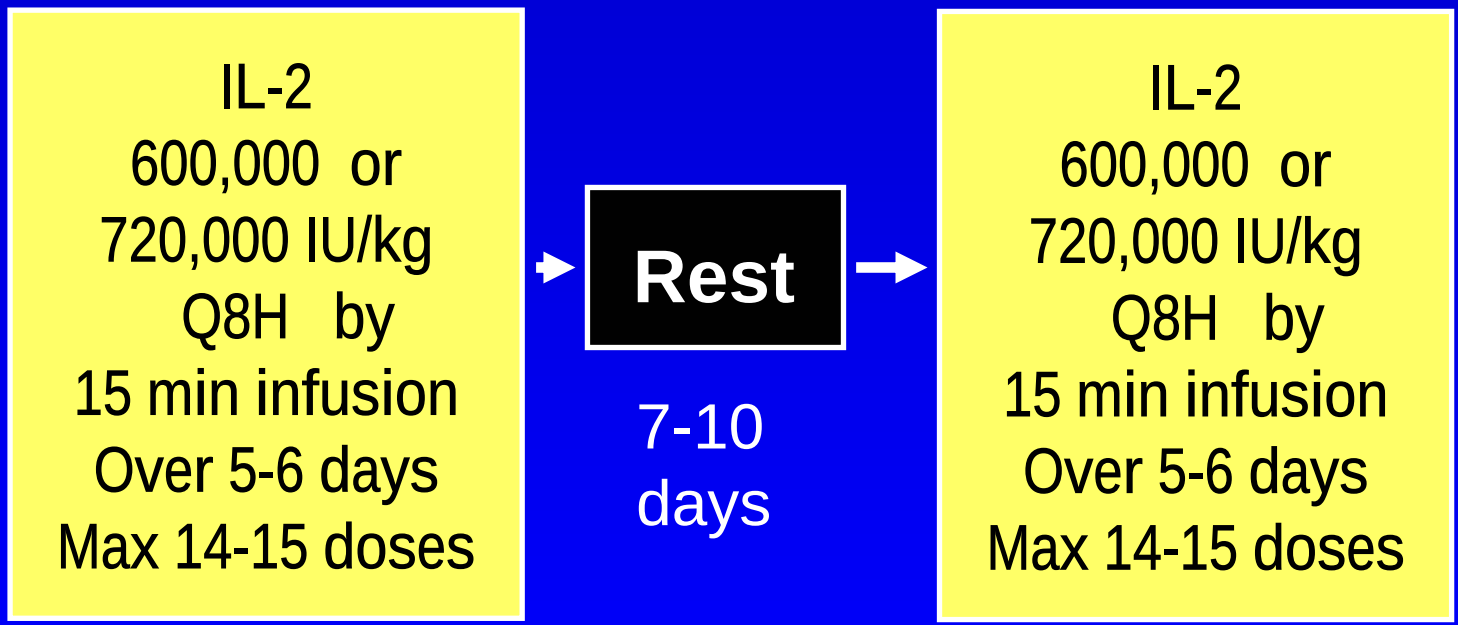
gp100 (209-2M) peptide and High Dose Interleukin-2 in HLA-A2+ Advanced Melanoma Patients

Cytokine Working Group Experience

Metastatic Melanoma- Progress in Past 30 years

Approved Therapies (USA)	Date
♦ DTIC	1970's
♦ High Dose Interleukin-2	1998

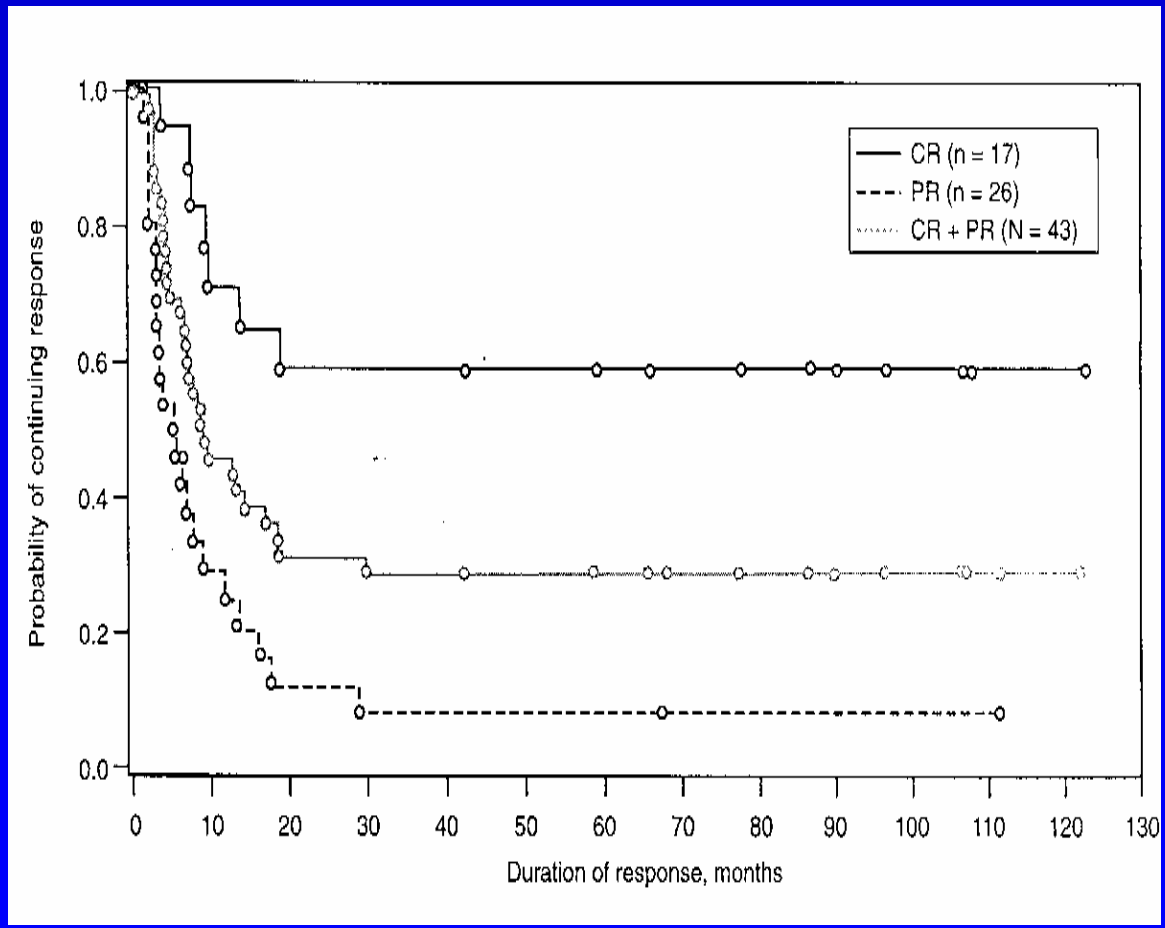
INTERLEUKIN-2 TREATMENT REGIMEN



Repeat at 8-12 weeks if responding

Maximum 3 or so courses

High Dose IL-2 Therapy* in Advanced Melanoma



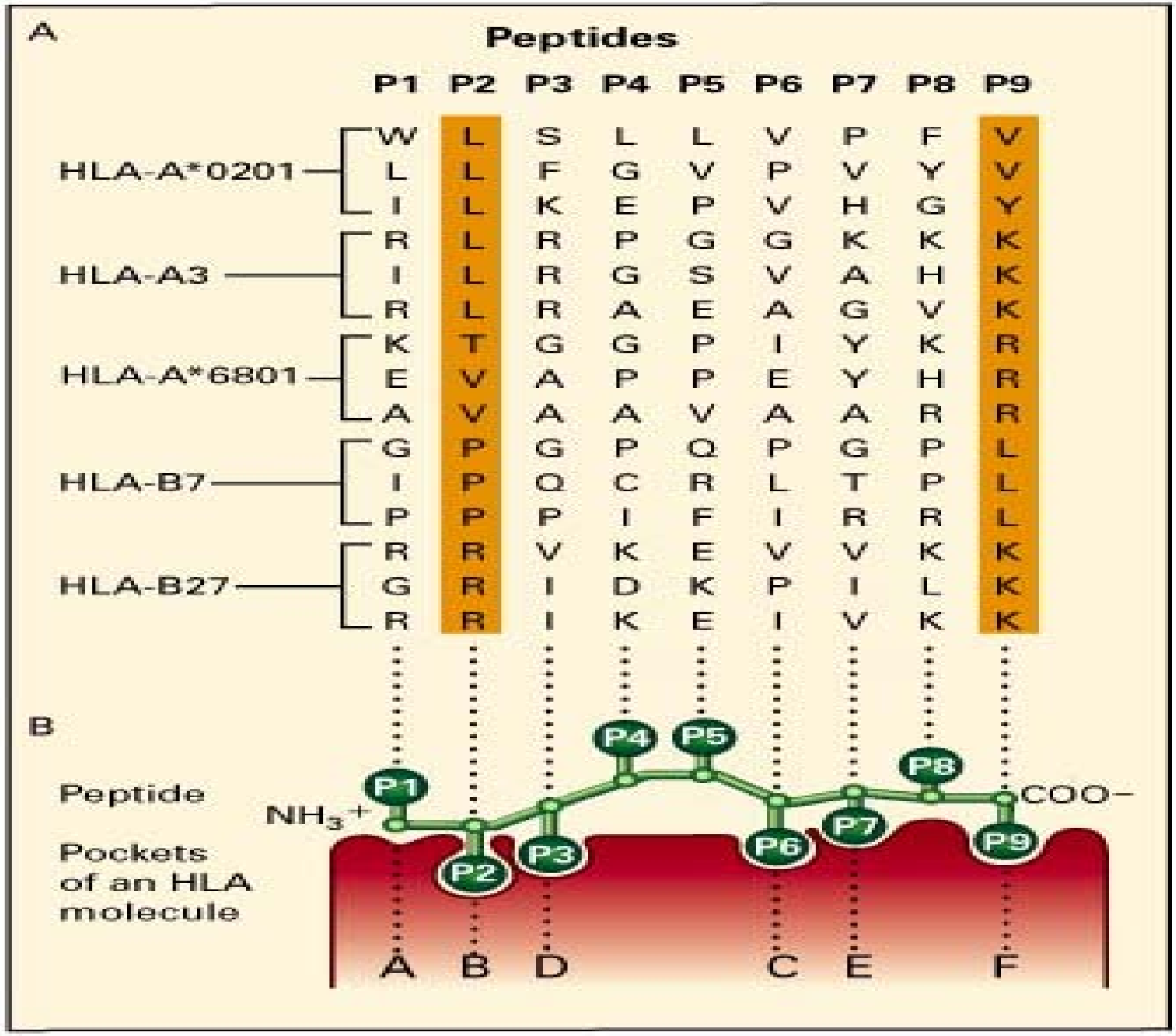
- RR: 16% (43 / 270)
- Durable responses
  - Median 8.9 mos
  - CR: median not reached
- Toxic
- Inpatient
- Expensive
- Use limited to selected pts and Rx Centers

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

High Dose IL-2: Survival in Melanoma

	median (mos)	range
overall	12.0	0.3 - 150+

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


A
Peptides
P1 P2 P3 P4 P5 P6 P7 P8 P9
HLA-A*0201
W L S L L V P F V
L L F G V P V Y V
I L K E P V H G Y
HLA-A3
R L R P G G K K K
I L R G S V A H K
R L R A E A G V K
HLA-A*6801
K T G G P I Y K R
E V A P P E Y H R
A V A A V A A R R
HLA-B7
G P G P Q P G P L
I P Q C R L T P L
P P P I F I R R L
HLA-B27
R R V K E V V K K
G R I D K P I L K
R R I K E I V K K
B
Peptide
Pockets of an HLA molecule
NH3+
COO−
P1 P2 P3 P4 P5 P6 P7 P8 P9
A B D C E F

MALIGNANT MELANOMA: PEPTIDE VACCINES

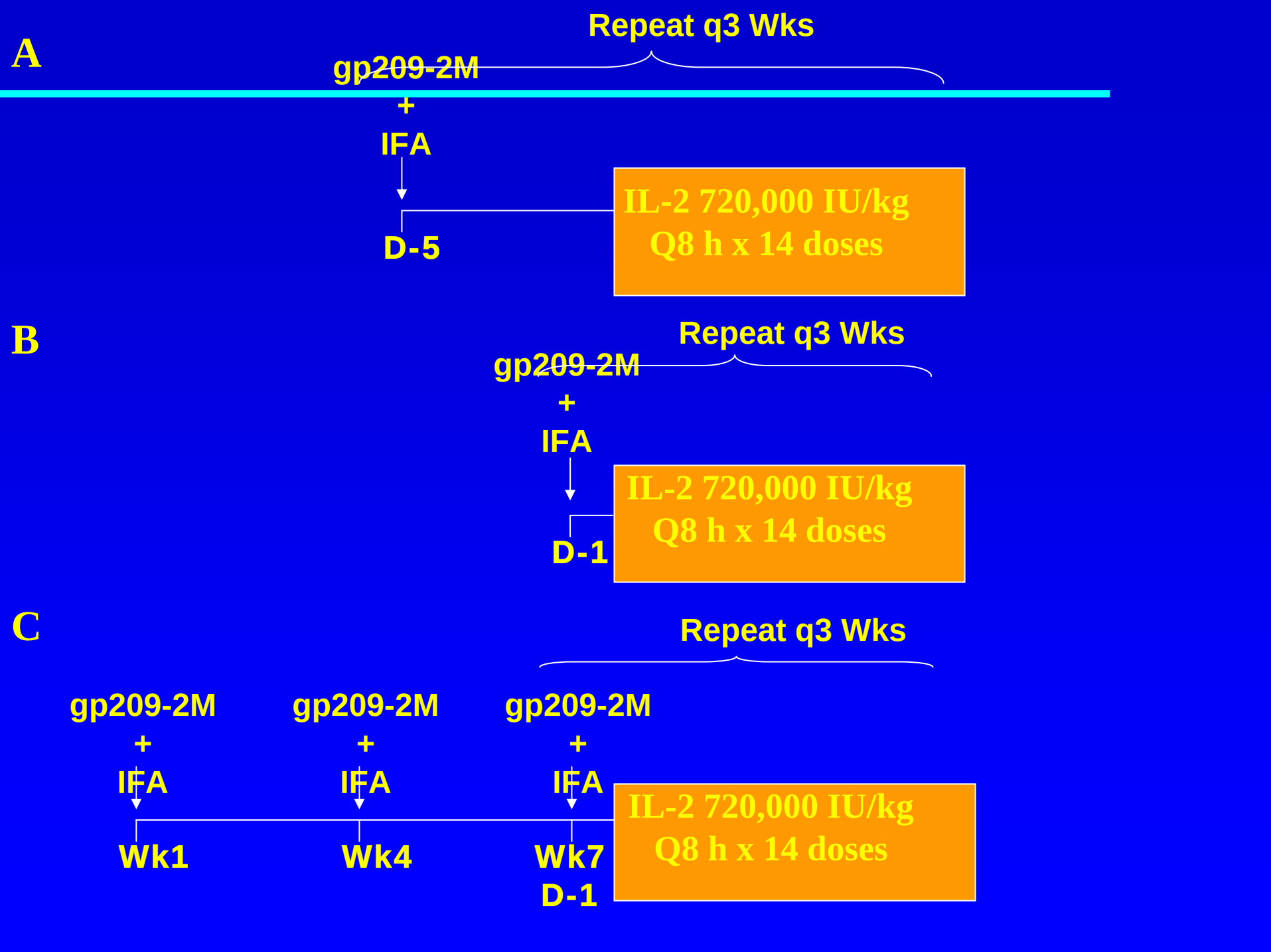
T cell defined epitopes shared by HLA-matched melanomas

HLA-A2 Epitopes	(nonapeptides)
gp100(209-2M)	IT(M)DQVPFSV
MART-1(26)	AA(L)GIGILTV
Tyrosinase(368)	YMN(D)GTMSQV

Heteroclitic peptides- modified to be more effective for T cell activation

Findings at the NCI-Surgery Branch with gp100 209-2M alone and with high Dose Interleukin-2

- 10/11 patients respond immunologically ELISPOT and tetramers to gp209-2M + IFA, while 0/11 clinical responses (Nat Med. 4,1998)
- Later followup report shows 0/32 clinical responses (Nat Med. 10, 2004)


A
Repeat q3 Wks
gp209-2M
+
IFA
D-5
IL-2 720,000 IU/kg
Q8 h x 14 doses
B
Repeat q3 Wks
gp209-2M
+
IFA
D-1
IL-2 720,000 IU/kg
Q8 h x 14 doses
C
Repeat q3 Wks
gp209-2M
+
IFA
Wk1
gp209-2M
+
IFA
Wk4
gp209-2M
+
IFA
Wk7
D-1
IL-2 720,000 IU/kg
Q8 h x 14 doses

IL-2 + gp100 209-2M Peptide Vaccine

- 13/31 (42%) respond to gp209-2M + HD IL-2 with 12 PR and 1 CR, while only 16% with immune response to peptide
- Follow-up (update) 15/47 (32%) respond clinically (14 PR and 1 CR) to peptide + HD IL-2

*Rosenberg et al Nat Med 4:1998

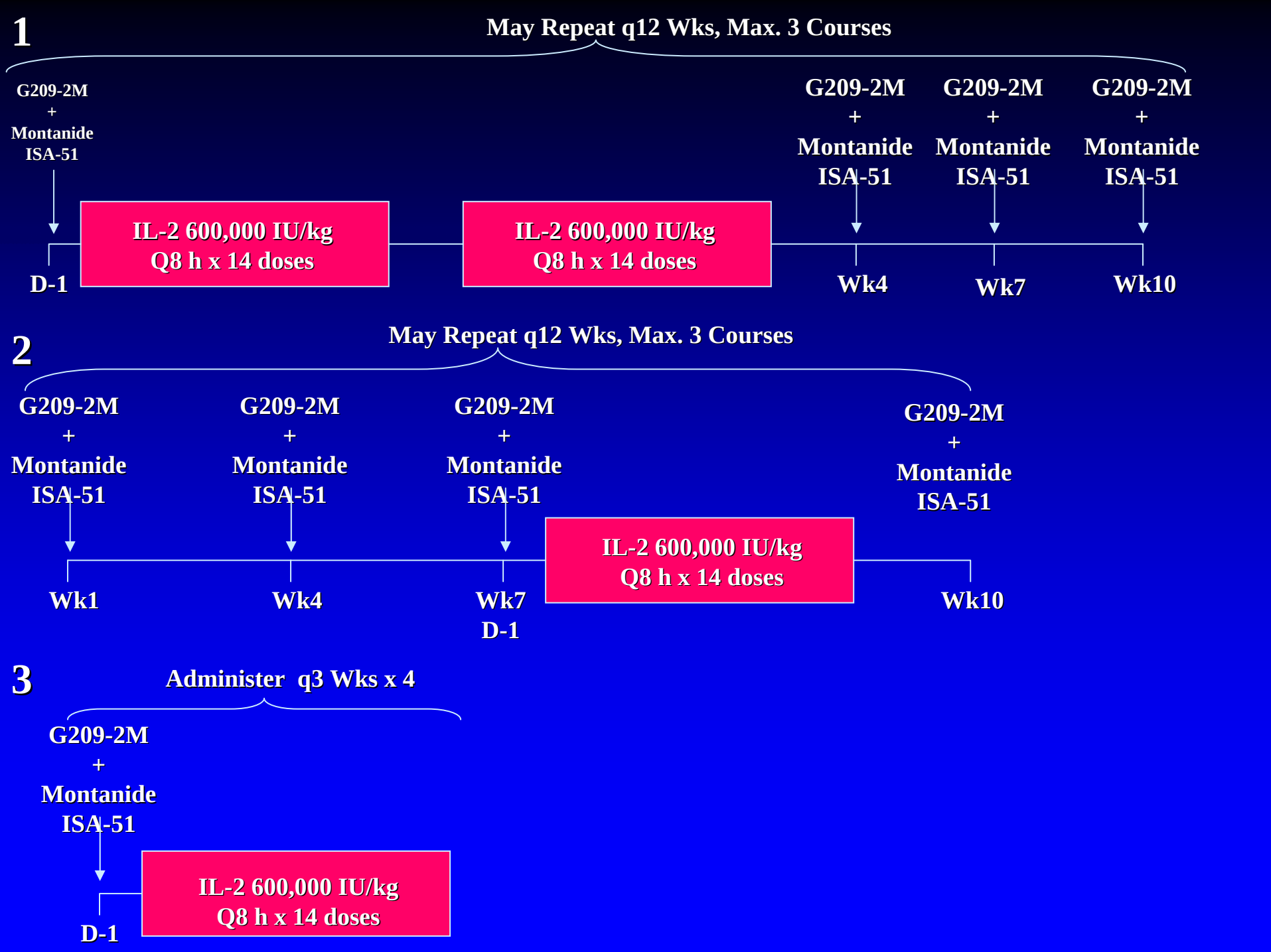
IL-2 + gp100 209-2M Peptide Vaccine in Melanoma

- NCI disseminate trial as phase III (concern results not sufficient)
- NCI SB Consortium Phase III Trial

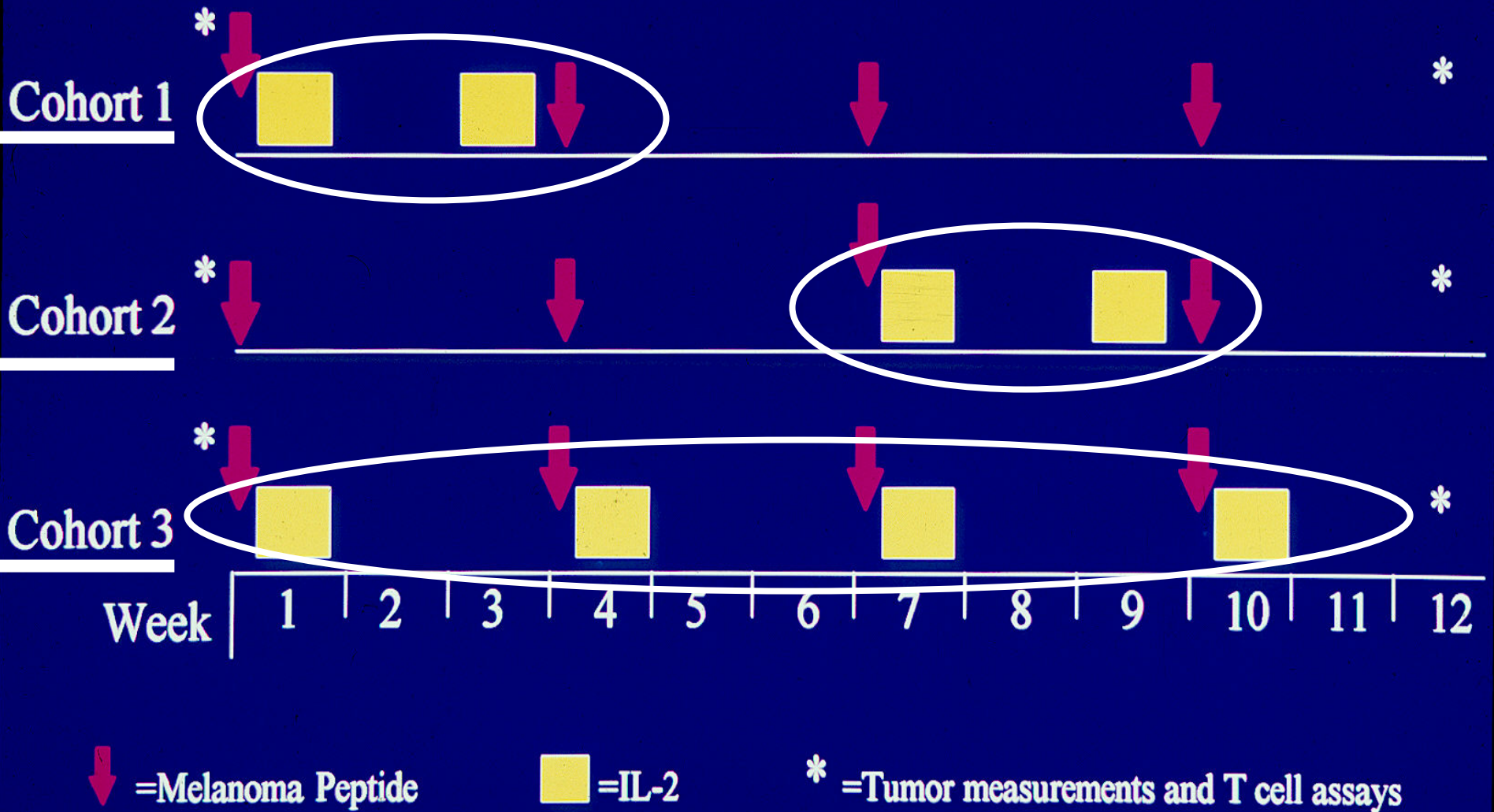
  HD IL-2 +/- vaccine (underway)
- This Report:

  CWG Three Arm Phase II trial

  Vaccine + various HD IL-2 Schedules


1
May Repeat q12 Wks, Max. 3 Courses
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
IL-2 600,000 IU/kg Q8 h x 14 doses
IL-2 600,000 IU/kg Q8 h x 14 doses
D-1
Wk4
Wk7
Wk10
2
May Repeat q12 Wks, Max. 3 Courses
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
G209-2M + Montanide ISA-51
IL-2 600,000 IU/kg Q8 h x 14 doses
Wk1
Wk4
Wk7 D-1
Wk10
3
Administer q3 Wks x 4
G209-2M + Montanide ISA-51
IL-2 600,000 IU/kg Q8 h x 14 doses
D-1

CWG IL-2 + Mutated gp100 Melanoma Peptide Protocol for Metastatic Melanoma



Eligibility Criteria

- Must have histologically confirmed melanoma which is advanced and measurable.
- Must be HLA typed and be shown to be HLA-A2+
- Must have a good performance status (ECOG 0 or 1)
- Must have adequate organ function (as for High dose IL-2)
- Must not have received prior IL-2. Patients who have received one prior chemotherapy regimen are eligible
- Patients with active brain metastases are ineligible.

CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

- **131 enrolled with follow-up available on 121 eligible patients**
  - **46 (42) pts on cohort 1**
  - **43 (40) pts on cohort 2**
  - **42 (39) pts on cohort 3**

CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

Characteristics	N=121
M/F	72/49
Median age	50 (20-76)
ECOG PS (0/1)	99/22
LDH	
Elevated	34 (46%)
Normal	40 (54%)
Unknown	47
Prior therapy	
IFNα	44 (36%)
Chemotx	16 (13%)

CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

Patient Characteristics

Cohort 3 (39 patients) had slightly less favorable characteristics

Otherwise very balanced

Prior therapy

IFNα	**18**	**(46%)**
Chemotx	**6**	**(18%)**

HD IL-2 + gp100 209-2M Peptide Vaccine Trial

Results

Therapy	IL-2 doses	Median(of max)	(range)
Cohort 1		20 of 28	(11-27)
Cohort 2		20 of 28	(9-27)
Cohort 3		35 of 56	(8-51)

- **15 patients (12%) did not receive IL-2 due to disease progression**
  - **12 (30%) of those pts not receiving IL-2 in cohort 2**

HD IL-2 + gp100 209-2M Peptide Vaccine Trial

Response (by WHO criteria):

Cohort:	Eval	CR	PR	RR %
Overall	121	10	10	16.5%
Cohort 1	42	6	4	23.8%
Cohort 2	40	3	2	12.5%
Cohort 3	39	0	4	10.2%

Characteristics of Responses

- Follow-up range from 17 to 62 months
- Median Follow-up of 44 months

- Complete Responses (10)
  - **8/10 progression-free at (18+, 26+, 27+, 27+, 29+, 35+, 37+, 62+ months)**
  - **2 progressed at 17 and 51 months**

- Partial Responses (10)
  - **Only 1 progression-free at 17 months**
  - **6 progressed in less than 12 months, 2 progressed at 15 months and 1 progressed at 29 months**

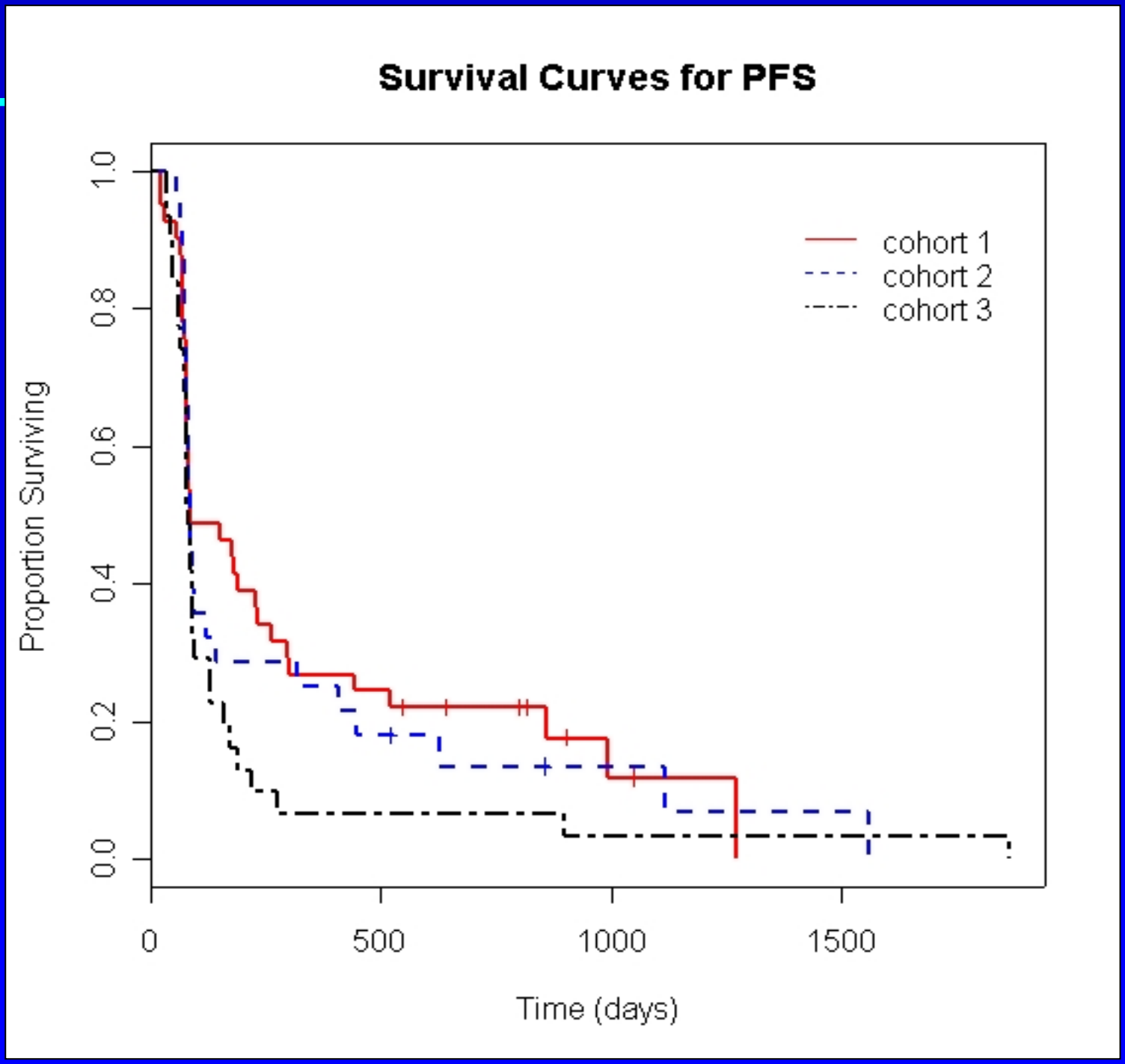
Clinical Outcome in PFS and OS

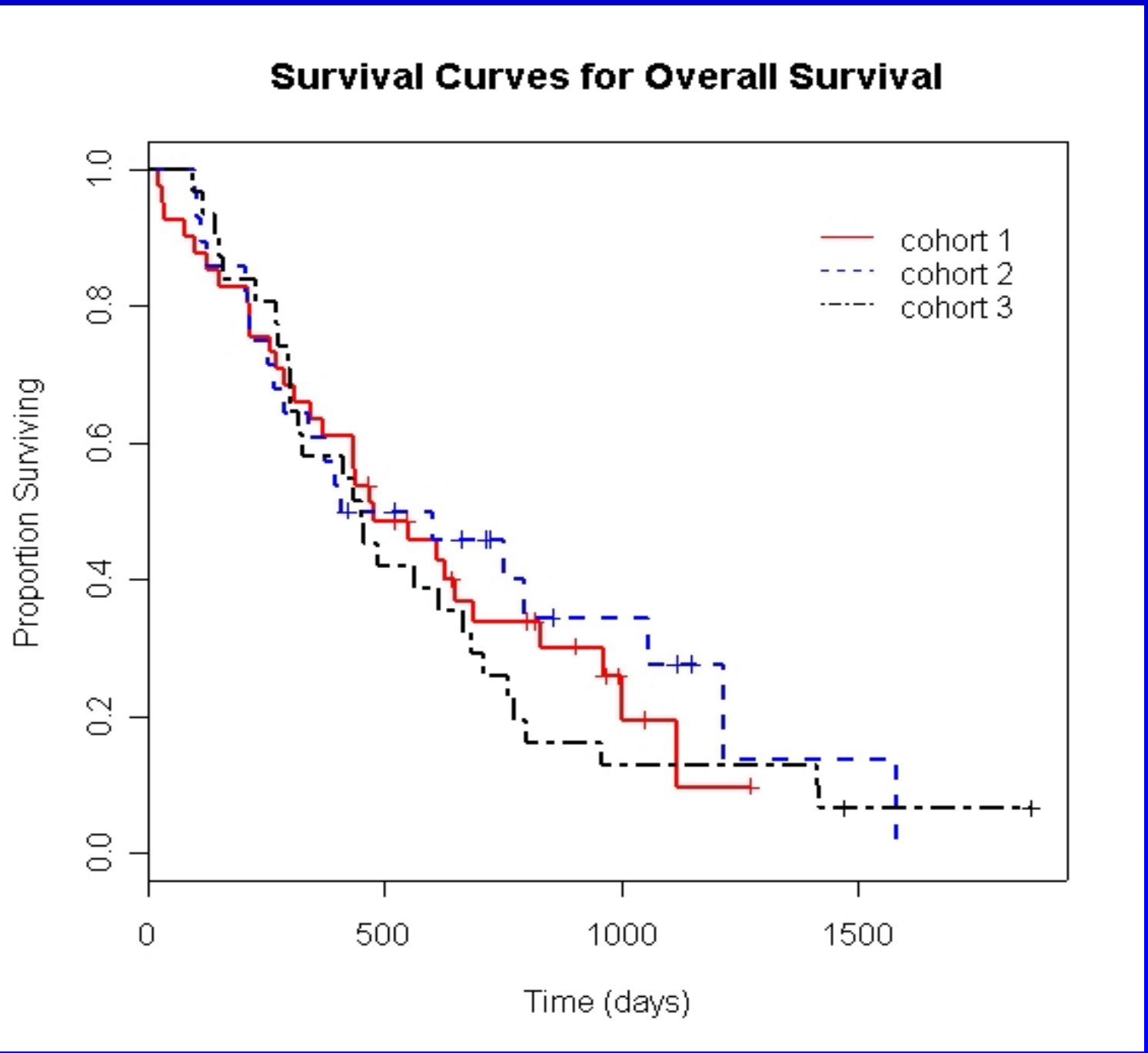
Progression Free Survival

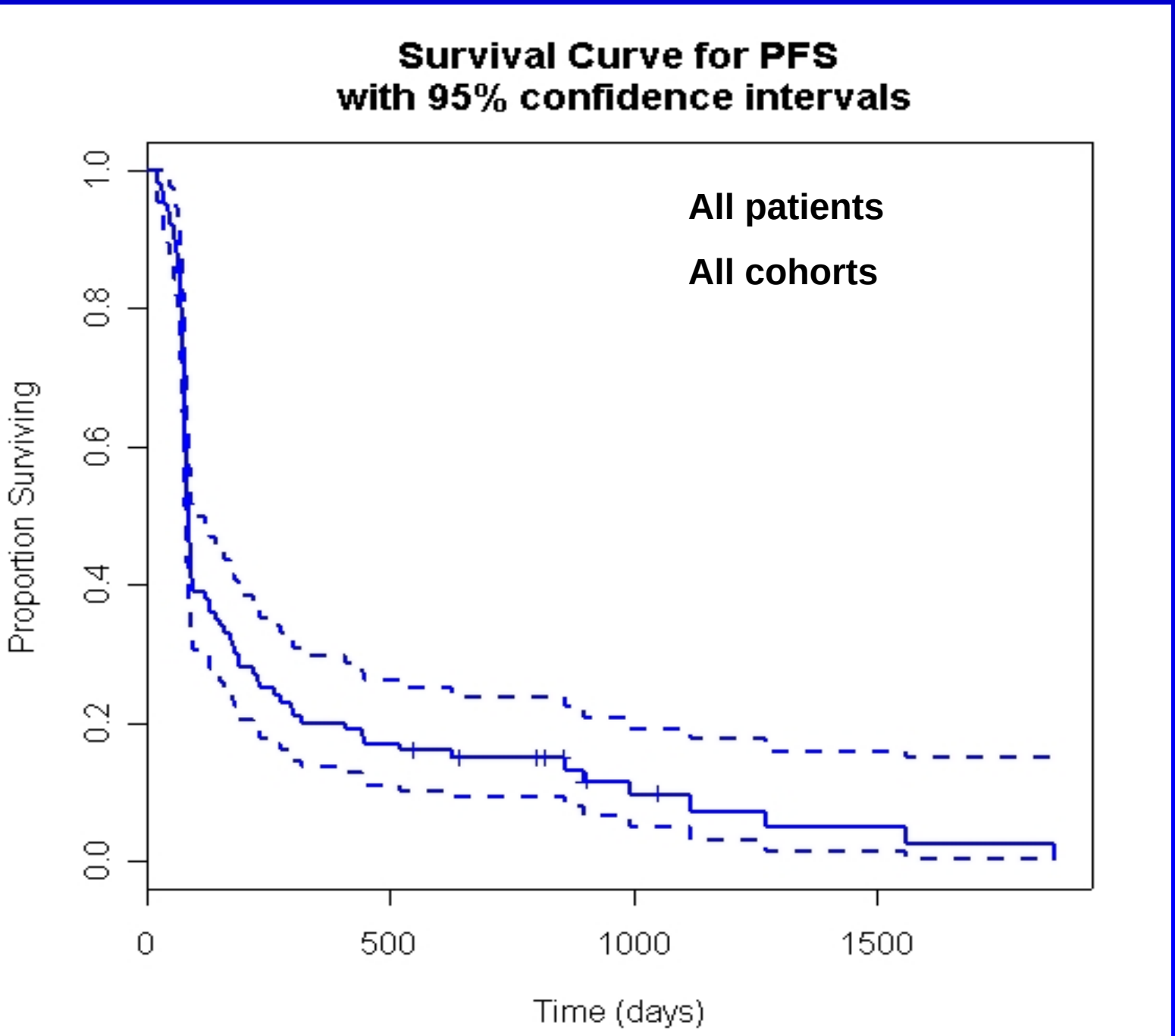
	mean days	median days
Overall	248d	84d

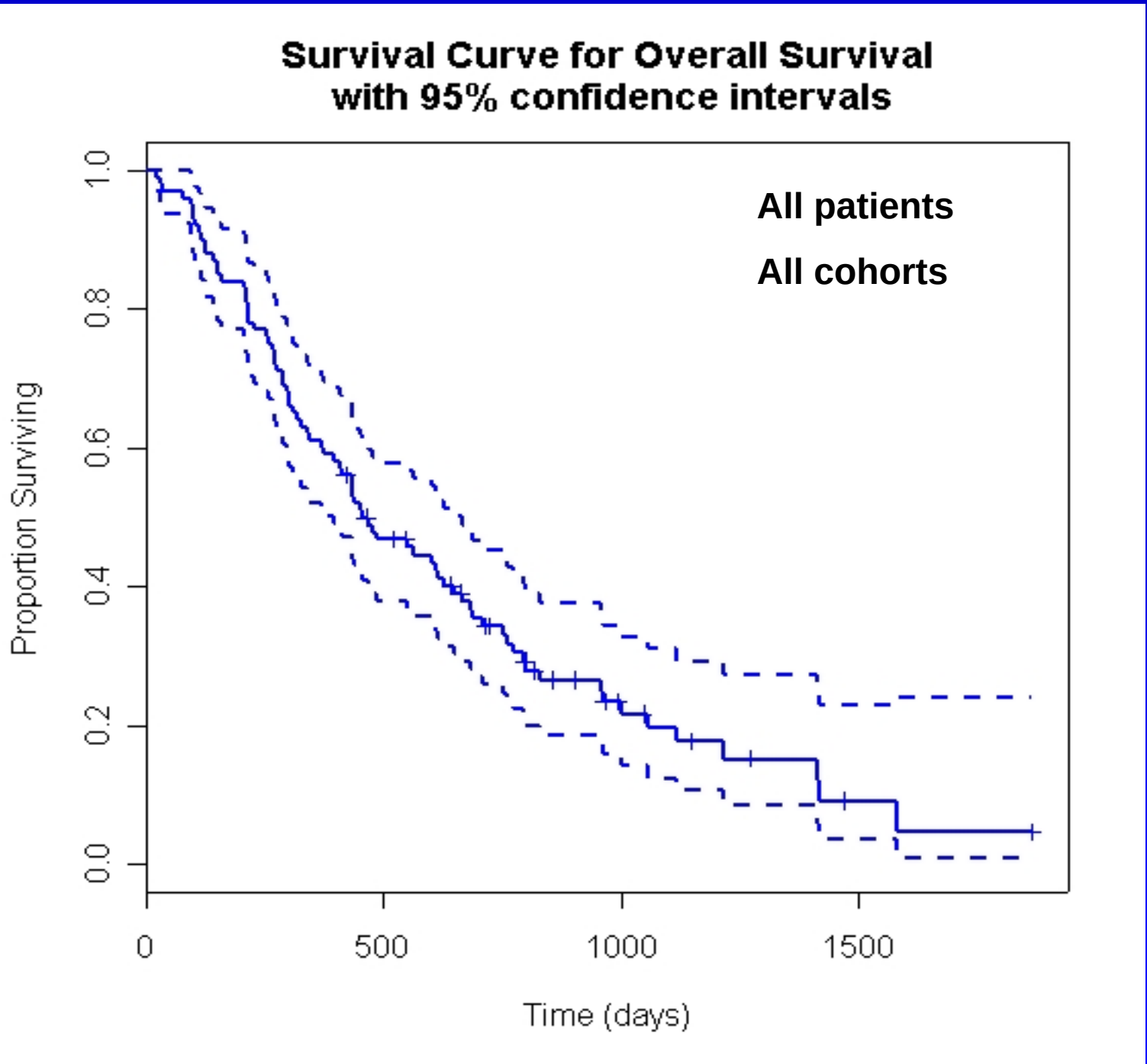
Overall Survival

	mean yrs	median yrs
Overall	1.47	1.24


Survival Curves for PFS
Proportion Surviving
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time (days)
cohort 1
cohort 2
cohort 3


Survival Curves for Overall Survival
Proportion Surviving
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time (days)
cohort 1
cohort 2
cohort 3


Survival Curve for PFS
with 95% confidence intervals
All patients
All cohorts
Proportion Surviving
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time (days)


Survival Curve for Overall Survival
with 95% confidence intervals
All patients
All cohorts
Proportion Surviving
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
Time (days)

Immune Assays Performed Pre-Tx and at Week 12

- Assess degree of immune dysfunction
  - **Percent of CD3+ expressing ζ chain (↓)**
  - **Percent of CD4+CD25+ Regulatory T cells (↓)**
  - **Percent of CD15+, CD14-CD18+ (Immature Myeloid Cells) (↓)**
- Assess Specific T cell response
  - **Percent gp100-209 tetramer expressing CD8+ T cells (↑)**
  - **Control percent Flu tetramer expressing CD8+T cells**
- Compare Pre-treatment, Post-treatment, and change from pre- to post-treatment

Immune Assays Performed Pre-Tx and at Week 12

♦ Preliminary Results

- **Complete sampling on 52 patients (Pre- and Week 12))**
  - **Including 10 responders (6 CR, 4 PR)**
  - **Including 13 PFS > 12 months (PFS responders)**
- **For % CD3+, ζ expressing cells**
- **For % CD4+, CD25+ cells**
- **For % CD15+, CD18+, CD14- cells**
- **For %CD8+, gp100 tetramer+ cells**
  - **No significant difference in Pre- and Post-Treatment levels or change in levels in CR/PR responders (10) compared to non-responders (42)**
  - **No significant difference in Pre- and Post-Treatment levels or change in levels in PFS responders (13) compared to non-responders (39)**

CWG HD IL-2 + gp100 209-2M Peptide Vaccine Trial

Conclusions

- gp100 209-2M vaccine does not appear to greatly enhance high dose IL-2 clinical activity in HLA- A2 + advanced melanoma patients

- No correlation of Immunologic Assays (Pre-, Post- and change from Pre- to Post-Treatment with clinical outcome in PFS and objective responses

CWG HD IL-2 + gp100 209-2M Peptide Vaccine Trial

Conclusions (continued)

Low overall response rates-in cohort 3- IL-2 and vaccine every 3 weeks

- **Prognostics characteristics of tumor were poor??**
- **Difficulty in tolerance to increased IL-2 doses??**

- Many patients (12; 30%) in cohort 2 do not receive IL-2 after 6 weeks of vaccine

- Results support the early initiation of standard HD IL-2 after the diagnosis of advanced melanoma in lieu of a clinical trial and the continued need to search for approaches to enhance IL-2's clinical effectiveness

Special Thanks

- Carol Carrillo, BS
- David Panka, PhD- laboratory correlates
- Bonnie LaFleur, PhD- statistics

- **Sosman JA, Urba W, Ernstoff M, Flaherty L, Atkins M, Clark J, Dutcher J, Margolin K, Weiss G, Kirkwood J, for the Cytokine Working Group**