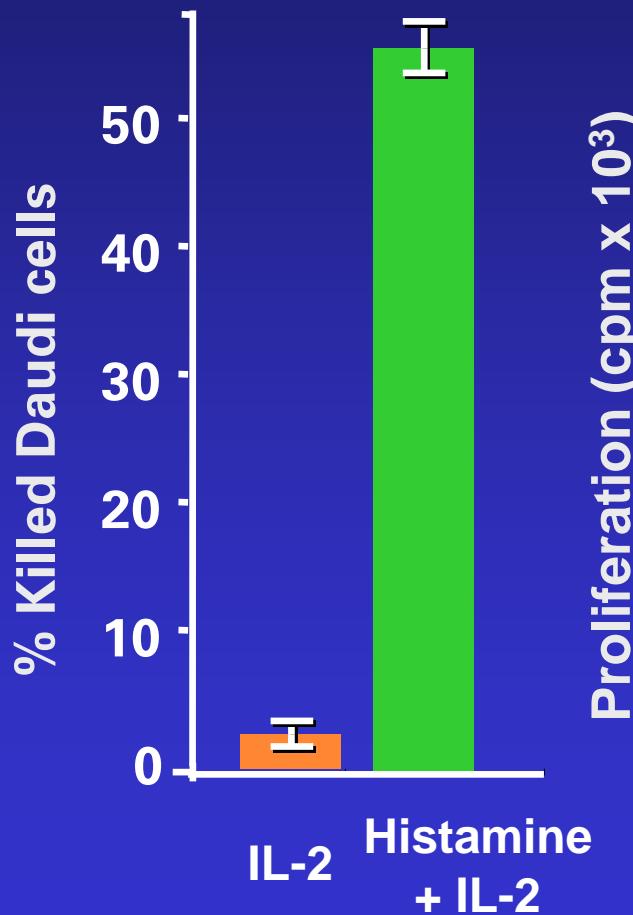
Human NK cell Function: Activation by Histamine + IL-2

Tumor cell killing

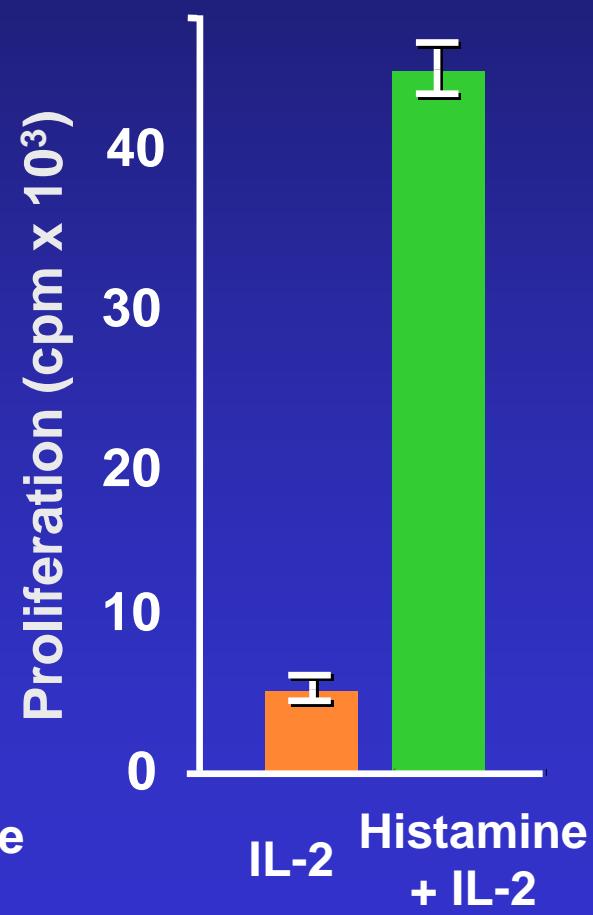


Human NK cell Function: Activation by Histamine + IL-2

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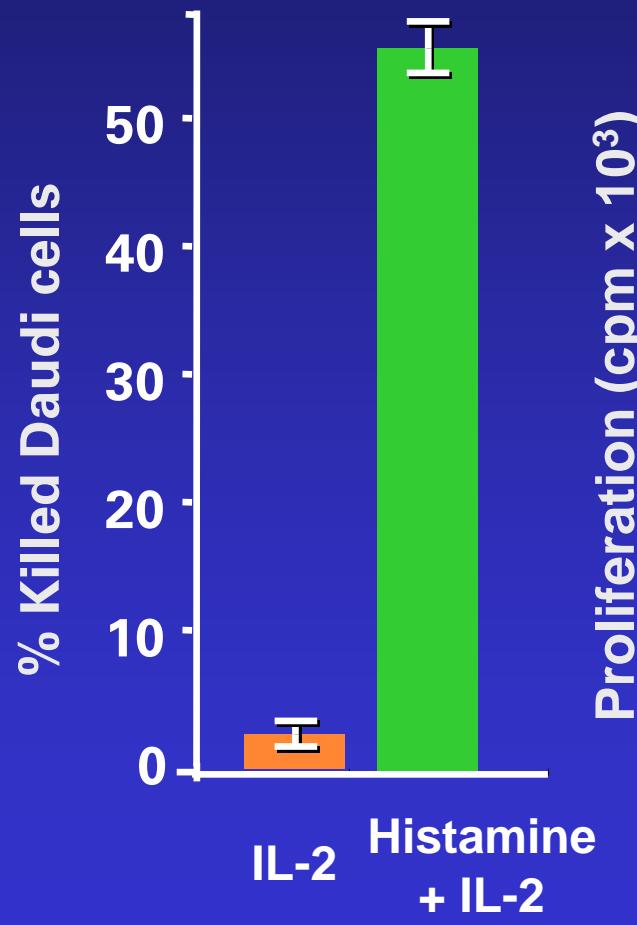


Proliferation

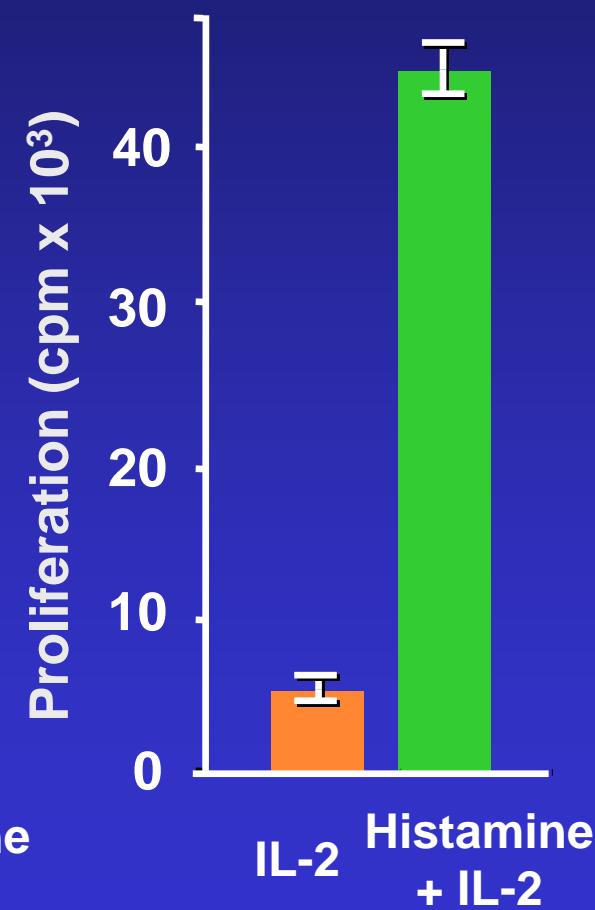


Human NK cell Function: Activation by Histamine + IL-2

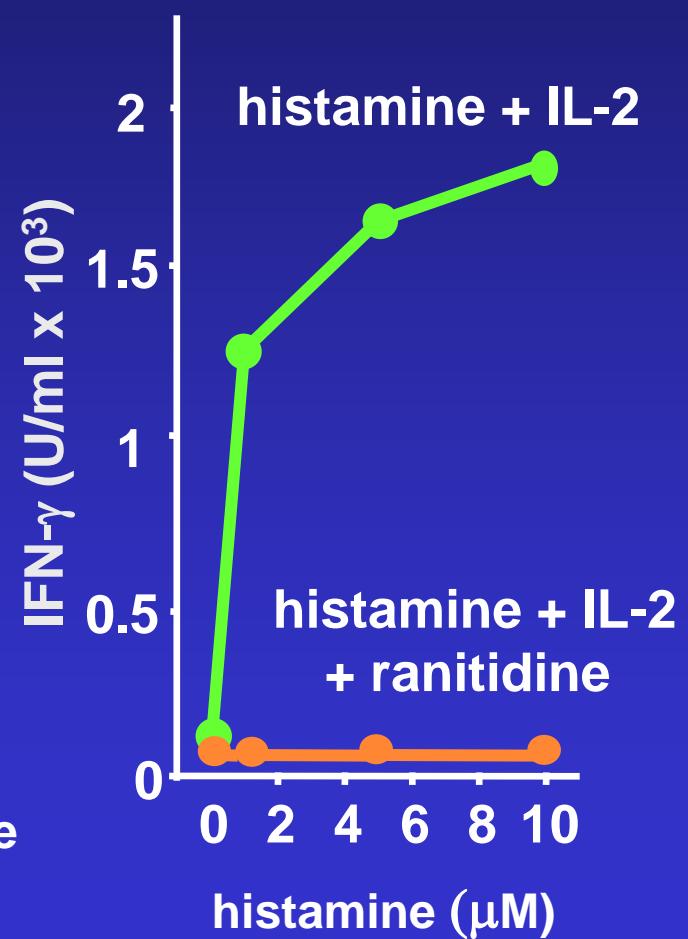
Tumor cell killing



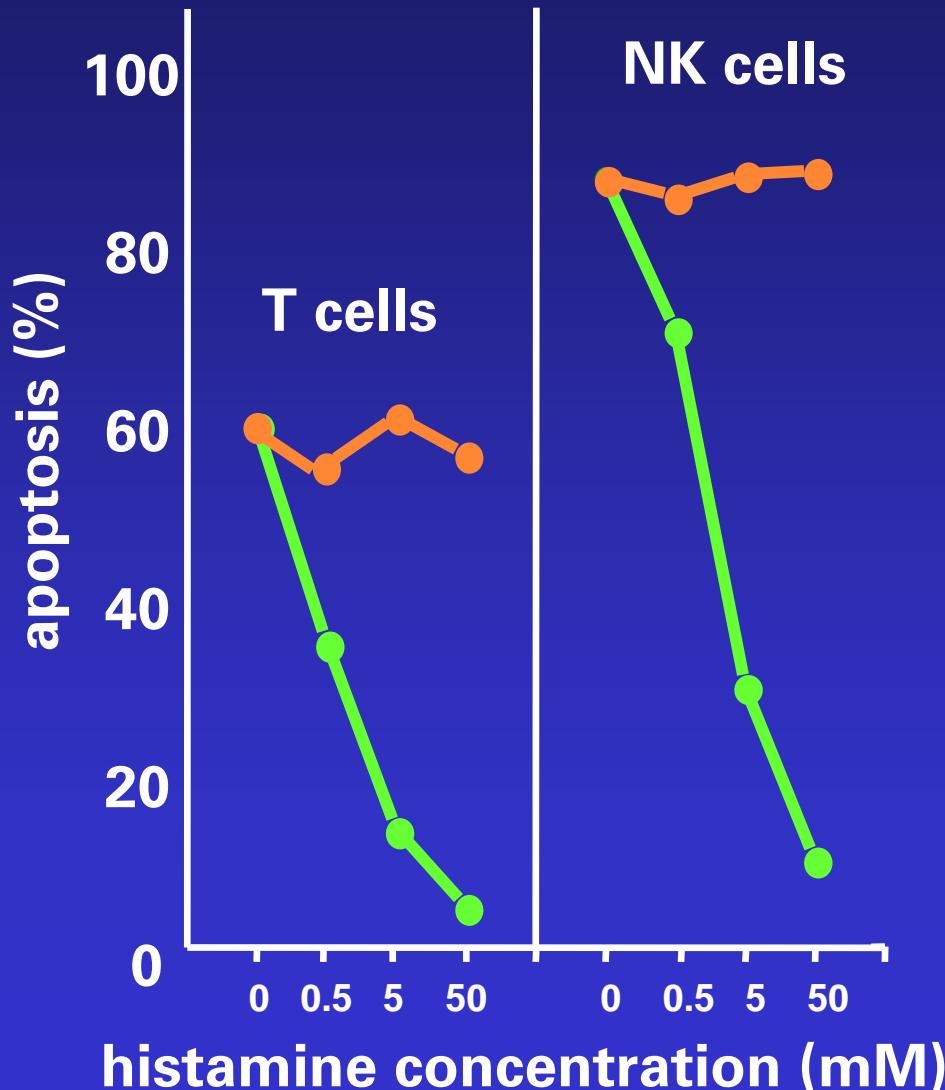
Proliferation



IFN- γ production



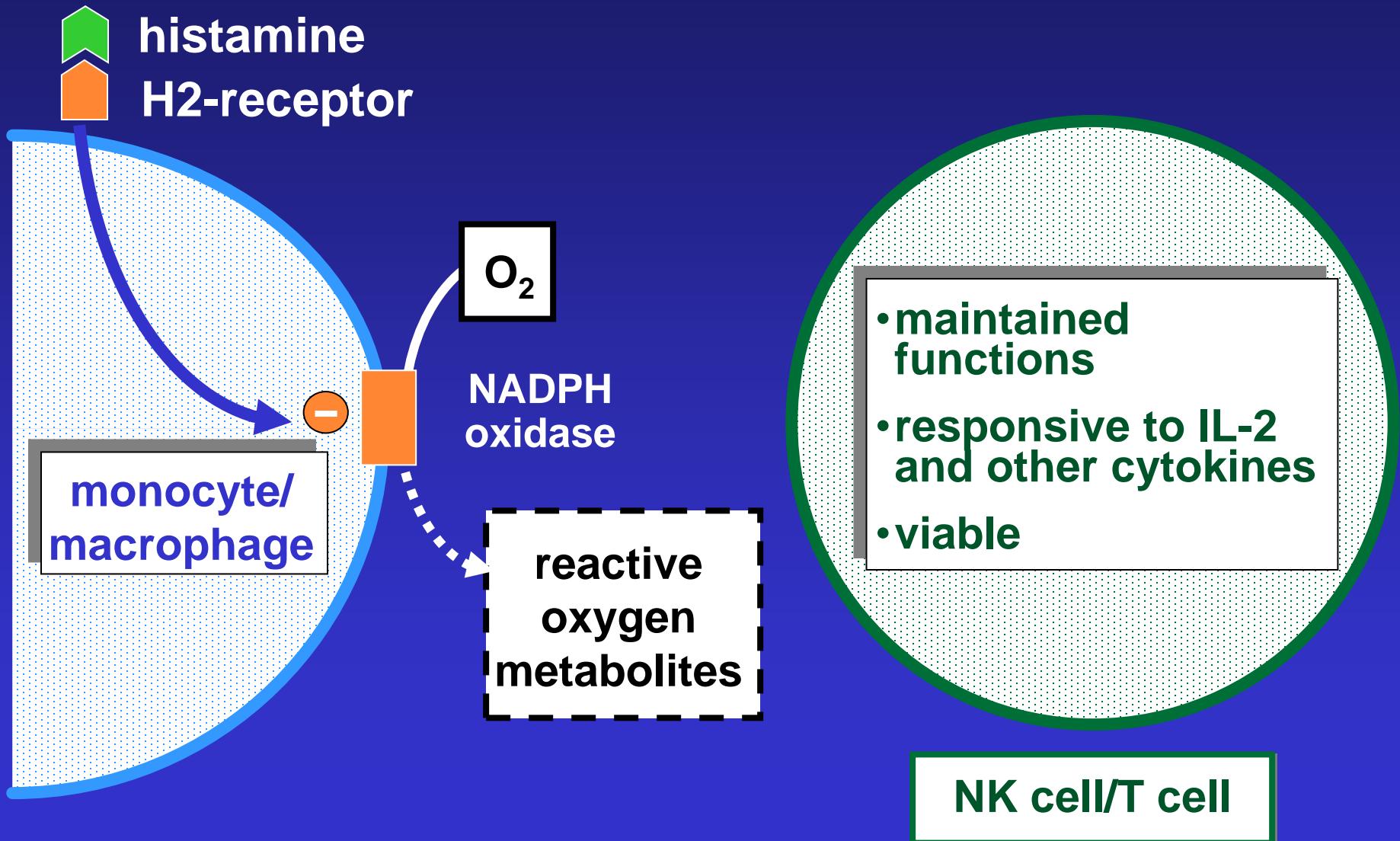
MO-induced Apoptosis in NK and T cells: Protection by Histamine



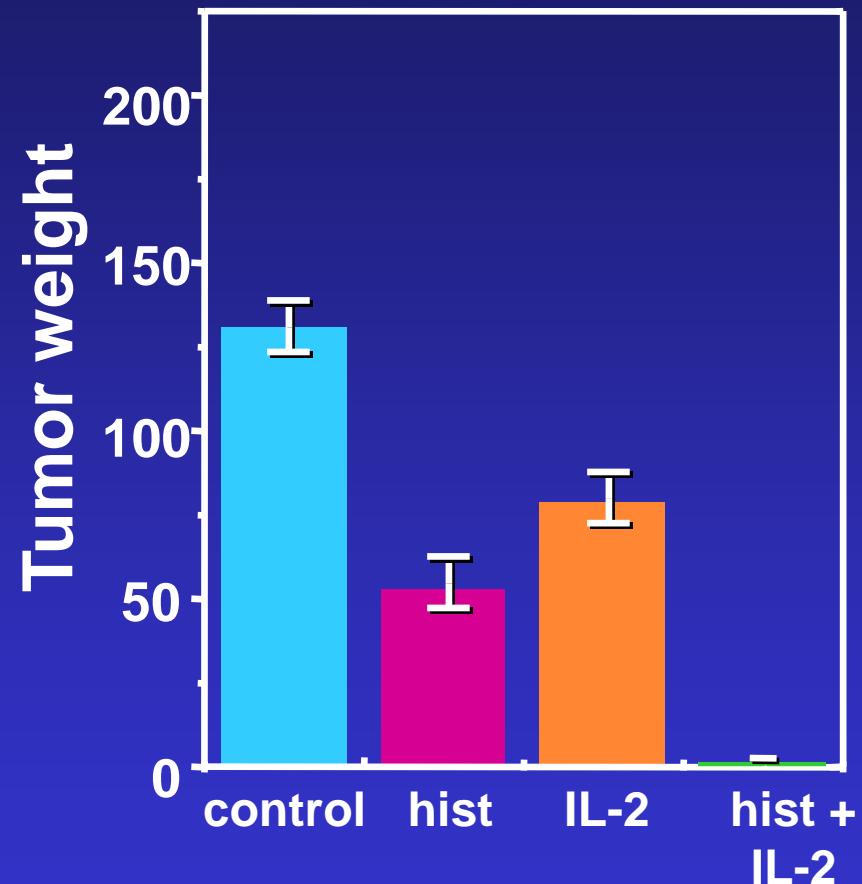
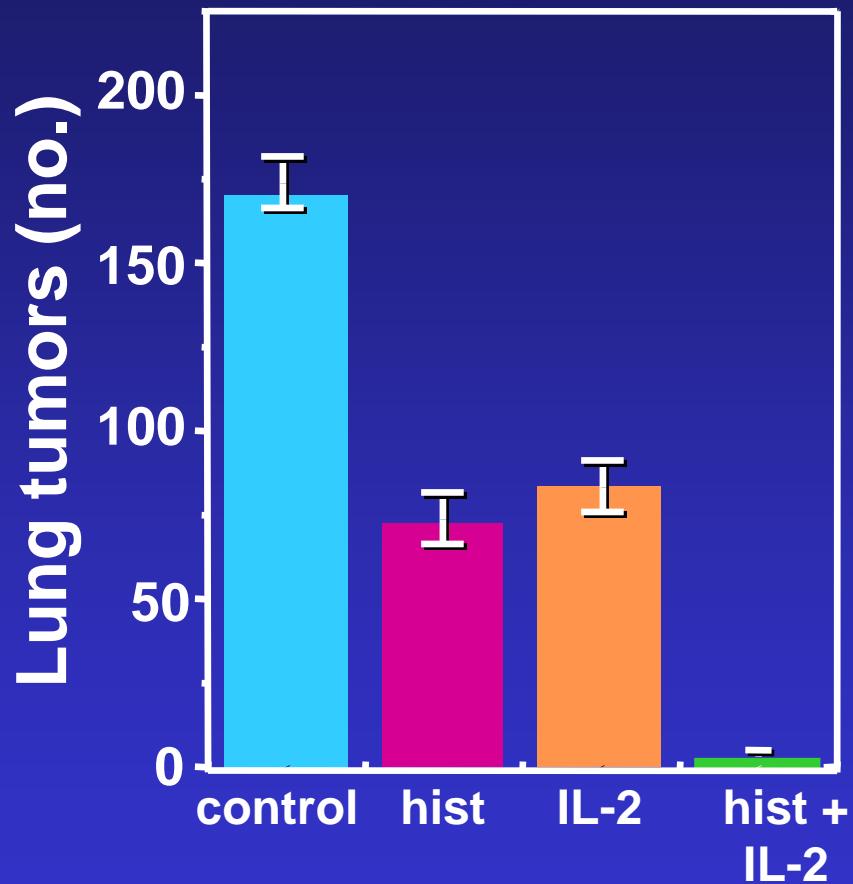
Apoptosis verified by:
DNA fragmentation assay
Annexin V staining
Apoptotic morphology

- Histamine + IL-2
- Histamine + IL-2 + Ranitidine

Histamine Blocks MO-induced Suppression of NK and T cell Functions



Anti-tumor Effects of Histamine + IL-2 in the B16 Mouse Melanoma Model



- ◆ Experimental metastasis model

Clinical Experience

Clinical Experience: Histamine Plus IL-2 or IFN- α

- ◆ Patients have been treated in Melanoma, AML, RCC, and HCV
 - 15 clinical trials
 - 1253 total patients enrolled
 - 817 patients treated with histamine
 - 6 phase 2 and 3 melanoma studies
 - 413 patients treated with histamine
 - 162 patients with liver metastases
 - 2 pharmacokinetic studies
 - 2 special population PK studies
- ◆ All patients included in NDA Safety Summary

Early Studies In Malignant Melanoma - Results

MEDIAN SURVIVAL

STUDY	IL-2 + IFN	HIST + IL-2 + IFN
MM1	7.6 mo. (n = 7)	16.3 mo. (n = 9)
MM2		11.3 mo. (n = 27)
MM1 + MM2 (Liver Mets)		10.8 mo. (n = 15)

MM1 and MM2

- ◆ # of Metastatic sites and overall response
 - 1 (5) 2 PR, 1 SD, 2 PD
 - 2 (5) 2 PR, 2 SD, 1 PD
 - >2 (5) 1 PR, 1 SD, 3 PD
- ◆ Liver Responses
 - 2 CR, 3 PR, 6 SD, 4 PD
- ◆ Median Survival, 10.8 months (n = 15)

Conclusions - Phase 2 Melanoma

- ◆ Histamine can be safely administered in combination with IL-2 and IFN- α
- ◆ Patients with liver metastases experienced longer survival duration than would be expected
- ◆ Patients with liver metastases should be analyzed in subsequent studies

Patients with Liver Metastases Have a Poor Prognosis

- ◆ May represent a more aggressive tumor
- ◆ Significant environment of oxidative stress - Kupffer cells/MO
- ◆ Part of reticular endothelial system
- ◆ Abundant pools of lymphocytes, including specialized NK cells
- ◆ More homogeneous population
 - Predictable survival outcome (median 4-5 mo)

Objective

Prove that the addition of Histamine to a SC regimen of IL-2 will improve the survival duration of patients with metastatic melanoma over treatment with IL-2 alone.

Phase 3 Trial

Study Design and Conduct

Phase 3 Trial: MP-US-M01

- ◆ A multi-center, randomized, prospective, open-label, parallel group study to evaluate the combination of Histamine plus IL-2 versus IL-2 alone in patients with advanced metastatic melanoma
- ◆ Patients were randomized to receive out-patient treatment with SC IL-2 +/- Histamine
- ◆ No cross-over allowed

Endpoints: MP-US-M01

◆ Primary: Survival

- Overall intent-to-treat population (ITT)
- Intent-to-treat patients having liver metastases at baseline (ITT-LM)
 - Multiple hypotheses were adjusted using Holm-Sidak (Sharper Bonferroni)

◆ Secondary

- Time to disease progression
- Tumor response rate
- Quality of Life
- Safety of combination therapy

Liver Metastases Subgroup Pre-specified in Original Protocol

- ◆ Stated in 2 separate places:
 - Page 33 - “**Patients will be stratified in subgroup analyses accordingly: a) presence with liver metastases or not...**”
 - Page 64 - “**Results will also be displayed stratified by patients presenting with liver metastases versus patients with no liver metastases...**”

Subgroup Acknowledged by FDA

- ◆ Acknowledgment in FDA briefing document, April 23, 1997 (page 6 briefing document)
 - “the sponsor decided NOT to prestratify by liver metastases and prior DTIC treatment but would perform subgroup analyses based on the presence or absence of liver metastases...”

Data Management and Analysis Plan

- ◆ Final Statistical Analysis Plan - November 18, 1999 states:
 - The null hypotheses will be tested in two patient populations within the framework of the study...all randomized patients.... And all randomized patients with liver metastases at entry on an intent-to-treat basis
 - Multiple hypotheses were adjusted using the Holm-Sidak Procedure
- ◆ No pre-stratification for liver metastases or other prognostic factors
- ◆ All site, medical and data monitoring done by CRO
- ◆ DSMB safety/efficacy review
- ◆ All efficacy data embargoed until April 11, 2000

Treatment Regimen

	Day 1	Day 2	Day 3	Day 4	Day 5
Interleukin-2					
Week 1, 3	9.0 MIU/m ² BID	9.0 MIU/m ² BID			
Week 2, 4	2.0 MIU/m ² BID				
Histamine					
Week 1-4	1 mg BID				
No treatment weeks 5/6 Each Cycle = 6 wks					

Entry Criteria - MP-US-M01

- ◆ Histologically proven metastatic melanoma
- ◆ WHO Performance status 0 to 1 (Karnofsky ≥ 70)
- ◆ May have received prior therapies, but not IL-2
- ◆ No concurrent cancer treatment
- ◆ Adequate hematologic, cardiac, renal, and hepatic function
- ◆ No brain metastases by MRI, unless controlled
- ◆ Ocular melanoma with systemic metastases allowed

Study Enrollment and Follow-Up

- ◆ Number of sites: **56 (all U.S.)**
- ◆ Accrual period: **July 1997 - March 1999**
- ◆ Analysis cut-off: **March 8, 2000
(12 month follow-up)**
- ◆ Survival update: **September 8, 2000
(18 month follow-up)**

Phase 3 Trial Results

Patient Characteristics

Demographic Summary: All Randomized Patients

CHARACTERISTIC	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
No. of Patients	153 (100)	152 (100)
AGE, YEARS		
Mean	56.3	53.6
≥65	50 (33)	35 (23)
GENDER		
Male	99 (65)	90 (59)
WHO PS		
1	50 (33)	48 (32)
Albumin (\leq 4g/dL)	80 (52)	71 (47)
LDH \geq ULN	57 (40)	52 (36)

Demographic Summary: All Randomized Patients

CHARACTERISTIC	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
Prior Chemotherapy	38 (25)	40 (26)
Prior Anticancer Therapy (Mean, SD)	4 ± 2.38	4.5 ± 2.91
NO. OF ORGAN SITES		
1	31 (20)	37 (24)
>2	75 (49)	67 (44)
DISEASE SITES		
Skin	40 (26)	47 (31)
Lymph Node	83 (54)	77 (51)
Lung	90 (59)	99 (65)
Viscera		
Liver	74 (48)	55 (36)
Bone	11 (7)	19 (13)
CNS	10 (7)	12 (8)
Other (spleen, adrenal, renal, GI)	76 (50)	62 (41)

Demographic Summary: Baseline Liver Metastases Patients

CHARACTERISTIC	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
No. of Patients	74	55
AGE, YEARS		
Mean	57.6	53.7
≥65	28 (38)	13 (24)
GENDER		
Male	46 (62)	27 (49)
WHO PS		
1	30 (41)	19 (35)
Albumin (\leq 4g/dL)	46 (62)	28 (51)
LDH \geq ULN	38 (56)	32 (63)

Demographic Summary: Baseline Liver Metastases Patients

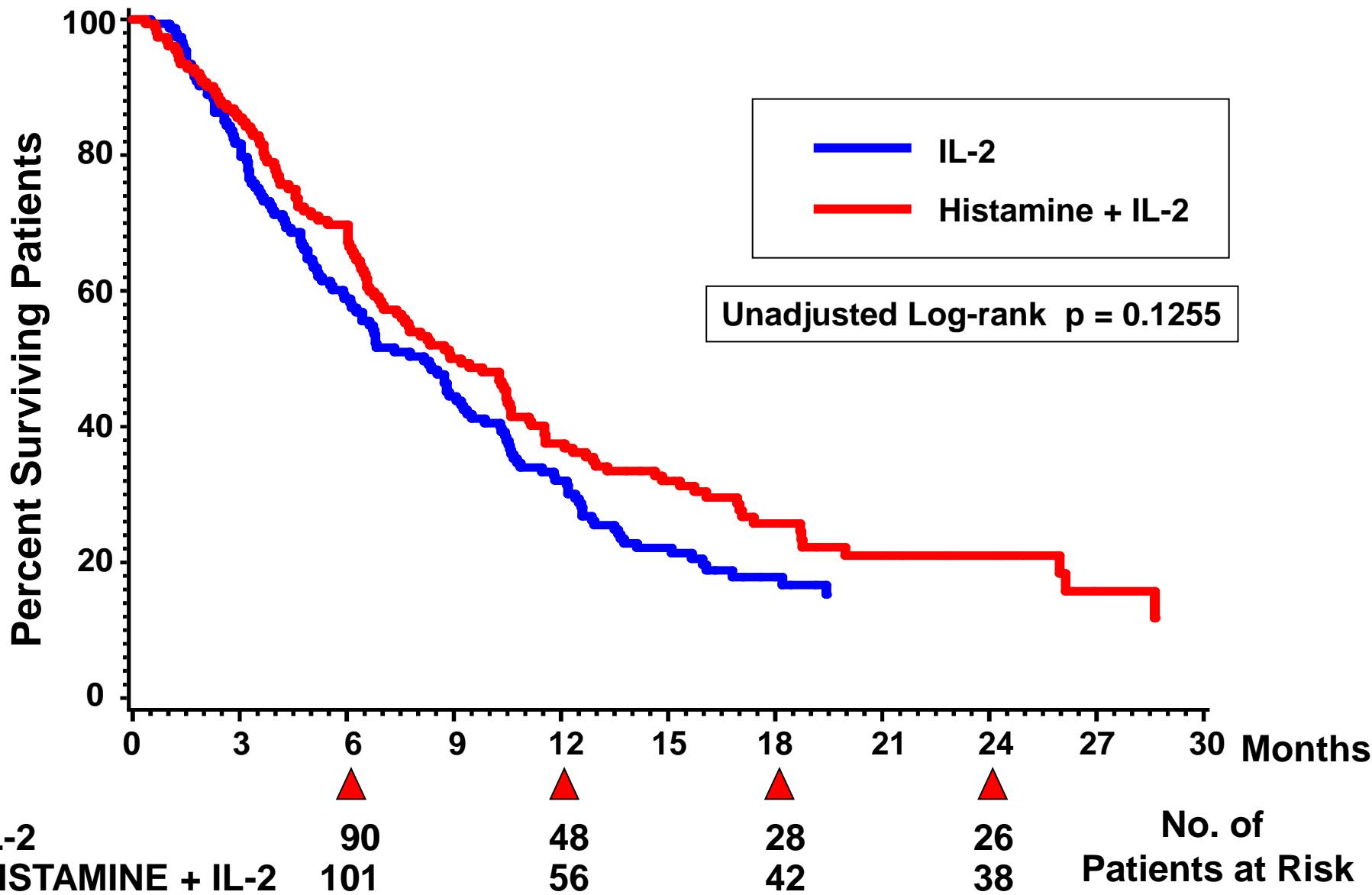
CHARACTERISTIC	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
Prior Chemotherapy	21 (28)	10 (18)
Prior Anticancer Therapy (Mean, SD)	3.9 ± 2.36	3.9 ± 2.87
NO. OF ORGAN SITES		
1	7 (9)	13 (23)
> 2	50 (68)	30 (55)
DISEASE SITES		
Lung + Liver	47 (64)	32 (58)
Liver	74 (100)	55 (100)
Bone	8 (11)	5 (9)
CNS	6 (8)	1 (2)
Other (spleen, adrenal, renal, GI)	37 (50)	22 (40)

Phase 3 Results

Efficacy and Safety

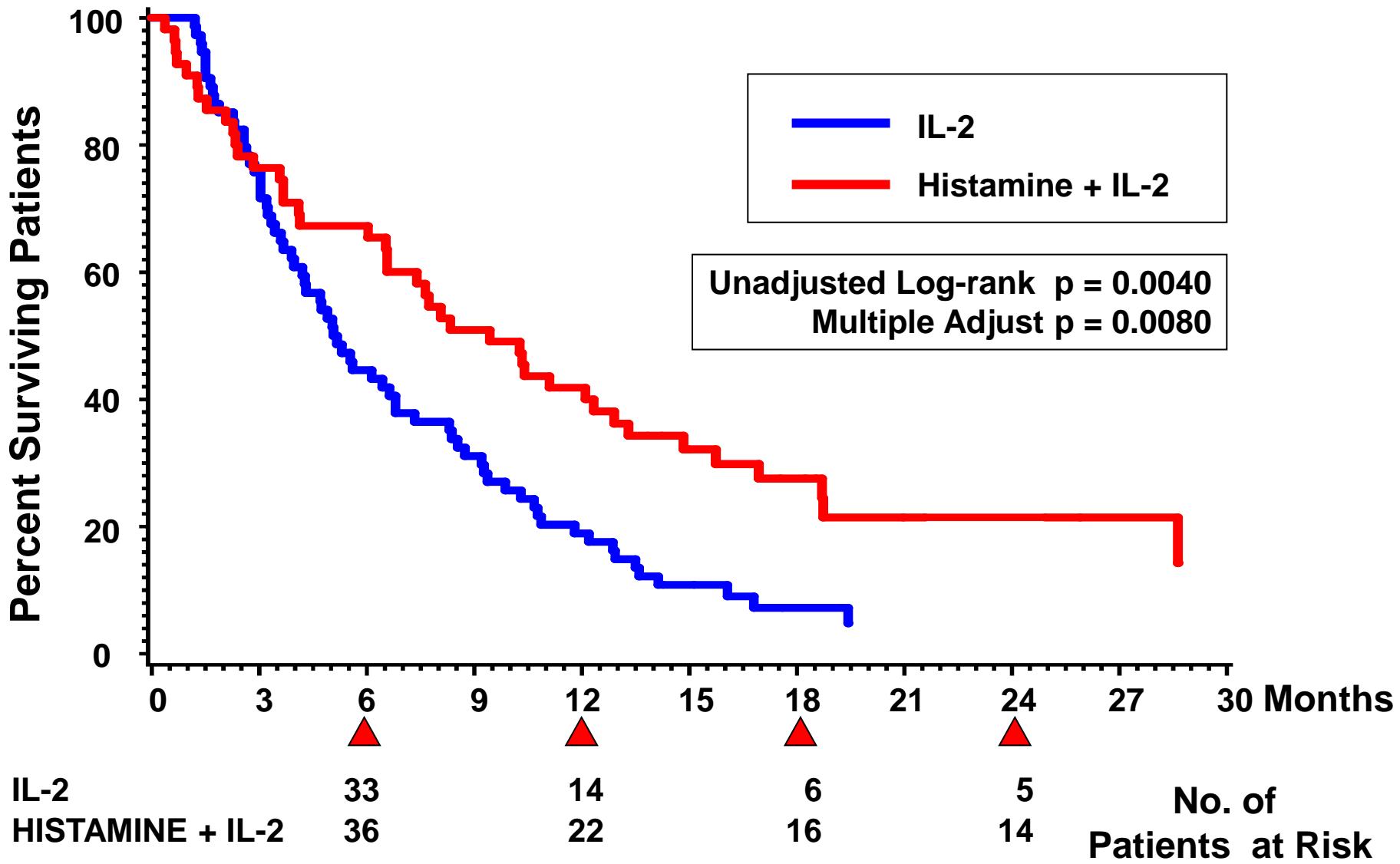
Survival

Intent-to-Treat Population (ITT)

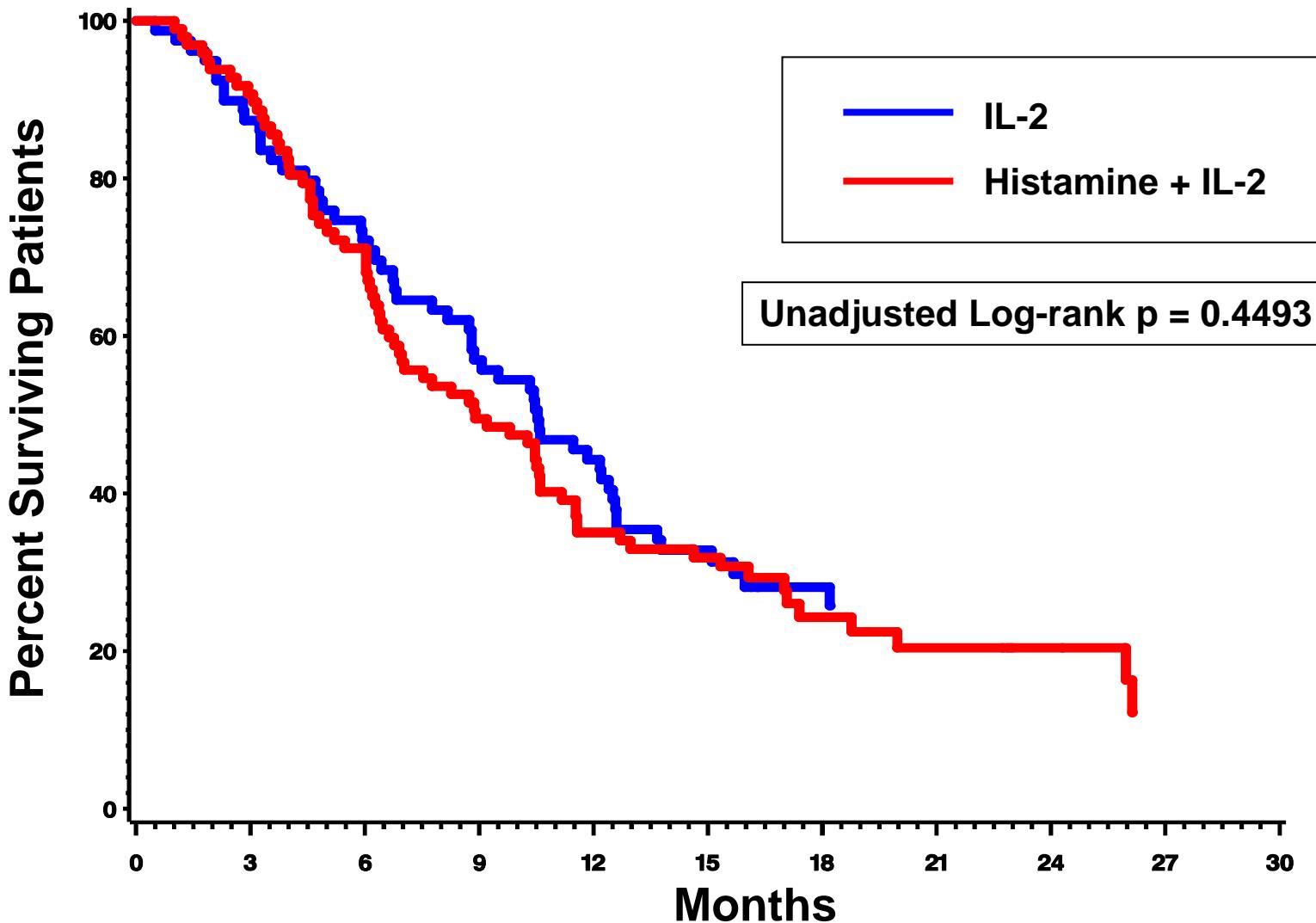


Survival

Patients with Baseline Liver Metastases (ITT- LM)



Survival Patients without Liver Metastases



Survival Analyses

Population (n)	Median Survival (days)		p-value*	p-value adjusted**
	IL-2	HISTAMINE + IL-2		
All Randomized (305)	245	272	0.1255	0.1255
Baseline Liver Mets (129)	154	283	0.0040	0.0080
Non Liver Mets (176)	316	267	0.4493	n/a

**Unadjusted log rank*

***p-values adjusted for multiple
analyses using Holm-Sidak method*

No patients were lost to follow-up at time of analysis

Cox Proportional Hazard Model

Intent-to-Treat (12 months)

COVARIATE	HAZARD RATIO	95% CI	p-value
Treatment (Histamine + IL-2 vs. IL-2)	0.821	0.638-1.057	0.1261

Patients with Liver Metastases (12 months)

COVARIATE	HAZARD RATIO	95% CI	p-value
Treatment (Histamine + IL-2 vs. IL-2)	0.567	0.384-0.839	0.0045

Cox Proportional Hazard Model: Adjusting for Covariates in All Patients with Liver Metastases (N = 129)

COVARIATE	HAZARD RATIO	95% CI	p-value
Age (≥ 65 vs. < 65)	1.154	0.733-1.819	0.5364
Geographic Region			
Mid-West vs. South	1.180	0.519-2.684	0.6931
North vs. South	1.150	0.525-2.520	0.7267
West vs. South	1.028	0.502-2.101	0.9406
Gender (Male vs. Female)	1.203	0.769-1.884	0.4179
Prior Chemotherapy (Yes vs. No)	1.224	0.707-2.117	0.4703
Prior Anti-Cancer Therapy (Yes vs. No)	0.319	0.100-1.017	0.0535
LDH (\geq ULN vs. $<$ ULN)	2.170	1.375-3.423	0.0009
Baseline Performance Status (1 vs. 0)	2.593	1.656-4.061	0.0001

Cox Proportional Hazard Model: Adjusting for Covariates in All Patients with Liver Metastases (N = 129)

COVARIATE	HAZARD RATIO	95% CI	p-value
Number of Disease Sites			
(1 vs. >2)	1.996	0.619-6.439	0.2475
(2 vs. >2)	0.913	0.413-2.020	0.8222
Race (Caucasian vs. All other)			
	0.698	0.200-2.445	0.5745
Skin (Yes vs. No)			
	1.452	0.839-2.512	0.1830
Lymph Node (Yes vs. No)			
	1.469	0.865-2.494	0.1549
Bone (Yes vs. No)			
	5.795	2.682-12.519	0.0001
Lung (Yes vs. No)			
	1.241	0.627-2.456	0.5358
CNS (Yes vs. No)			
	1.330	0.557-3.174	0.5212
Other (Yes vs. No)			
	1.058	0.630-1.778	0.8503
Treatment (Histamine + IL-2 vs. IL-2)			
	0.463	0.286-0.750	0.0017*

*The statistics given for treatment are for the multivariate model.

Geographic region included in the model.

New Covariates

- ◆ Albumin ($\leq 4\text{g/dL}$ vs. >4)
- ◆ Skin/lymph/lung only (yes vs. no)
- ◆ Disease-free survival interval
(≥ 1 yr vs. <1 yr)
- ◆ Time from initial metastases to randomization (≥ 1 yr vs. <1 yr)
- ◆ $\log_e \text{LDH}$

FDA Table 11b: Page 17 (Statistical Review Section)

COVARIATE	HAZARD RATIO	95% CI	p-value
Treatment (Histamine + IL-2 vs. IL-2)	1.067	0.741-1.535	0.7281
Disease Site: Liver (Yes vs. No)	1.223	0.799-1.873	0.3543
Treatment x Liver Met	0.589	0.338-1.027	0.0618
Baseline Albumin (>=4 vs. <4)	0.814	0.584-1.135	0.2254
Baseline Performance Status (1 vs. 0)	1.951	1.449-2.628	0.0001
Log _e LDH	1.639	1.369-1.962	0.0001
Prior Chemotherapy (Yes vs. No)	1.047	0.769-1.425	0.7704
Number of Disease Sites	1.141	1.045-1.246	0.0032
Gender (Male vs. Female)	0.718	0.543-0.950	0.0205
Age (\geq 65 vs. < 65)	1.199	0.888-1.618	0.2354
Disease Free Interval (>=1yr vs. <1yr)	1.151	0.861-1.540	0.3421
Skin/Lymph node/Lung only (yes vs. no)	0.848	0.580-1.239	0.3939

FDA Table 11b: Reparameterized Interaction Term

COVARIATE	HAZARD RATIO	95% CI	p-value
Treatment (Histamine + IL-2 vs. IL-2)	0.628	0.415-0.949	0.0273
Disease Site: Liver (Yes vs. No)	1.223	0.799-1.873	0.3543
Treatment x Liver Met	1.699	0.974-2.962	0.0618
Baseline Albumin (>=4 vs. <4)	0.814	0.584-1.135	0.2254
Baseline Performance Status (1 vs. 0)	1.951	1.449-2.628	0.0001
Log _e LDH	1.639	1.369-1.962	0.0001
Prior Chemotherapy (Yes vs. No)	1.047	0.769-1.425	0.7704
Number of Disease Sites	1.141	1.045-1.246	0.0032
Gender (Male vs. Female)	0.718	0.543-0.950	0.0205
Age (\geq 65 vs. < 65)	1.199	0.888-1.618	0.2354
Disease Free Interval (>=1yr vs. <1yr)	1.151	0.861-1.540	0.3421
Skin/Lymph node/Lung only (yes vs. no)	0.848	0.580-1.239	0.3939

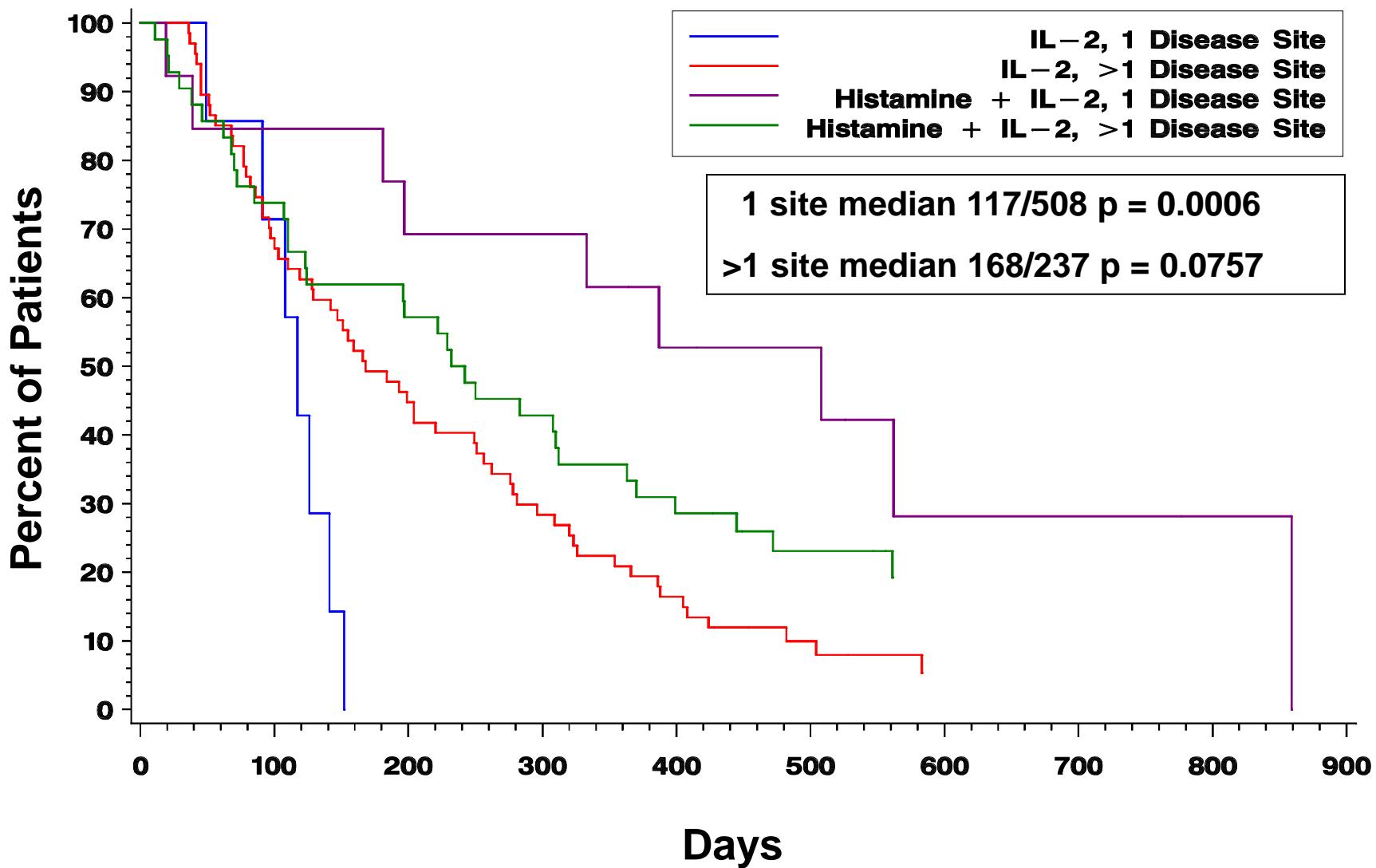
FDA Table 2c: Page 13

Statistical Review Section

Population	IL-2	IL-2 + Histamine	Hazard Ratio (95% C.I.)	Unadjusted P-value (Log-rank test)
<u>With >1 metastatic site</u>				
N	67	42		
Number who died	62	33		
Number censored	5	9		
Median (95% C.I.)	5.5 (4.2, 8.2)	7.7 (4.0, 11.9)	0.681 (0.445, 1.051)	0.0757
<u>With 1 metastatic site</u>				
N	7	13		
Number who died	7	9		
Number censored	0	4		
Median (95% C.I.)	3.8 (3.0, 4.6)	16.6 (6.4, 28.1)	0.091 (0.018, 0.468)	0.0006

*Hazard Ratio = Histamine + IL-2 / IL-2

Baseline ITT-LM Disease Sites



Conclusions - Primary Analyses

- ◆ The addition of histamine to SC IL-2 significantly improves survival in patients with liver metastases ($p = 0.0080$)
- ◆ Cox Proportional Analyses adjusting for significant covariates further supports the treatment effect of histamine plus IL-2
- ◆ These data meet the pre-established criteria for a compelling survival benefit ($> 50\%$ increase in median survival duration)

Secondary Endpoints

- ◆ Time to Disease Progression
- ◆ Time to Treatment Failure
- ◆ Tumor Response Rate
- ◆ Safety
- ◆ Quality of Life

Time to Disease Progression

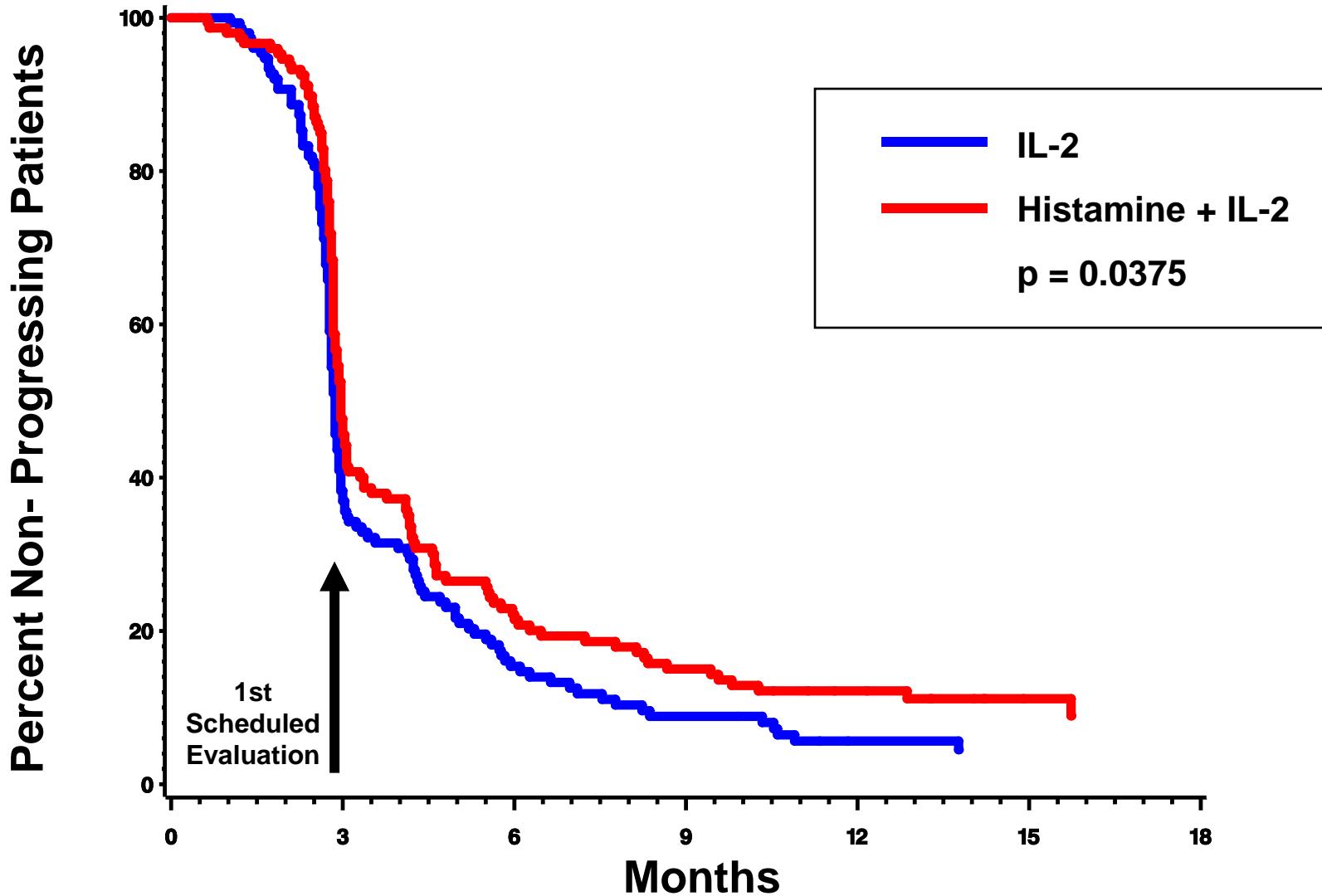
- ◆ Time to Disease Progression = time from date of randomization to first observation of PD or death due to melanoma
- ◆ Time to Treatment Failure = time from date of randomization to the last observed PD resulting in removal from study, or death due to melanoma

Clinically Significant PD

- ◆ Patients required to receive a minimum treatment of 12 weeks (2 cycles) before first response evaluation
- ◆ Patients could continue if PD not associated with changes in PS > than WHO of 1 or Karnofsky of 20
- ◆ Disease Progression based on changes in tumor dimension plus performance status

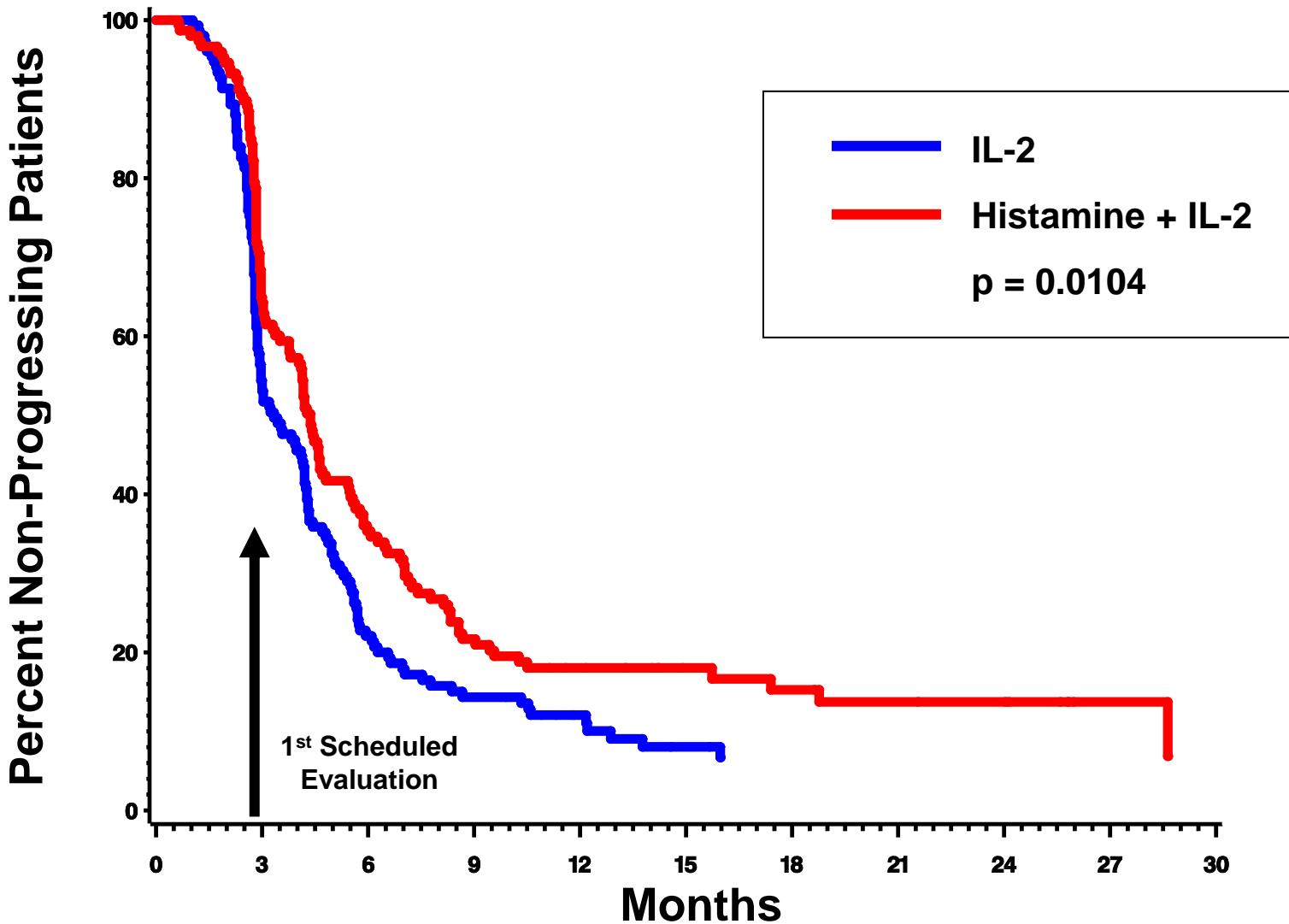
Time to Disease Progression - All Patients

Intent-to-Treat Population

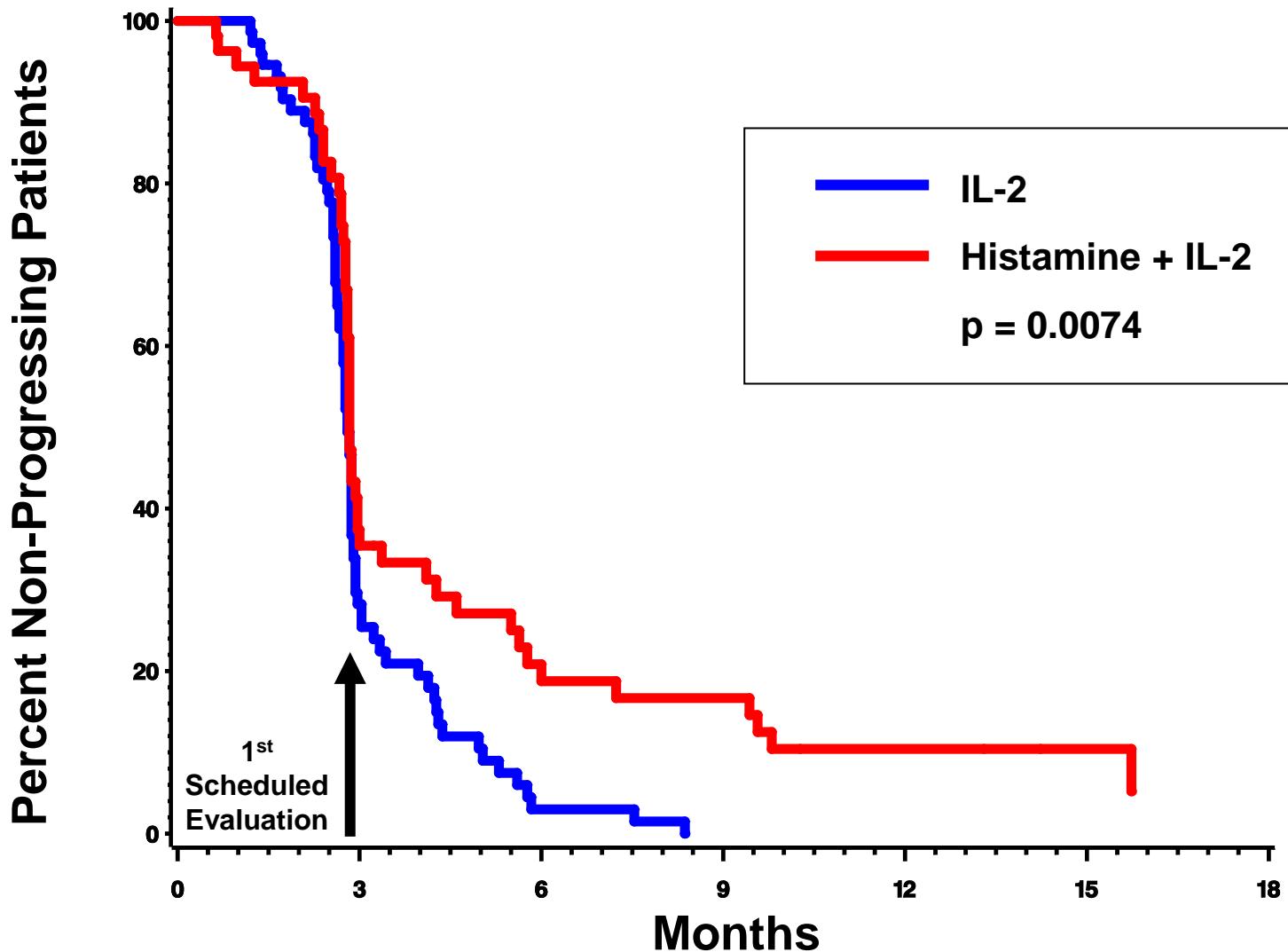


Time to Treatment Failure - All Patients

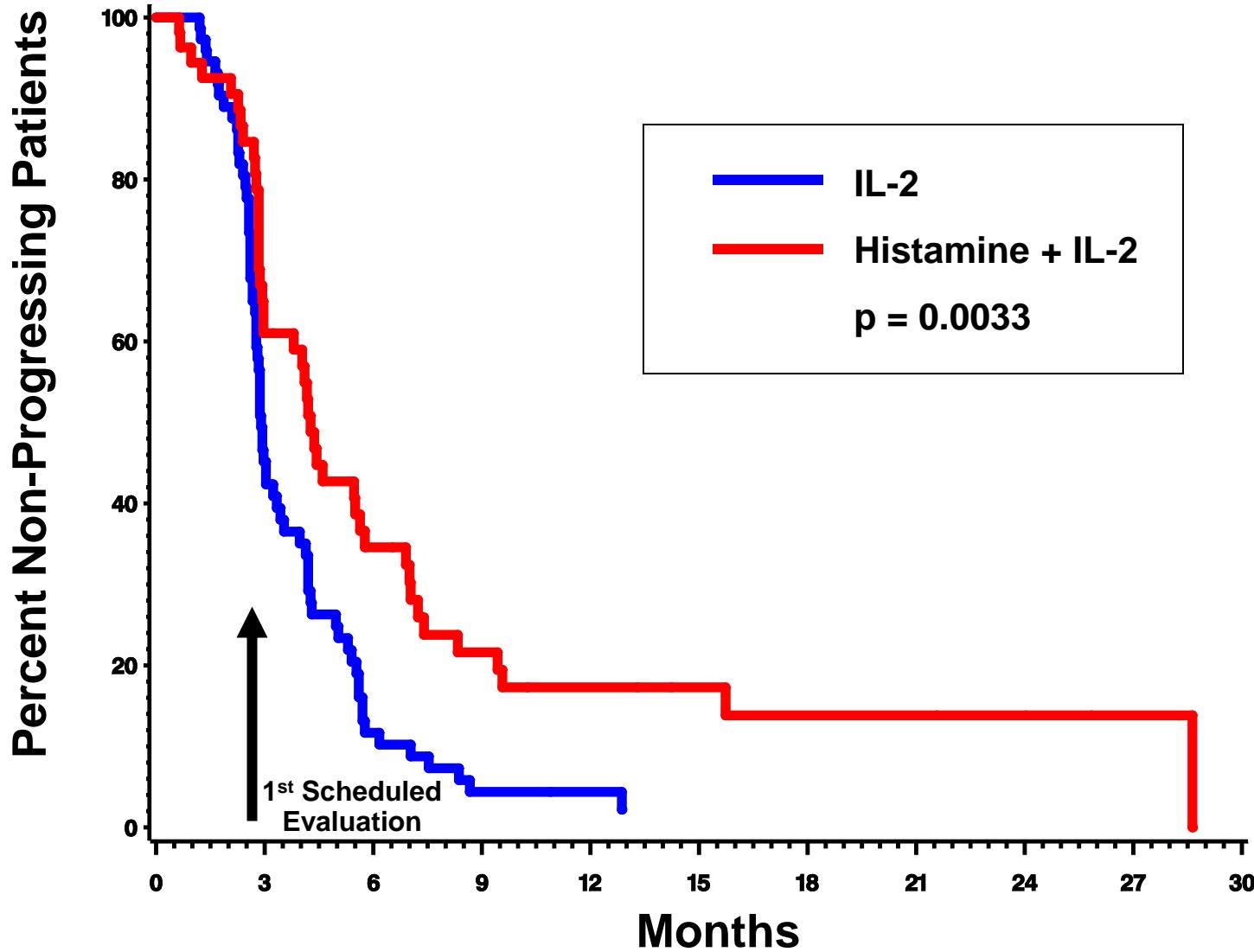
Intent-to-Treat Population



Time to Disease Progression - Patients with Baseline Liver Metastases



Time to Treatment Failure - Patients with Baseline Liver Metastases



Tumor Response - Intent-to-Treat

	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
Complete Response	2 (1)	1 (1)
Partial Response	3 (2)	4 (3)
Minimal Regression	3 (2)	7 (5)
Stable Disease	21 (14)	29 (19)
Lack of Disease Progression (CR+PR+MR+SD)	29 (19)	41 (27)
Progressive Disease	75 (49)	68 (45)
Not Evaluable	49 (32)	43 (28)

Tumor Response - ITT-LM Population

	Number of Patients (%)	
	IL-2	HISTAMINE + IL-2
Complete Response	0	0
Partial Response	0	2 (5)
Minimal Regression	2 (4)	4 (11)
Stable Disease	7 (15)	8 (22)
Lack of Disease Progression (CR+PR+MR+SD)	9 (20)	14 (38)
Progressive Disease	37 (80)	23 (62)
Not Evaluable	28 (38)	18 (33)

Phase 3 Results

Safety

Adverse Events - Histamine

- ◆ Majority of Adverse Events were expected and mild to moderate (Grade 1-2)
- ◆ Histamine-related AE's were transient (30-60 min) and without sequelae
 - Flushing
 - Hypotension
 - Tachycardia/palpitation
 - Injection site reaction
 - Headache
 - Dyspepsia
 - Dizziness
 - Rhinitis

Incidence of Severe Adverse Events: Grade 3 & 4

EVENT		% of Patients	
	IL-2	HISTAMINE + IL-2	HD IL-2*(%)
CARDIOVASCULAR			
Hypotension	1%	1%	45%
Tachycardia	0	1%	3%
Myocardial Infarction	0	<1%	1%
GASTROINTESTINAL			
Nausea	8%	7%	6%
Vomiting	5%	6%	37%
Diarrhea	3%	1%	32%
Stomatitis	0	0	1%
NEUROLOGICAL			
Confusion	3%	2%	13%
Somnolence	3%	2%	3%
Coma	1%	0	1%

*HD IL-2 from Atkins et al. *Journal of Clinical Oncology*. Vol 17(7): 2105-2116. 1999.

Incidence Severe Adverse Events: Grade 3 & 4

EVENT	% of Patients		HD IL-2* (%)
	IL-2	HISTAMINE + IL-2	
PULMONARY			
Dyspnea	8%	5%	10%
ARDS, Pulmonary Edema	0	<1%	9%
HEPATIC			
Elevated Bilirubin	2%	1%	9%
Elevated Transaminase	0	2%	7%
Elevated Alkaline Phosphatase	1%	1%	2%
RENAL			
Oliguria	0	0	39%
Elevated Creatinine	0	0	1%
Anuria	0	0	8%

*HD-IL-2 from Atkins et al. *Journal of Clinical Oncology*. Vol 17(7):2105-2116. 1999.

Incidence of Severe Adverse Events: Grade 3 & 4

EVENT		% of Patients	
	IL-2	HISTAMINE + IL-2	HD IL-2* (%)
HEMATOLOGIC			
Thrombocytopenia	1%	<1%	17%
Anemia	4%	2%	2%
Leukopenia	1%	0	2%
SKIN			
Rash	<1%	<1%	2%
Exfoliative Dermatitis	0	0	0
GENERAL			
Fever and/or Chills	7%	8%	19%
Malaise	1%	1%	14%
Infection	0	1%	11%
Sepsis	0	<1%	2%

*HD-IL-2 from Atkins et al. *Journal of Clinical Oncology*. Vol 17(7):2105-2116. 1999

Patient Disposition: Grade 3 & 4 Toxicities

M01 Patients

	Safety Population (Overall) N = 303		Safety Population (Liver Mets) N = 128	
	IL-2 N = 152	Histamine + IL-2 N = 151	IL-2 N = 73	Histamine + IL-2 N = 55
Grade 4 toxicity	17	20	9	10
Grade 4 - PD Melanoma	12 <i>(71% of ttl)</i>	12 <i>(60% of ttl)</i>	8 <i>(89% of ttl)</i>	7 <i>(78% of ttl)</i>
Grade 3 toxicity	90	82	49	32
Grade 3 - PD Melanoma	10 <i>(11% of ttl)</i>	9 <i>(11% of ttl)</i>	6 <i>(12% of ttl)</i>	3 <i>(9.4% of ttl)</i>

Patient Disposition: Deaths on Study or within 28 Days of Study Drug

M01 Patients

	Safety Population (Overall)		Safety Population (Liver Mets)	
	IL-2 N = 152	Histamine + IL-2 N = 151	IL-2 N = 73	Histamine + IL-2 N = 55
Death within 28 days of Study Drug(s)	15	16	9	9
Death due to Melanoma	13 (87% of total)	12 (75% of total)	8 (89% of total)	7 (78% of total)

Safety Summary

- ◆ **No unexpected treatment emergent adverse events were observed**
 - most AE's mild to moderate in severity
 - differences between treatment arms mostly due to expected physiological side effects
- ◆ **The addition of histamine to SC IL-2 was safe and well tolerated in patients with advanced metastatic melanoma in an outpatient setting**

Quality of Life Assessment

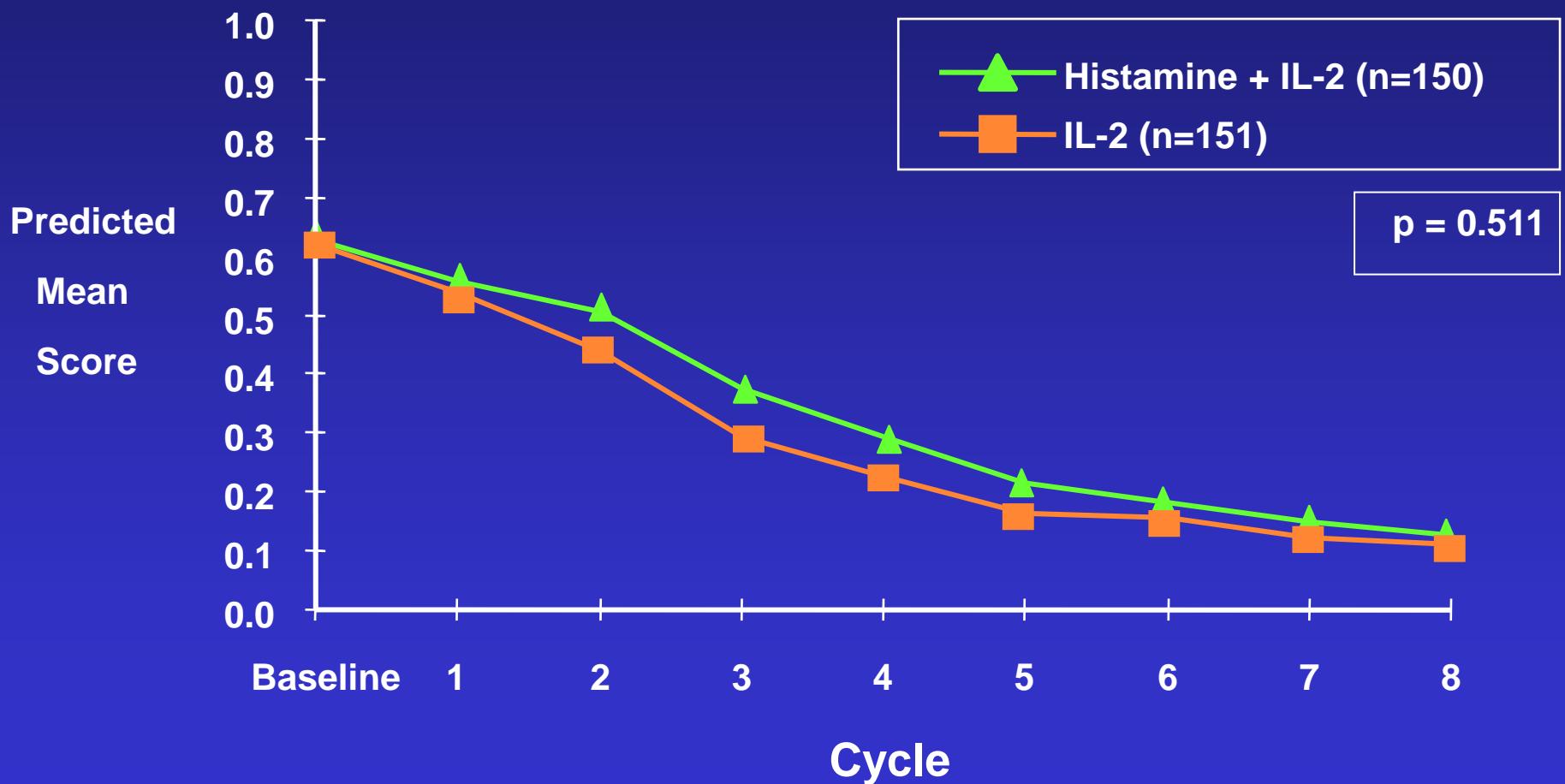
Quality of Life

- ◆ Study Hypothesis:
 - *The addition of histamine to IL-2 will not negatively effect QoL*
- ◆ Quality of Well-being (QWB-SA ver 1.04)

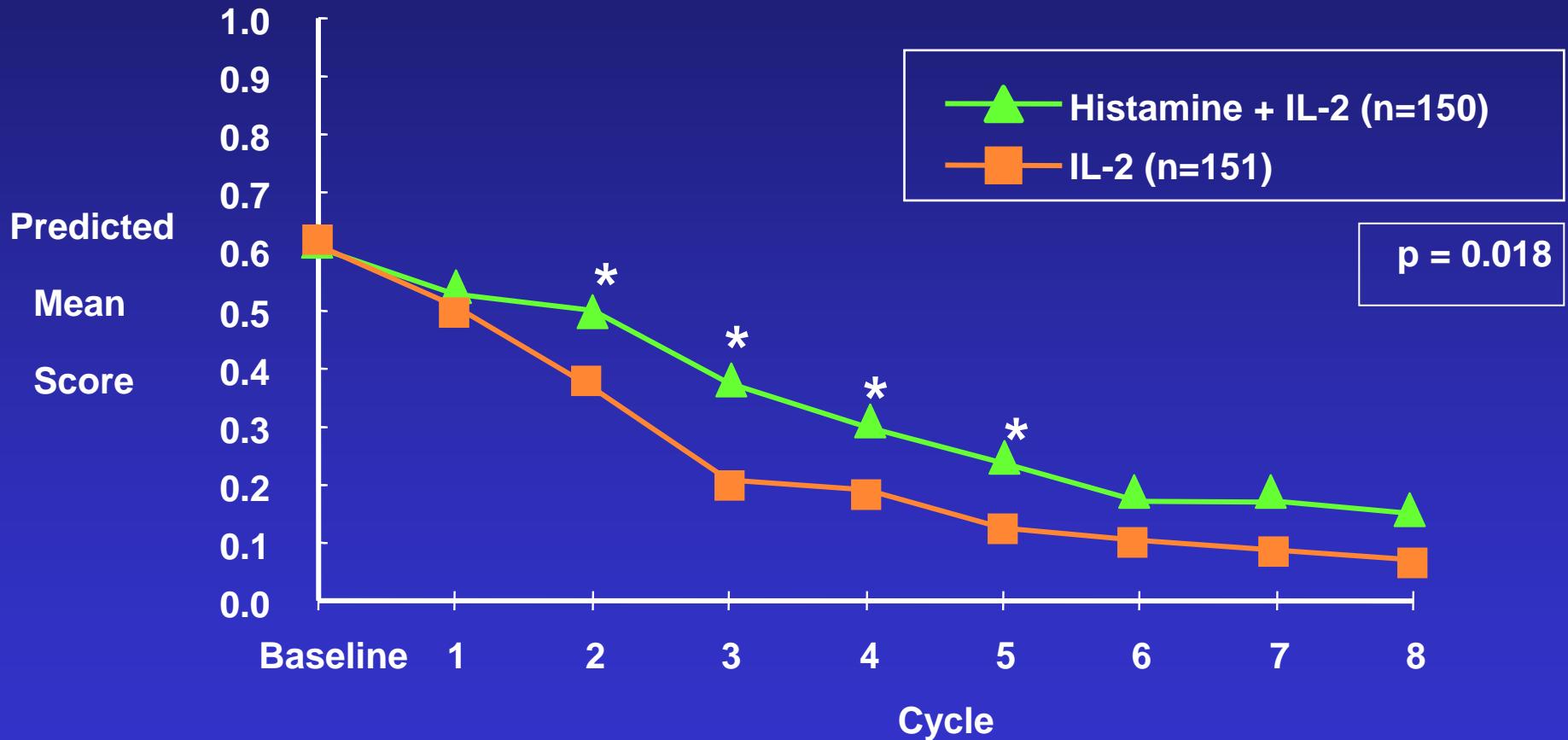
Quality of Well-Being

- ◆ QWB-SA is self administered, 76 item questionnaire, administered at the start of each cycle
- ◆ Focuses on mobility, physical activity, social activity and symptoms or problems
- ◆ Integrates morbidity and mortality into common unit
- ◆ Scores from 0 (death) to 1 (optimum functioning w/o symptoms)

Predicted Mean QWB-SA Scores by Treatment Group Intent-to-Treat Population



Predicted Mean QWB-SA Scores by Treatment Group Liver Metastases Intent-to-Treat Population



Median Quality-Adjusted Survival

	MEDIAN ^a			
	HISTAMINE + IL-2 (N)	IL-2 (N)	DIFFERENCE ^b	p-value ^c
All Randomized Patients	105.6 (N = 150)	74.3 (N = 151)	31.3	0.007
All Randomized Patients with Liver Metastases	113.0 (N = 53)	62.8 (N = 73)	50.2	0.010

^a Area under the curve analysis using imputed predicted QWB-SA scores generated from random intercept linear regression model

^b Difference in median predicted quality-adjusted survival; Histamine plus IL-2 minus IL-2 alone

^c Mann-Whitney U test.

Conclusion

Combination therapy using Histamine plus SC IL-2 is safe and significantly improves survival of metastatic melanoma patients with liver involvement without added toxicity or a decrease in QoL.

Interim Efficacy Update

- ◆ **Phase 3 Study - MP-US-M01**

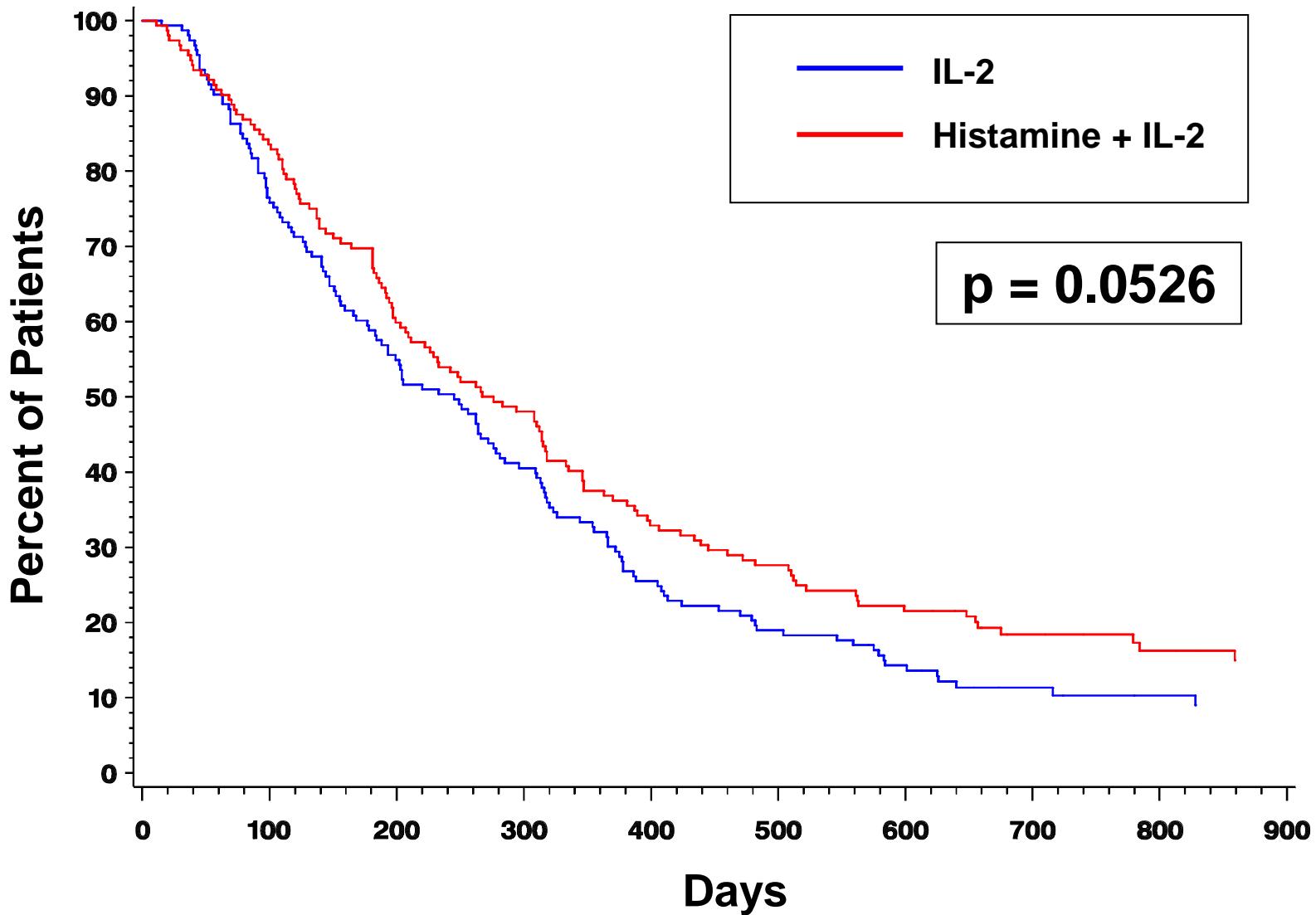
- September 8, 2000

- ◆ **Phase 2 Study - MP-MA-0103**

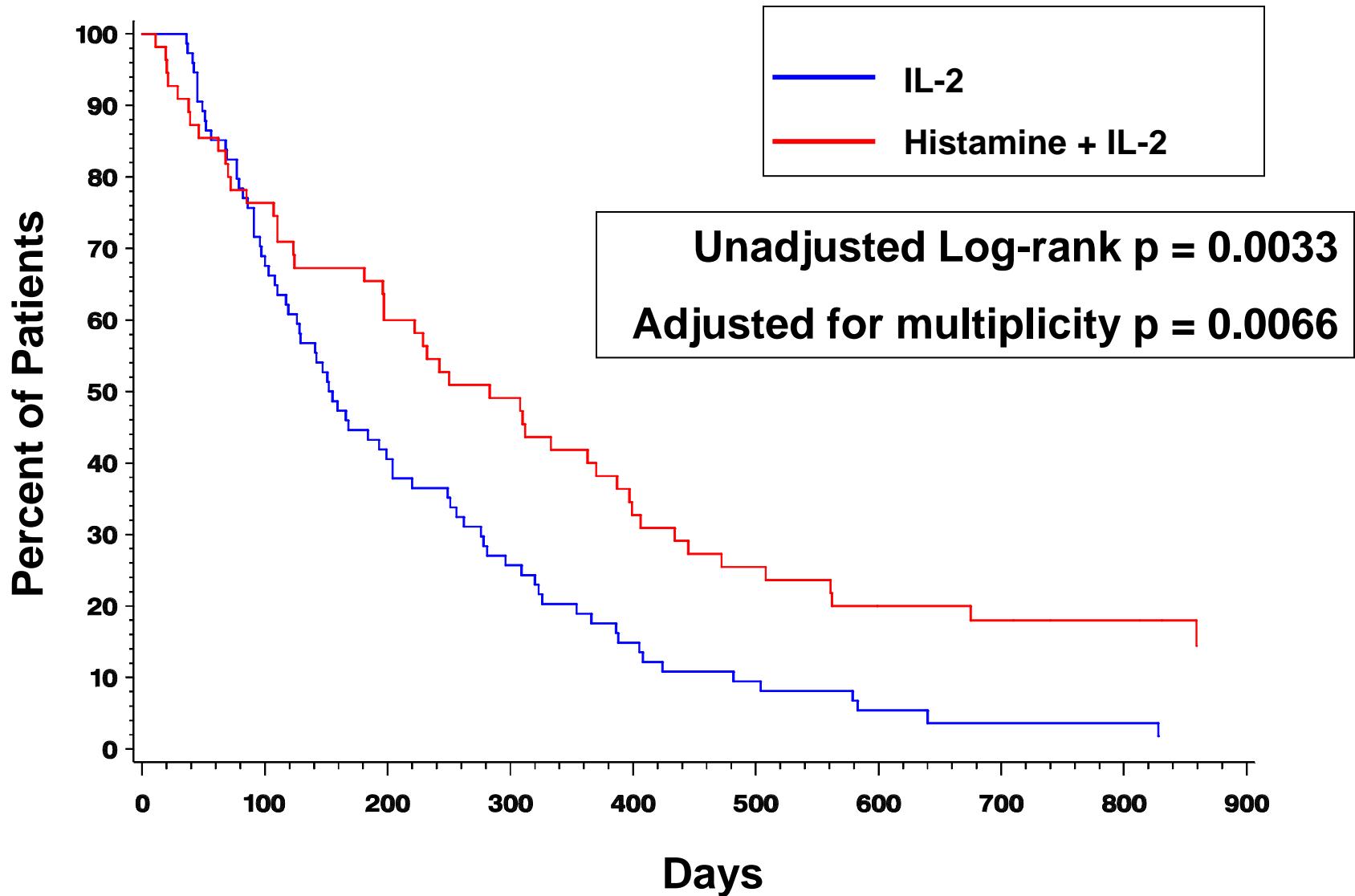
- March 8, 2000 Analysis

- September 8, 2000 Analysis

Survival ITT Population (18 Month Follow-Up)



Survival ITT-LM Population (18 Month Follow-Up)



FDA Table 11b: MO1 18 Month Update

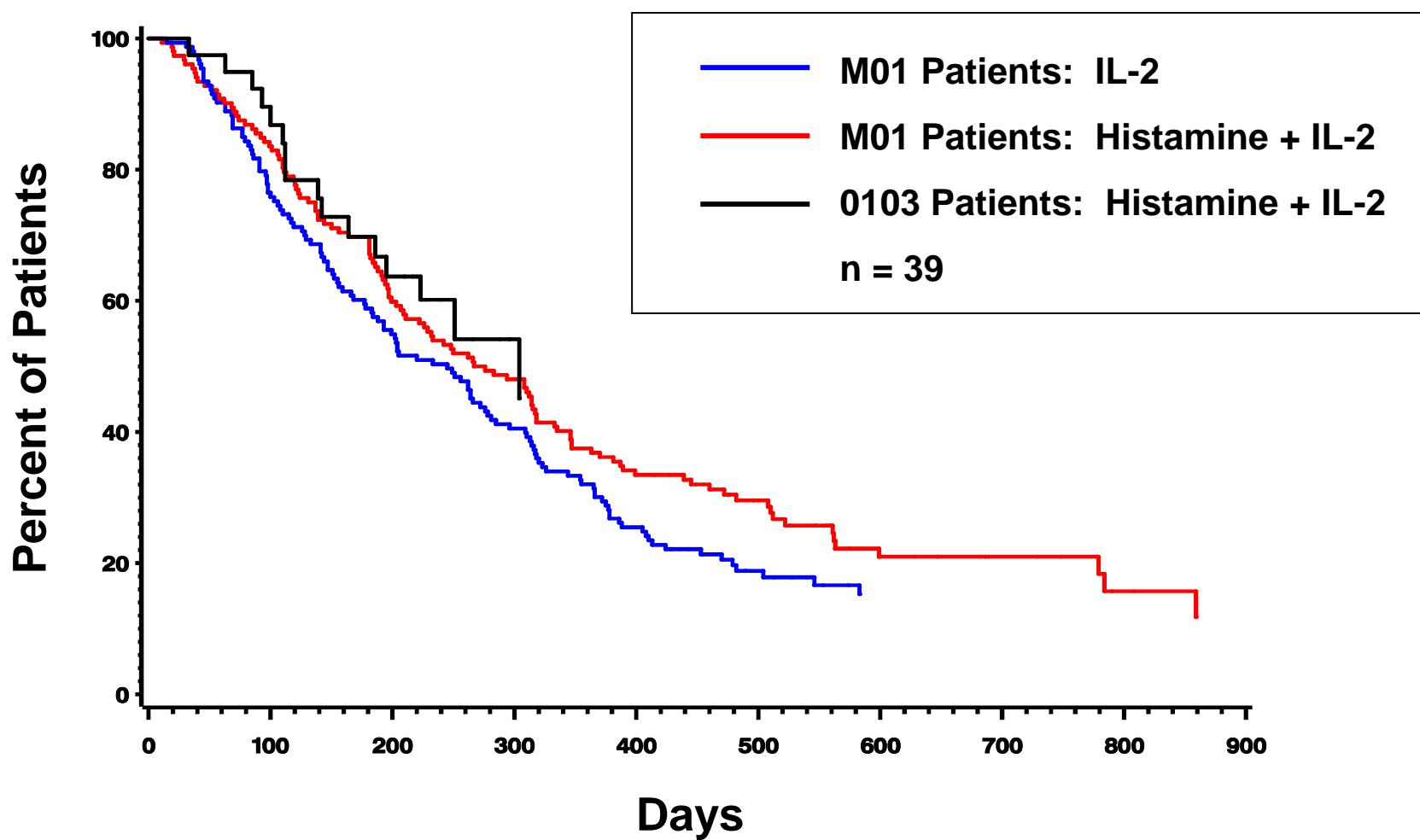
COVARIATE	HAZARD RATIO	95% CI	p-value
Treatment (Histamine + IL-2 vs. IL-2)	0.584	0.390-0.875	0.0091
Disease Site: Liver (Yes vs. No)	1.207	0.802-1.816	0.6372
Treatment x Liver Met	1.675	0.982-2.859	0.0584
Baseline Albumin (>=4 vs. <4)	0.817	0.592-1.128	0.2193
Baseline Performance Status (1 vs. 0)	1.959	1.468-2.614	0.0001
Log _e LDH	1.594	1.337-1.900	0.0001
Prior Chemotherapy (Yes vs. No)	1.066	0.793-1.433	0.6735
Number of Disease Sites	1.155	1.060-1.259	0.0011
Gender (Male vs. Female)	0.734	0.562-0.959	0.235
Age (\geq 65 vs. < 65)	1.188	0.888-1.588	0.2466
Disease Free Interval (>=1yr vs. <1yr)	1.113	0.843-1.468	0.4505
Skin/Lymph node/Lung only (yes vs. no)	0.893	0.622-1.282	0.5393

Phase 2 Study - MP-MA-0103

- ◆ Single-arm study at 7 centers
- ◆ Same treatment regimen as Phase 3 except prior IL-2 patients eligible
- ◆ 39 patients evaluable for NDA
- ◆ 88 patients evaluable as of Sept. 8, 2000 with median follow-up of 5 months
- ◆ 125 patients enrolled to date
- ◆ Patient demographics are similar to Phase 3 study

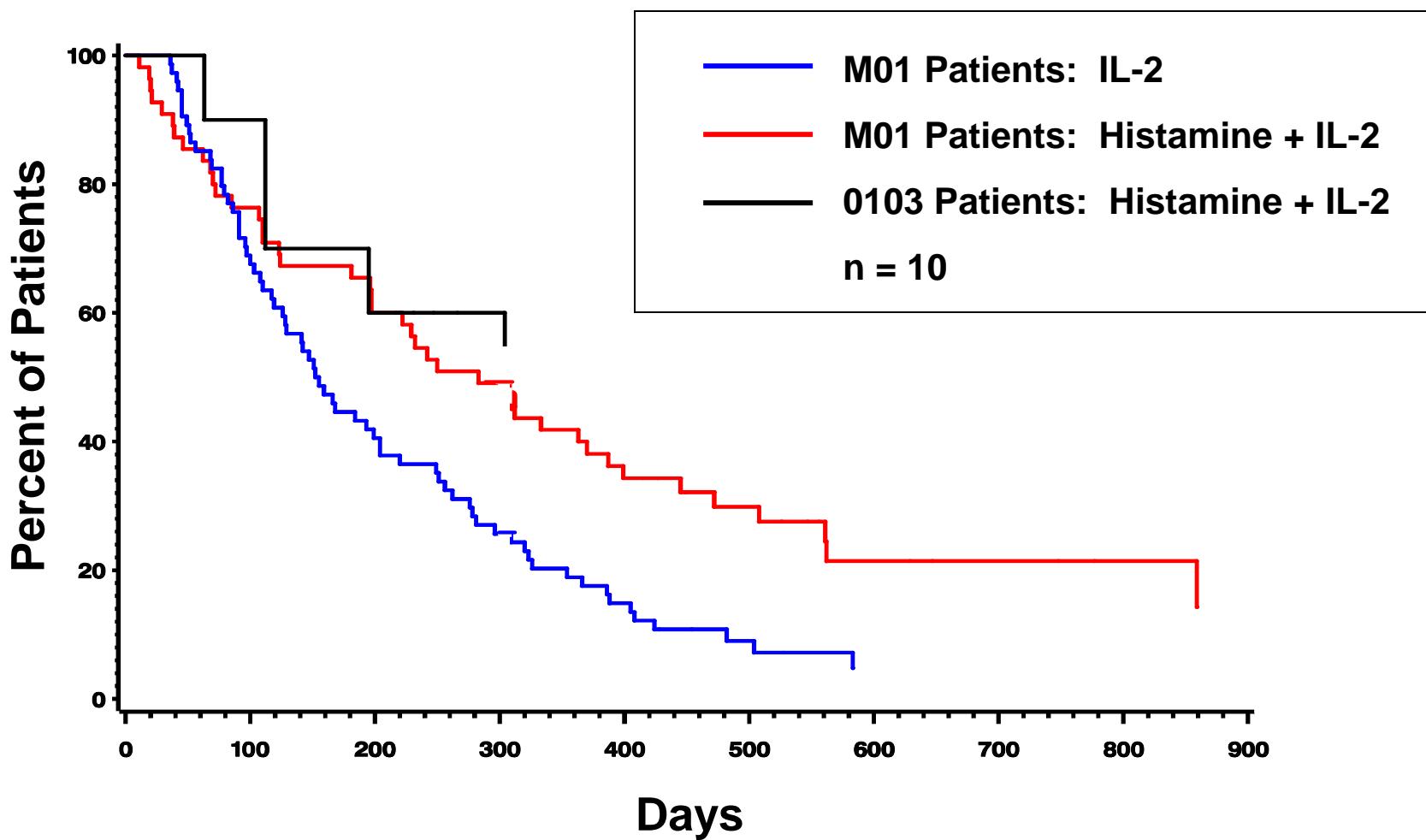
Survival - 0103

ITT Population

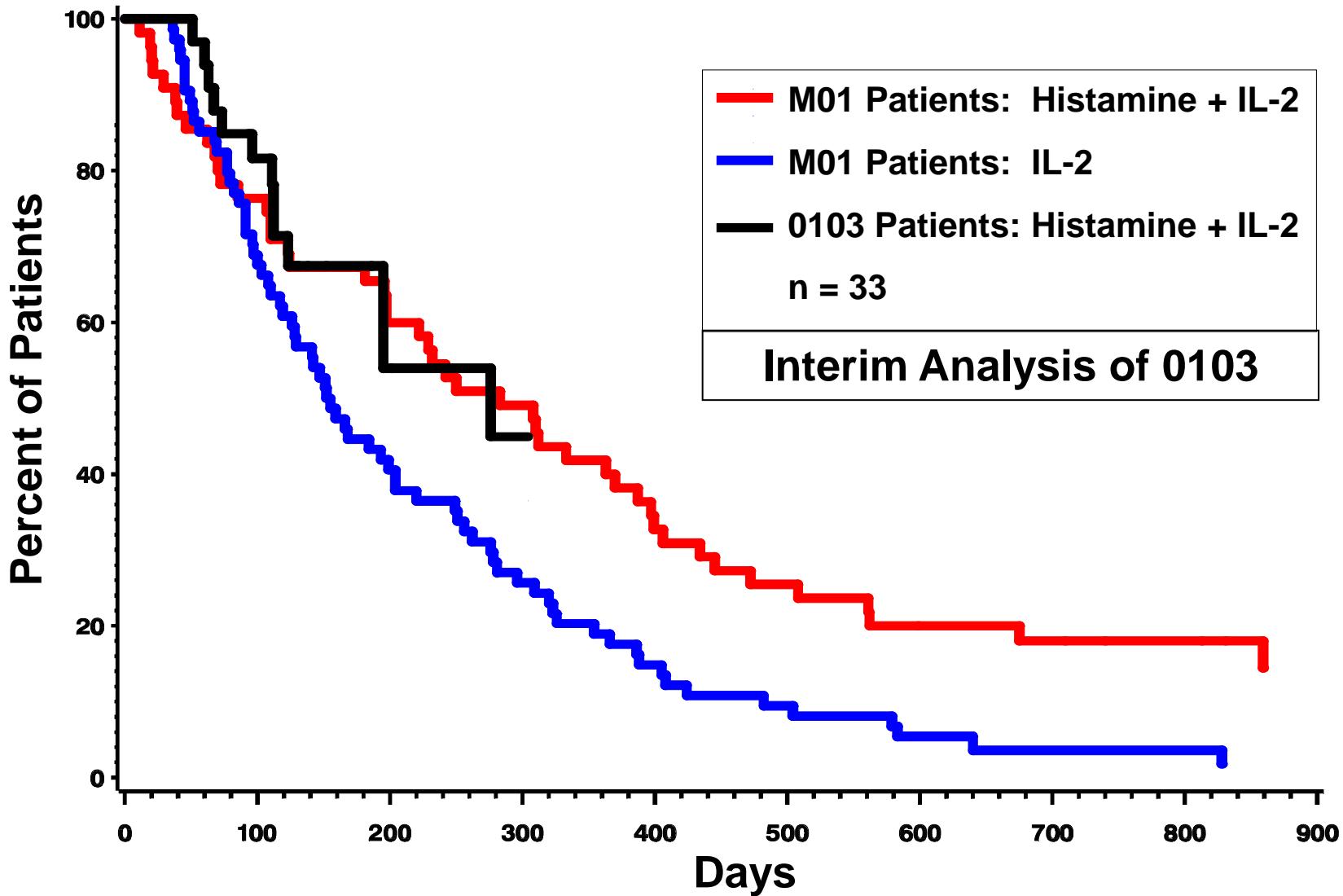


Survival - 0103

ITT-LM Population



Survival - ITT-LM Population (18 Month Follow-Up)



Summary and Conclusions

Efficacy Summary - LM

Study	(n)	Median Survival
MM1 + MM2	15	10.8 months
M01 0103	55	9.1 months
	33	10.0 months
M01 Control	74	5.0 months
<u>Historical</u>		
Balch et al., JCO, 1983		2.4 months
Barth et al., J Am Col Surg, 1995		4.0 months
Sirott et al., Cancer, 1993		4.7 months
Manola et al., JCO 2000		3.9 months
Manola et al., JCO, 1999		2.9 months
Bedikian et al., Cancer, 1995		7.0 months (ocular only)

Overall Summary

- ◆ Combination therapy with Histamine plus IL-2 significantly improved:
 - survival for patients with liver metastases
 - time to disease progression
 - time to treatment failure
 - median quality-adjusted survival
- ◆ Interim results from phase 2 (0103) confirms favorable survival seen in randomized trial

Key Concerns Addressed

- ◆ Liver metastases population was pre-specified
- ◆ Large, well-controlled, randomized trial
- ◆ Survival was primary endpoint
- ◆ DSMB monitored safety and efficacy
- ◆ Cox models support treatment effect
- ◆ Treatment with Histamine plus IL-2 in liver metastases population provides a compelling result

Metastatic Melanoma Patients Need New Treatment Options

- ◆ No established standard of care
- ◆ Treatment options limited for most patients
- ◆ No confirmed randomized trials establishing a survival benefit, even in a subpopulation
- ◆ The combination of histamine plus IL-2 provided a significant clinical benefit, in an outpatient setting, for patients with liver metastases
- ◆ Little risk for patients with a potentially significant benefit

Proposed Indication

We propose that histamine be indicated for use as an adjunct to IL-2 for the treatment of adult patients with advanced metastatic melanoma that has metastasized to the liver.

Acknowledgments

- ◆ Investigators
- ◆ Nurse Coordinators
- ◆ Other Site personnel
- ◆ CRO's (Covance and Omnicare)
- ◆ Maxim Staff (everyone)
- ◆ CDER review team
- ◆ Our Patients

Discussion

Cox Proportional Hazard Model: All Randomized Patients with Liver Metastases (N = 129)

COVARIATE	HAZARD RATIO	95% CI	p-value
Age (\geq 65 vs. < 65)	1.206	0.758-1.920	0.4292
Baseline Albumin ($\geq=4$ vs. <4)	0.770	0.478-1.243	0.2850
Gender (Male vs. Female)	0.850	0.541-1.337	0.4829
Prior Chemotherapy (Yes vs. No)	1.249	0.682-2.284	0.4714
Prior Anti-Cancer Therapy (Yes vs. No)	0.496	0.128-1.916	0.3093
LDH (\geq ULN vs. < ULN)	2.383	1.480-3.835	0.0003
Baseline Performance Status (1 vs. 0)	2.402	1.494-3.864	0.0003
Disease Free Interval ($\geq=1$ yr vs. <1yr)	0.571	0.331-0.986	0.0445

Cox Proportional Hazard Model: All Randomized Patients with Liver Metastases (N = 129)

COVARIATE	HAZARD RATIO	95% CI	p-value
Number of Disease Sites (1 vs. >1)	1.985	0.799-4.935	0.1400
Time from initial met to rand (\geq =1yr vs. >1yr)	0.810	0.446-1.471	0.4884
Skin (Yes vs. No)	1.313	0.770-2.237	0.3170
Lymph Node (Yes vs. No)	1.366	0.829-2.250	0.2204
Bone (Yes vs. No)	5.453	2.520-11.800	0.0001
Lung (Yes vs. No)	1.230	0.715-2.114	0.4542
CNS (Yes vs. No)	1.252	0.534-2.933	0.6052
Other (Yes vs. No)	1.059	0.657-1.706	0.8150
Treatment (Histamine + IL-2 vs. IL-2)	0.574	0.342-0.962	0.0352

*The statistics given for treatment are for the multivariate model.
Geographic region included in the model.

IL-2 Dose Rationale

- ◆ Most patients ineligible or intolerant to high dose (HD) IL-2
- ◆ Majority of clinicians investigating lower dose SC IL-2 regimens
- ◆ Dose and schedule designed to facilitate observation of histamine effect

MP-US-M01 was not designed to prove SC IL-2 plus histamine is superior to HD IL-2