Cytokines (IL-2 and IFN):

Indications and Clinical Management

Richard L White, Jr MD FACS
Chief, Division of Surgical Oncology
Levine Cancer Institute and Department of Surgery

CHANGING THE COURSE OF CANCER CARE

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Disclosures

- **Prometheus – Advisory Board**
- **Merck – Advisory Board**

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JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Next Generation of Immunotherapy for Melanoma

John M. Kirkwood, Ahmad A. Tarhini, Monica C. Panelli, Stergios J. Moschos, Hassane M. Zarour, Lisa H. Butterfield, and Helen J. Gogas

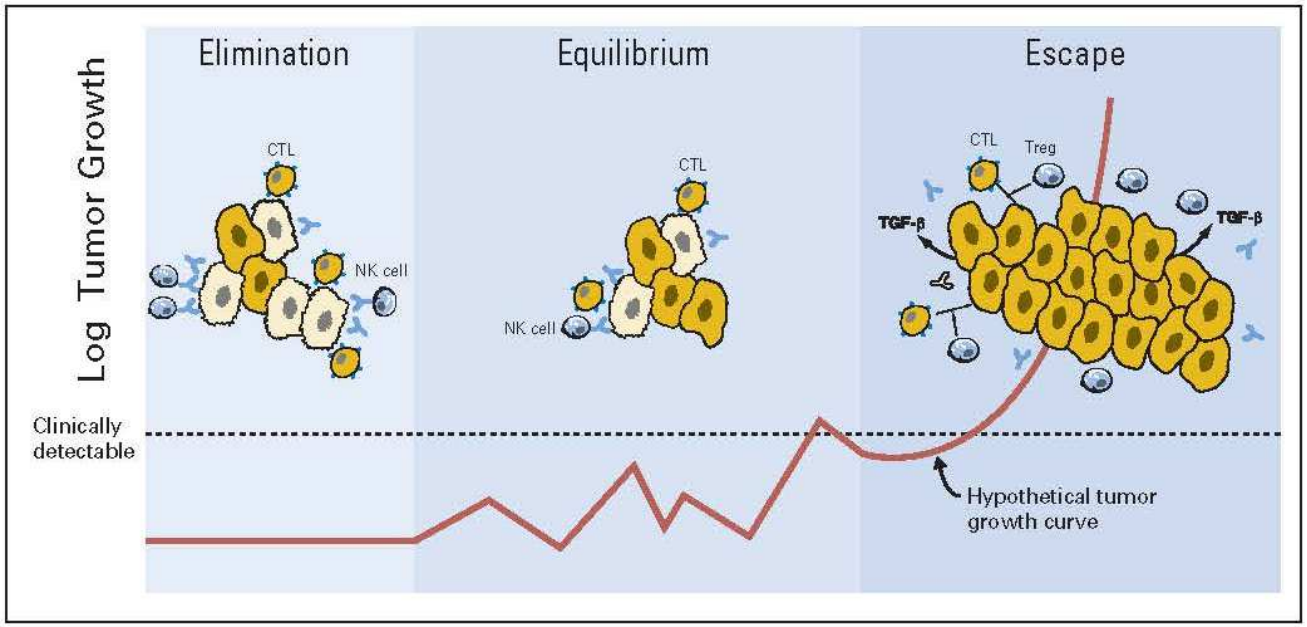

Fig 2. Overview of immunoediting. The tumor and immune system exist in a dynamic state of equilibrium between two extremes: elimination of the tumor by the immune system and development of characteristics that allow the tumor to evade the immune response and proliferate unchecked. CTL, cytotoxic T lymphocyte; NK, natural killer; Treg, regulatory T cells; TGF-β, transforming growth factor-beta.

Interferon

Properties

- Naturally secreted glycoproteins
- Produced by most cell types as host defense to microbe attack (Rees *Blood Rev* 1990)
- Called interferons based on interfering with viral infection (Nagano Y 1954, Lindenmann 1957)
- Function through activation of Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) pathway (Stark GR *Immunity* 2012)
- Antiangiogenic
- Pro apoptotic (Chawla-Sarkar M *Clin Ca Res* 2001)
- Enhance natural killer activity (Edwards BS *Cancer Res* 1984)
- Direct antimitotic effects on malignant cells (Goldstein D *Cancer Res* 1986)
- Increased surface density of tumor associated or MHC antigens (Hokland M *Cancer Met Rev* 1988)
- Changes in oncogene expression (Clemens M *Nature* 1985)
- Responses in Hairy Cell Leukemia (Golomb HM *Semin Oncol* 1988)

ECOG Trial EST 1684

- Adjuvant Interferon alfa-2b
  - 20 mu/m^2 daily 5 days x 4 weeks
  - 10 mu/m^2 Subcut 3 x per week for 48 weeks
- Small Survival Benefit, but very high risk group of patients
  - Palpable Nodes, Recurrent Nodal Disease, Thick lesions

Kirkwood JM, et al. JCO 1996;14(1):7-17

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ECOG Trial EST 1684

	N	%
1. >4mm, LN neg	31	11%
2. CS1, PS2	34	12%
3. CS2, PS2	41	15%
4. Recurrent LN Mets	174	62%

***No analysis of results by number of positive LN**

Kirkwood JM, et al. JCO 1996;14(1):7-17

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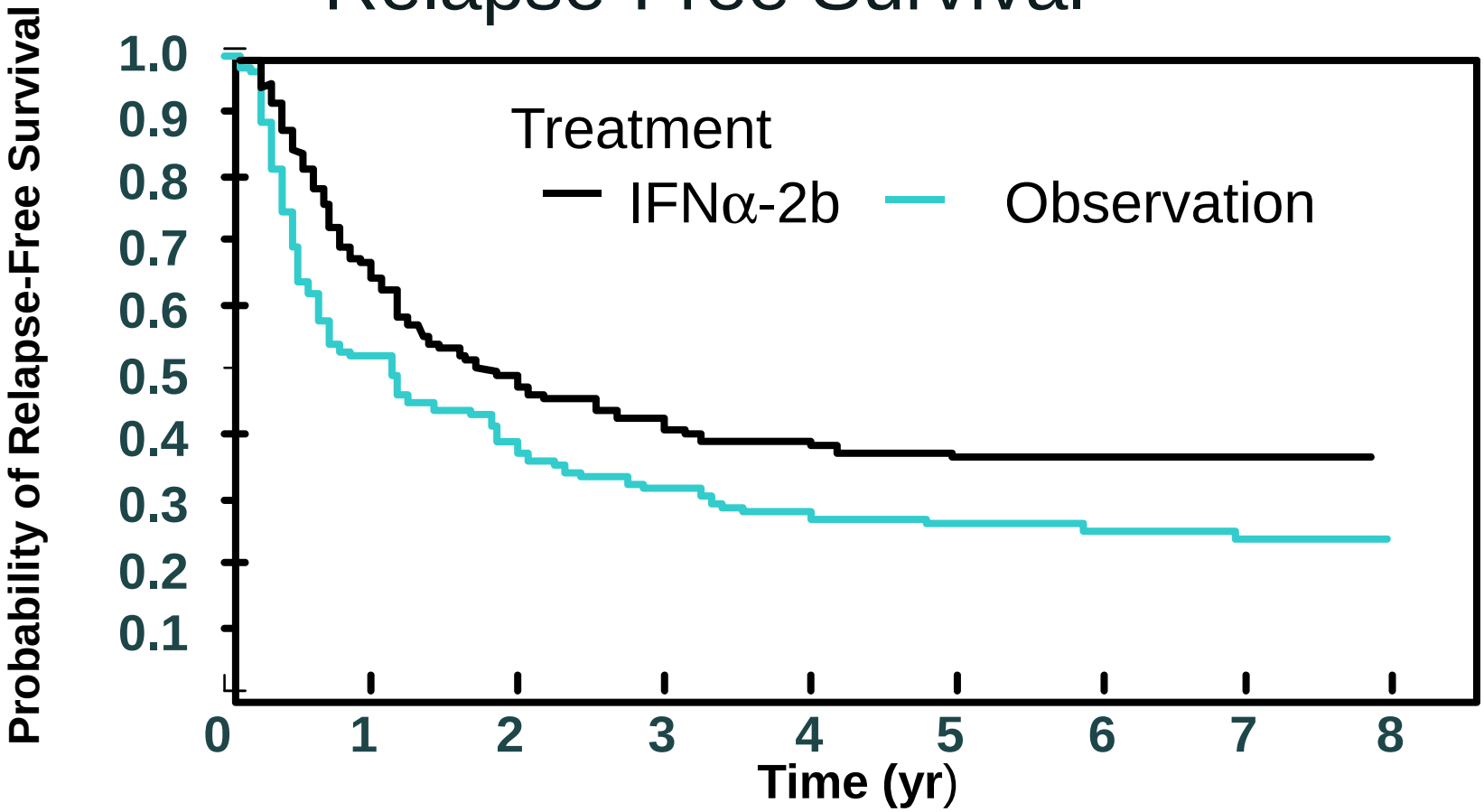
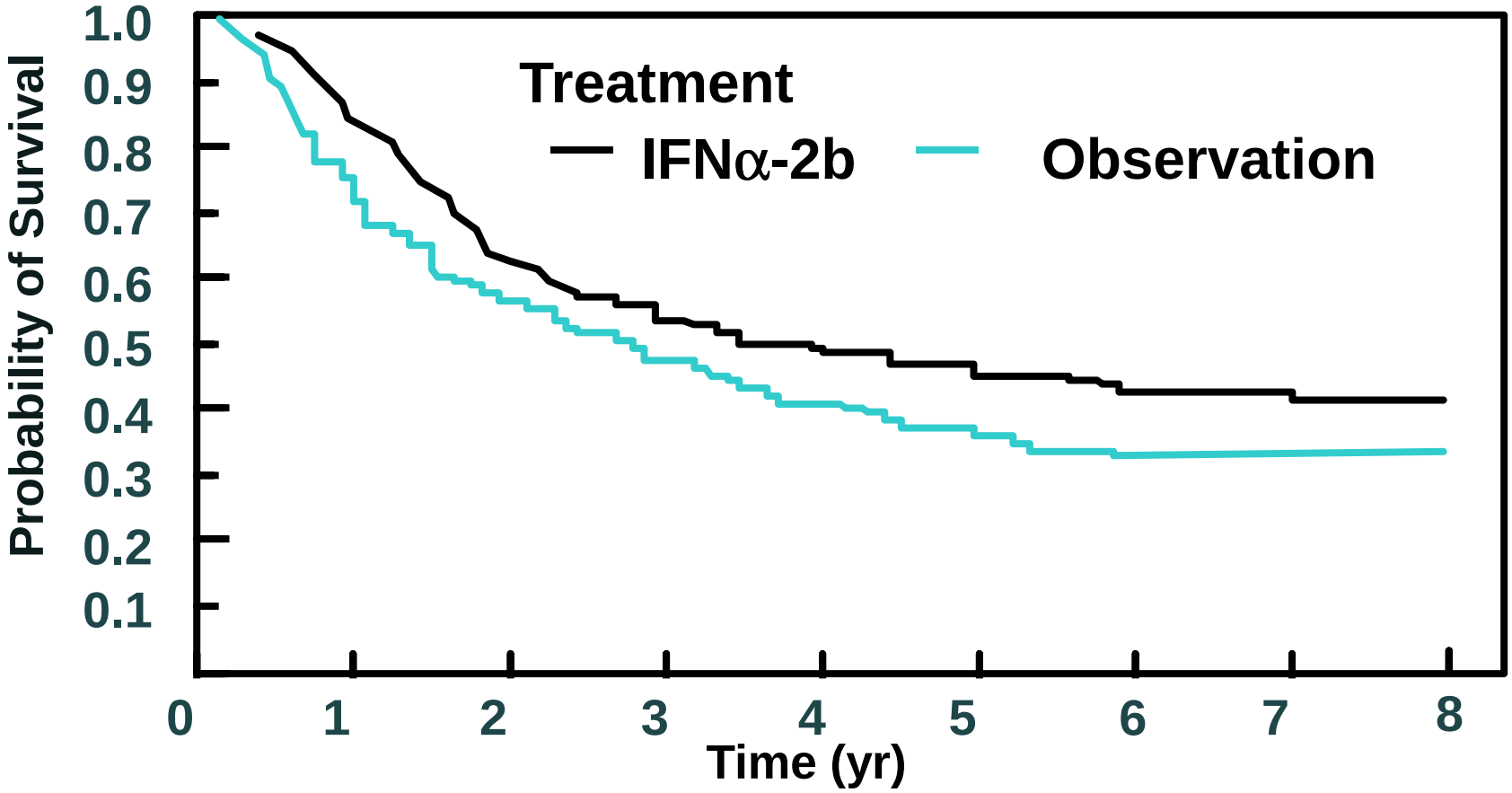
Relapse-Free Survival



	No Patients	No Relapsed	Median (yr)	*P* Value	5-Year RFS
IFNα-2b	143	88	1.72	< .01	37%
OBS	137	101	.98		26%

Kirkwood JM, et al. JCO 1996;14(1):7-17

Overall Survival



	No Patients	No Dead	Median (yr)	*P* Value	5-Year Survival
IFNα-2b	143	76	3.82	.047	46%
OBS	137	85	2.78		37%

Kirkwood JM, et al. JCO 1996;14(1):7-17

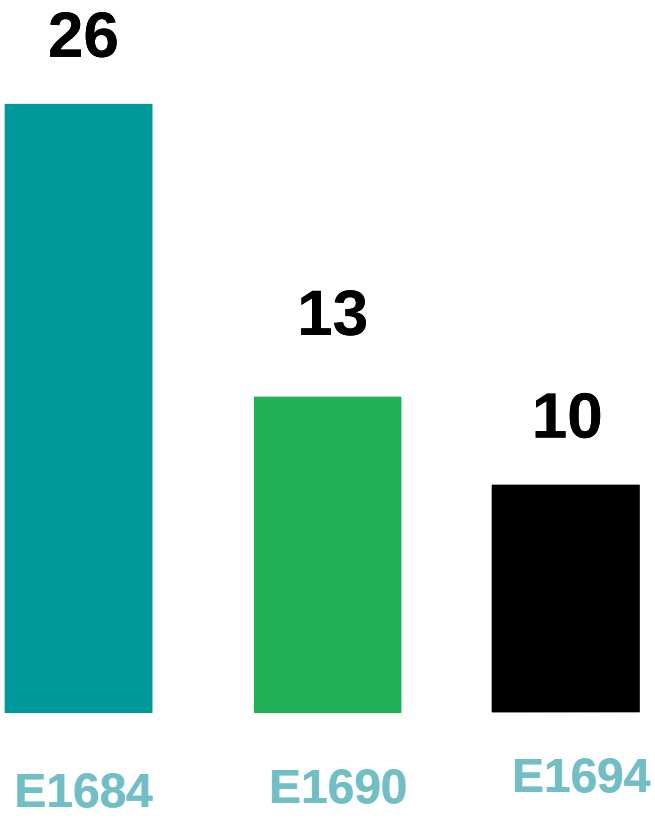
ECOG 1684 Toxicities

Type	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constitutional	18	53	64	5	0
Myelosuppression	37	57	34	0	0
Hepatotoxicity	30	39	20	0	2*
Neurologic	31	47	33	7	0
Worst grade/patient	2	30	96	10	2

* Liver toxicities early in trial and addressed with investigators

Discontinuations due to Adverse Events in IFN-α2b Clinical Trials

With experience more patients tolerated a full course of therapy.



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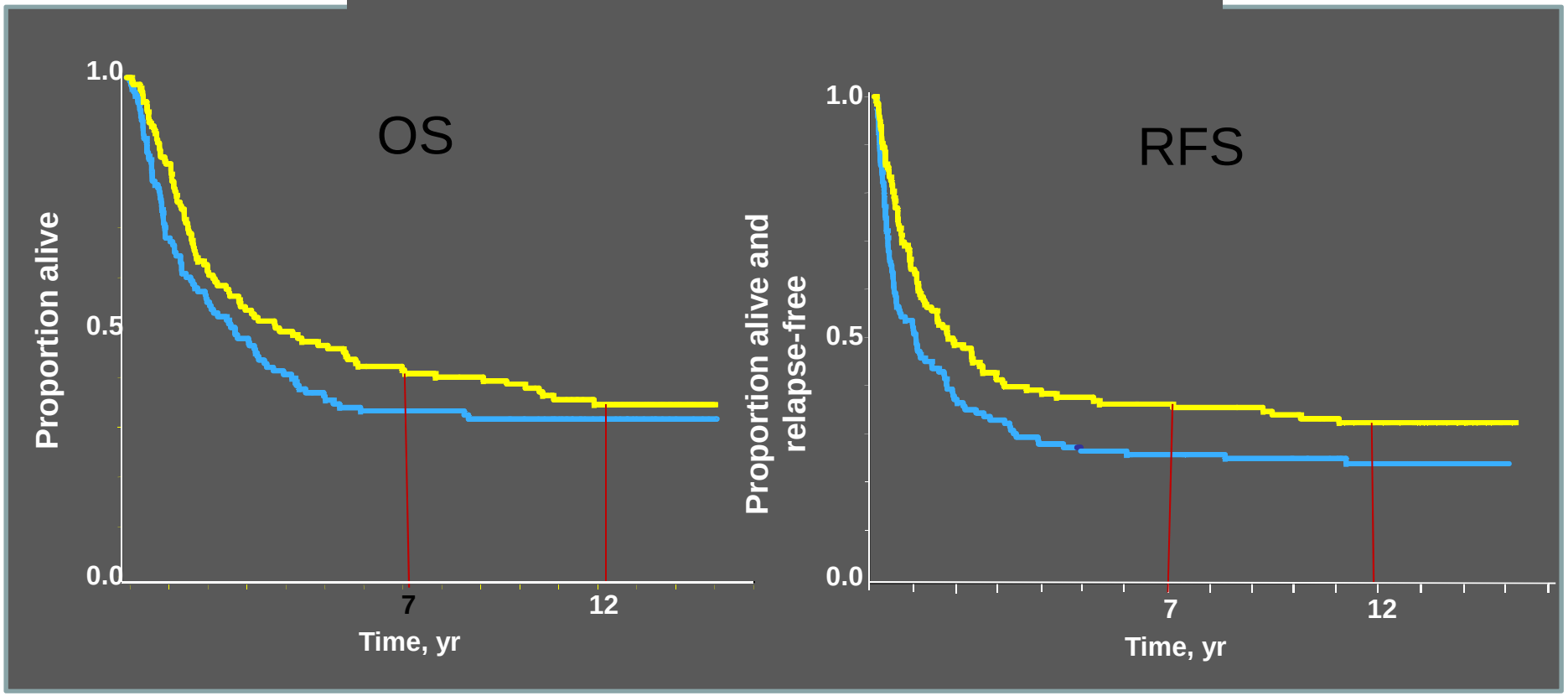
Interferon

- Approved by FDA for therapy
- Multiple other trials: varying routes of administration and dosing

  - ECOG 1690 (Kirkwood 2000)
  - ECOG 1694 (Kirkwood 2001)
  - WHO (Cascinelli 2001)
  - EORTC 18871 (Kleeberg 2004)
  - EORTC 18952 (Eggermont 2005)
  - Sidney Mel group (Cameron 2001)
  - UKCCCR (Hancock 2004
  - AMCG (Pehamberger 1998
  - FCGM (Grob 1996)

ECOG 1684 – 12 year follow up

Standard Interferon vs Observation
Stage III Resected



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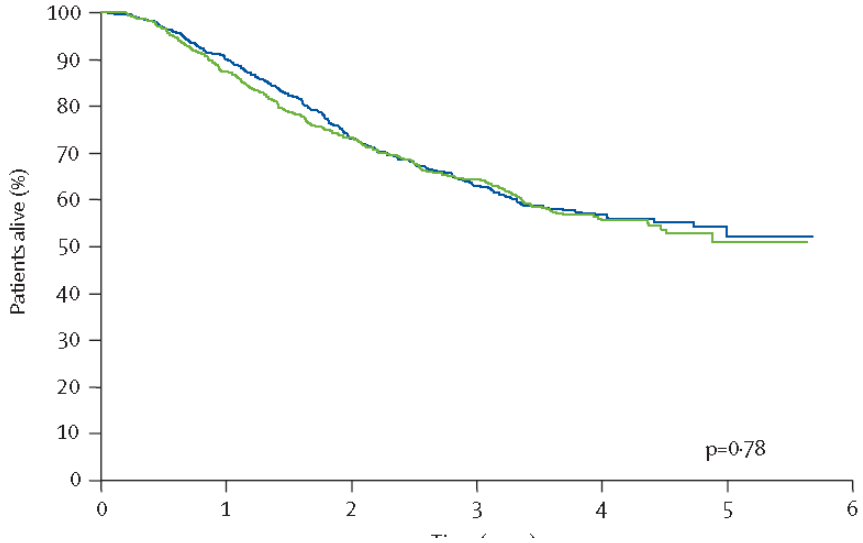
Pegylated interferon alfa-2b

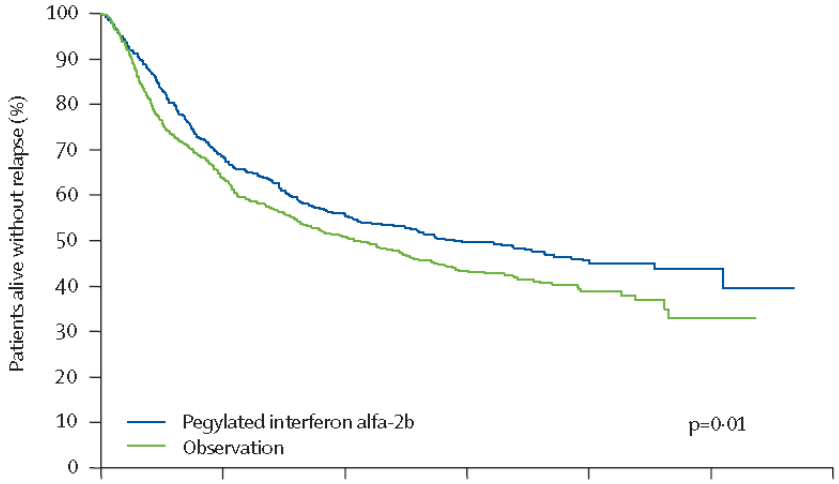
- **EORTC 18991**
- **Randomized**
  - Observation (n=629)
  - Pegylated interferon alfa-2b (n=627)
    - 6 microg/kg per week for 8 weeks then 3 microg/kg per week for an intended 5 years
- **Results**
  - Improved Recurrence free survival (4 yr RFS 45.6% vs 38.9%)
  - No benefit Overall Survival
  - 40% grade 3 events ifn (vs 10%)
  - At 12 months 50% actually receiving Interferon. At 4 years 22.5%

PEG-Interferon: EORTC 18991

Overall Survival



Relapse Free Survival

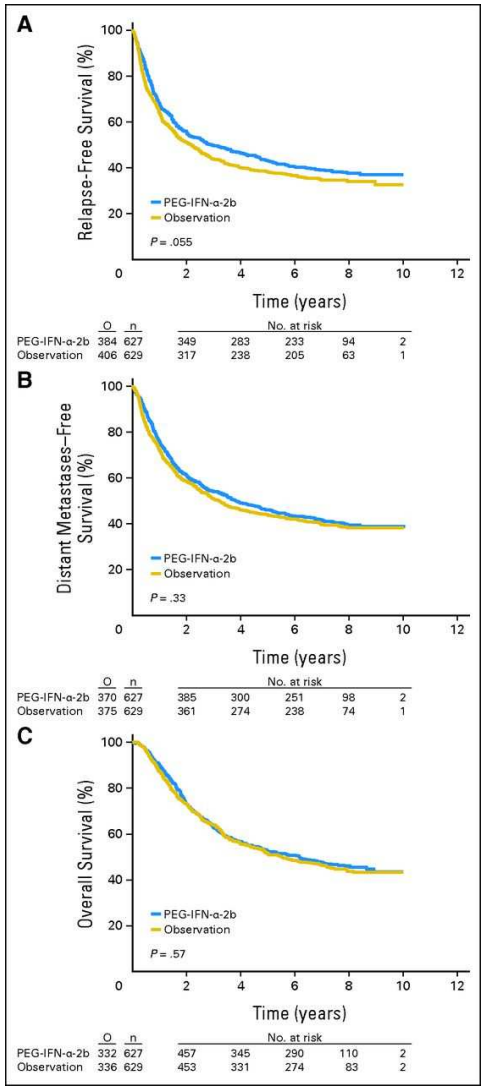


Eggermont A et al. Lancet 2008;372:117-26

Survival comparison for overall population

"Patients allocated to PEG-IFN-α-2b had a median RFS of 3.0 years versus 2.2 years for observation. This equates to a 13% reduction in risk of recurrence or death with PEG-IFN-α-2b (HR, 0.87; 95% CI, 0.76 to 1.00) compared with observation (*P* = .055).

There was a 4.5% (95% CI, 0.6% to 12.8%) absolute difference in the estimated 7-year rate of RFS: 39.1% for PEG-IFN-α-2b versus 34.6% for observation."



Eggermont A M et al. JCO 2012;30:3810-3818

JOURNAL OF CLINICAL ONCOLOGY ASCO

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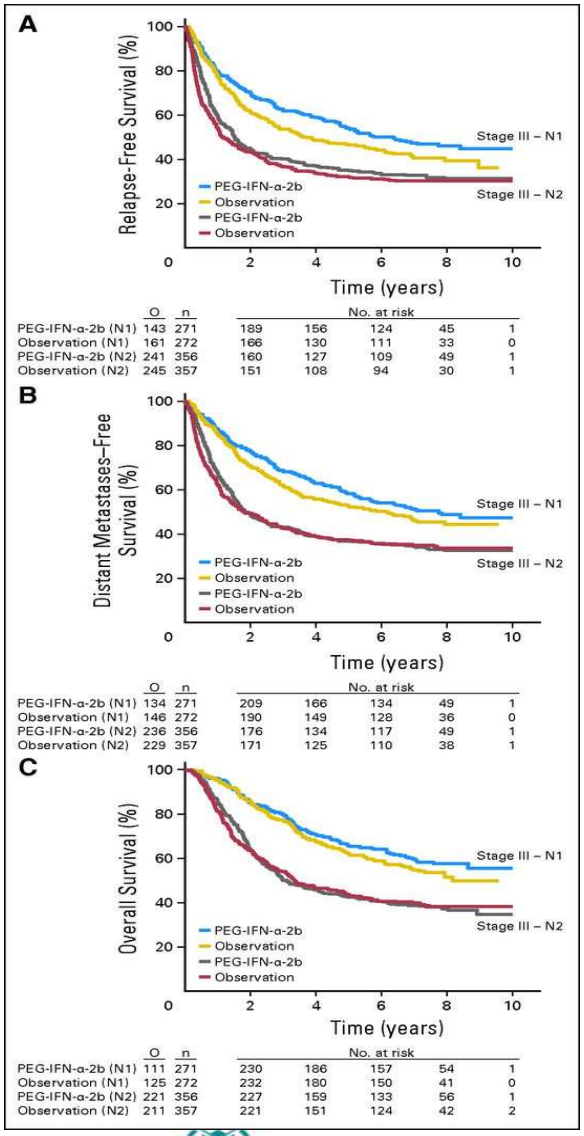
Outcome according to stage III (microscopic vs macroscopic nodal involvement) and randomly assigned treatment arm.

"The benefits of PEG-IFN-α-2b treatment were more pronounced in patients with earlier-stage III melanoma than in those with later-stage disease…In patients with microscopic nodal disease (N1), an 18% reduction in the risk of recurrence or death (RFS HR, 0.82; 99% CI, 0.61 to 1.10; *P* = .08) was observed"



Eggermont A M et al. JCO 2012;30:3810-3818

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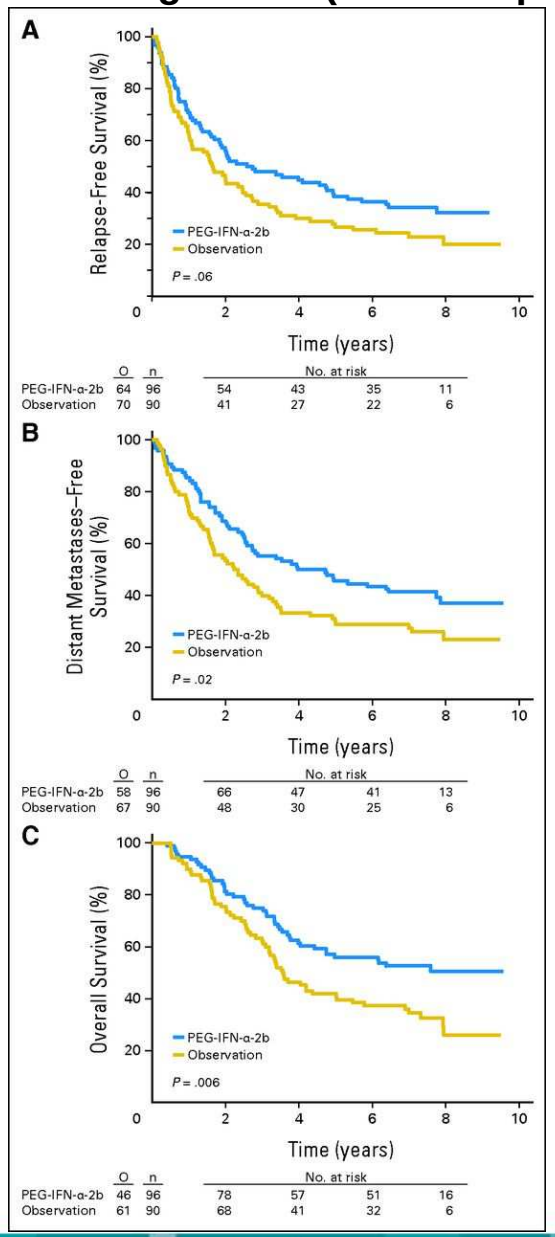
Stage III-N1 (microscopic nodal involvement only) patients with ulcerated melanoma.



An unplanned analysis was conducted in the subgroup of 186 patients with microscopic nodal involvement of any number of nodes who had an ulceration in the primary tumor. For this subgroup only, the impact of PEG-IFN-α-2b was important and was sustained over time for RFS (median 2.7 *v* 1.7 years; HR, 0.72; 99% CI, 0.46 to 1.13; *P* = .06), DMFS (median 4.0 *v* 2.3 years; HR, 0.65; 99% CI, 0.41 to 1.04; *P* = .02), and OS (not reached *v* median 3.6 years; HR, 0.59; 99% CI, 0.35 to 0.97; *P* = .006).

JOURNAL OF CLINICAL ONCOLOGY ASCO

Eggermont A M et al. JCO 2012;30:3810-3818

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PEG- IFN Toxicities

Adverse Event	PEG-IFN-α-2b (n = 608)						Observation (n = 613)					
	All		Grade 3		Grade 4		All		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any	606	99	348	57	49	8	527	86	77	13	23	4
Fatigue	579	95	90	15	8	1	265	43	7	1	0	
Liver function test*	483	79	66	11	2	< 1	237	39	9	1	2	< 1
Pyrexia	459	75	23	4	1	< 1	58	9	0		0	
Headache	430	71	25	4	0		123	20	4	1	0	
Myalgia	413	68	23	4	1	< 1	147	24	3	< 1	0	
Depression	366	60	39	6	1	< 1	155	25	2	< 1	1	< 1

Eggermont AM Lancet 372:117, 2008

ARTICLE

Interferon Alpha Adjuvant Therapy in Patients With High-Risk Melanoma: A Systematic Review and Meta-analysis

Simone Mocellin, Sandro Pasquali, Carlo R. Rossi, Donato Nitti

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.76	0.56	1.04	0.16	264	77/85
E1684 (Kirkwood, 1996)	0.67	0.50	0.88	0.14	287	90/103
AMCG (Pehamberger, 1998)	0.61	0.40	0.93	0.21	311	37/57
FCGM (Grob, 1998)	0.74	0.56	0.98	0.14	499	100/119
E1690 (Kirkwood, 2000)	0.81	0.65	1.01	0.11	642	236/254
SMG (Cameron, 2001)	0.80	0.52	1.23	0.22	96	32/35
E1694 (Kirkwood, 2001)	0.67	0.53	0.85	0.12	880	98/151
WHO (Cascinelli, 2001)	0.88	0.60	1.28	0,20	444	162/158
E2696 (Kirkwood, 2001)	0.59	0.32	1.07	0.31	107	28/38
UKCCCR (Hancock, 2004)	0.91	0.75	1.10	0.10	674	211/215
EORTC18871 (Kleeberg, 2004)	1.05	0.84	1.31	0.11	484	159/218
EORTC18952 (Eggermont, 2005)	0.88	0.75	1.03	0.08	1388	596/328
DeCOG (Garbe, 2008)	0.69	0.51	0.94	0.16	296	84/102
EORTC18991 (Eggermont, 2008)	0.84	0.72	0.97	0.08	1256	322/361
	0.82	0.77	0.87	0.03		

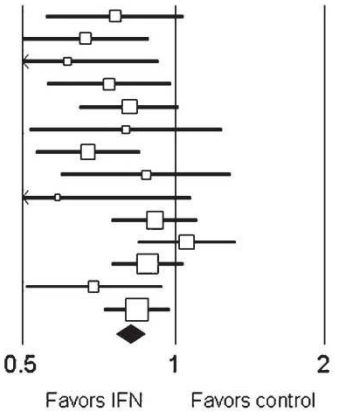


Figure 1. Forest plot of hazard ratios (HRs) (interferon alpha [IFN-α] vs control) for disease-free survival. **Squares** represent the hazard ratio of each single randomized controlled trial (RCT): The area is proportional to the weight in the meta-analysis according to the fixed-effect method, and the **horizontal line** represents the 95% confidence interval (CI). The **diamond** represents the estimated overall effect based on the fixed-effect meta-analysis of all RCTs (the **width of diamond** represents the 95% CI of the HR). LL = 95% confidence interval lower limit; UL = 95% confidence interval upper limit.

Mocellin S, et al. JNCI 2010;102:493-500

ARTICLE

Interferon Alpha Adjuvant Therapy in Patients With High-Risk Melanoma: A Systematic Review and Meta-analysis

Simone Mocellin, Sandro Pasquali, Carlo R. Rossi, Donato Nitti

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		

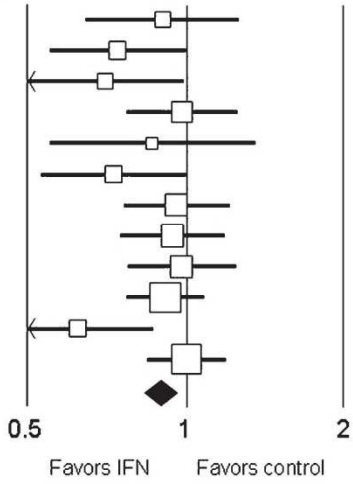
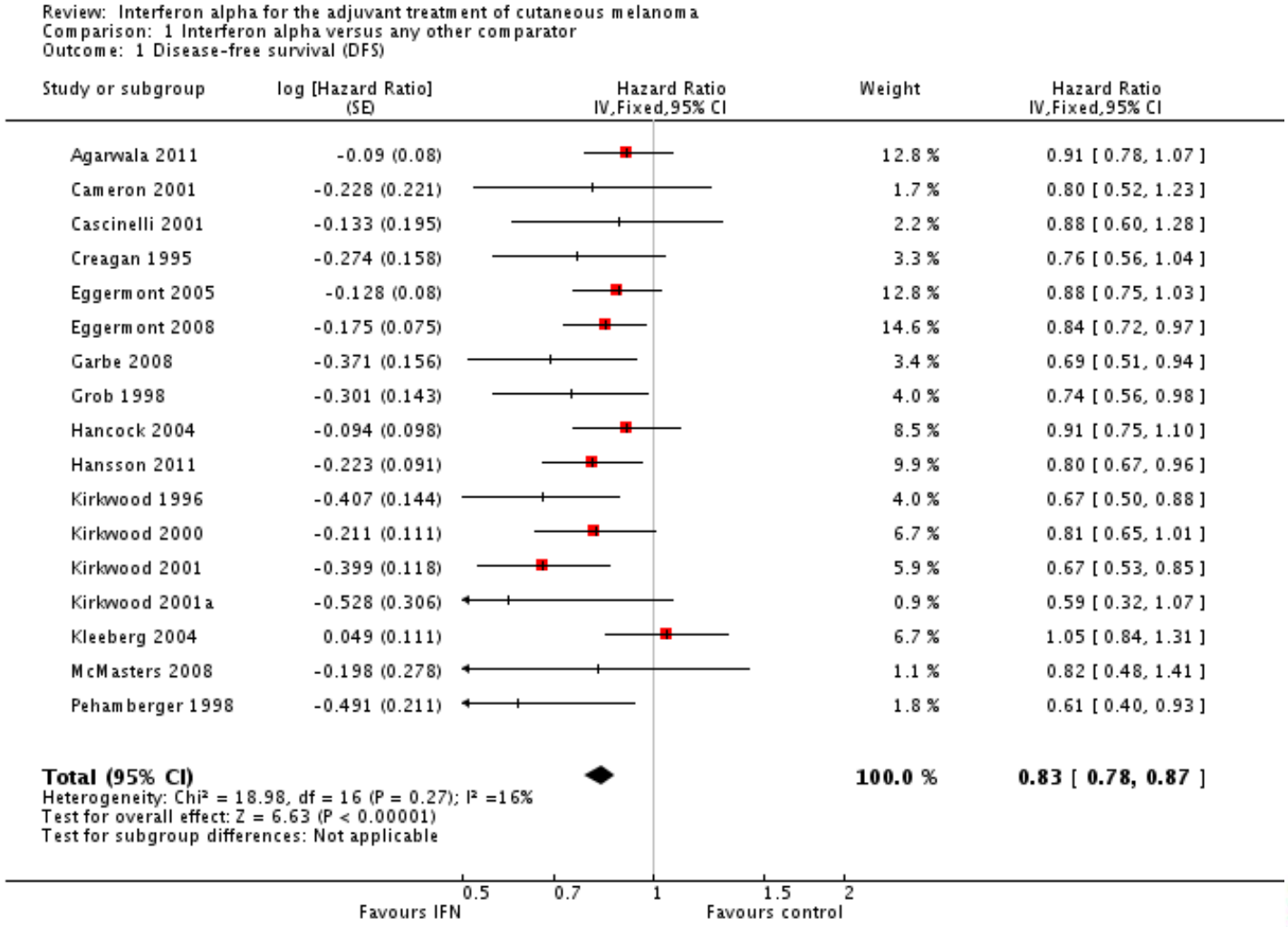


Figure 2. Forest plot of hazard ratios (HRs) (interferon alpha [IFN-α] vs control) for overall survival. **Squares** represent the hazard ratio of each single randomized controlled trial (RCT): The area is proportional to the weight in the meta-analysis according to the fixed-effect method, and the **horizontal line** represents the 95% confidence interval (CI). The **diamond** represents the estimated overall effect based on the fixed-effect meta-analysis of all RCTs (the **width of diamond** represents the 95% CI of the HR). LL = 95% confidence interval lower limit; UL = 95% confidence interval upper limit.

Mocellin S, et al. JNCI 2010;102:493-500

Disease-Free Survival



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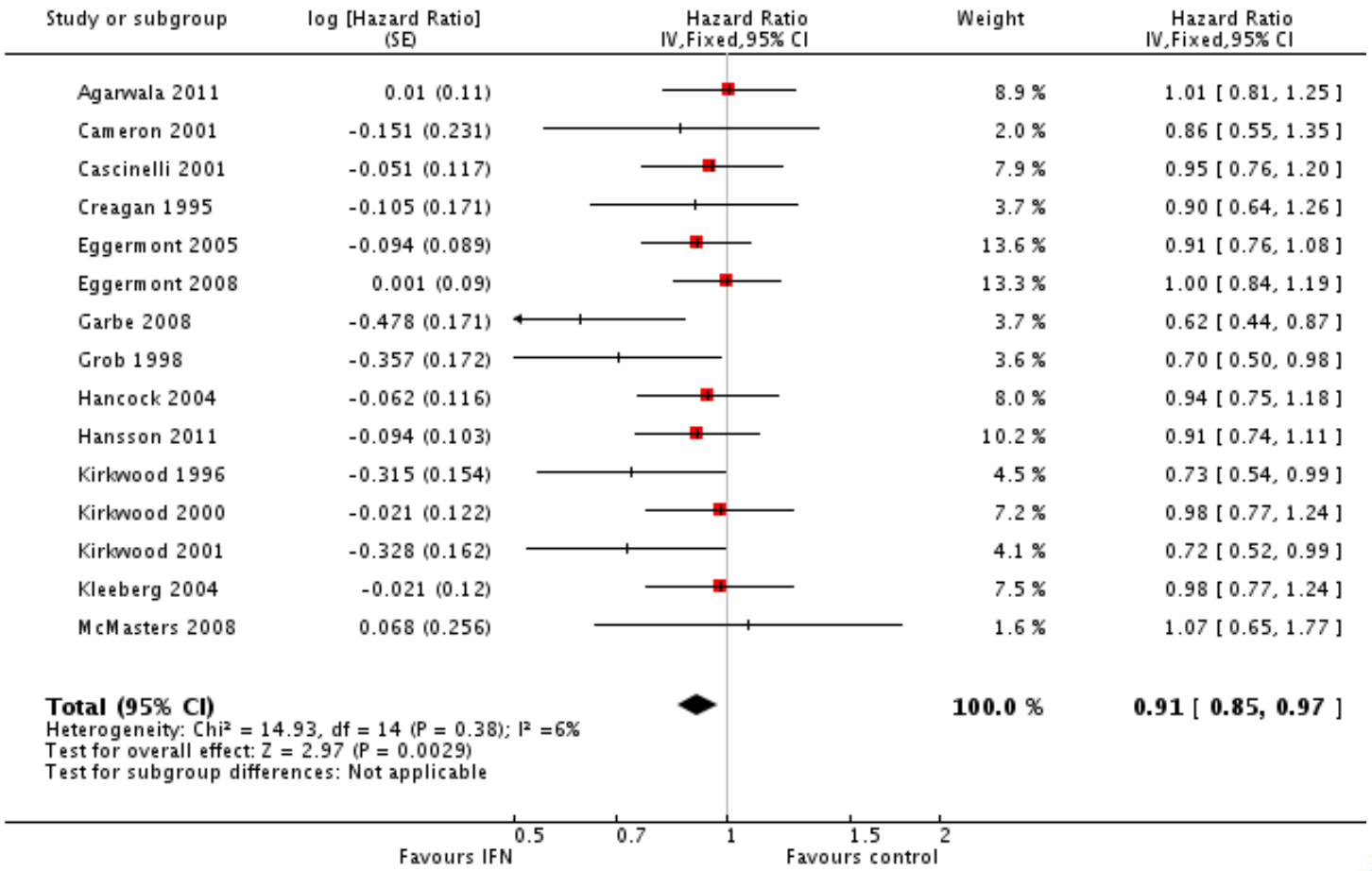
Overall Survival

Review: Interferon alpha for the adjuvant treatment of cutaneous melanoma
Comparison: 1 Interferon alpha versus any other comparator
Outcome: 2 Overall Survival (OS)



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Interferon Conclusions

- **Clear effect on the natural history of melanoma**
- **Improvement in Disease Free survival**
  - Mocellin JNCI 2010 Hazard Ratio 0.82
- **Improvement in Overall Survival**
  - Mocellin JNCI 2010 Hazard Ratio 0.89
- **No optimal IFN-a dose and/or treatment duration or a subset of patients more responsive to adjuvant therapy was identified**

Question 1

Patients that appear more likely to benefit from pegylated interferon have:

A. Macroscopic regional nodal disease found on SLN biopsy

B. Palpable regional nodal disease

C. Stage IV subcutaneous disease

D. Ulcerated primary tumors with micrometastatic disease in regional nodes

Answer: D

Interleukin-2 (IL-2)

- **15.5 kD glycoprotein hormone produced by lymphocytes (described by Gallo in 1976, recombinant IL-2 available in 1984)**
- **Major functional role in immune regulation because of its ability to stimulate the proliferation of activated T lymphocytes**

Course of Therapy

Cycle 1

Interleukin-2
600,000
or
720,000 IU/kg
q8h by short
IV infusion

5 to 6 days
14 doses

Rest
7 to 9 days

Cycle 2

Interleukin-2
600,000
or
720,000 IU/kg
q8h by short
IV infusion

5 to 6 days
14 doses

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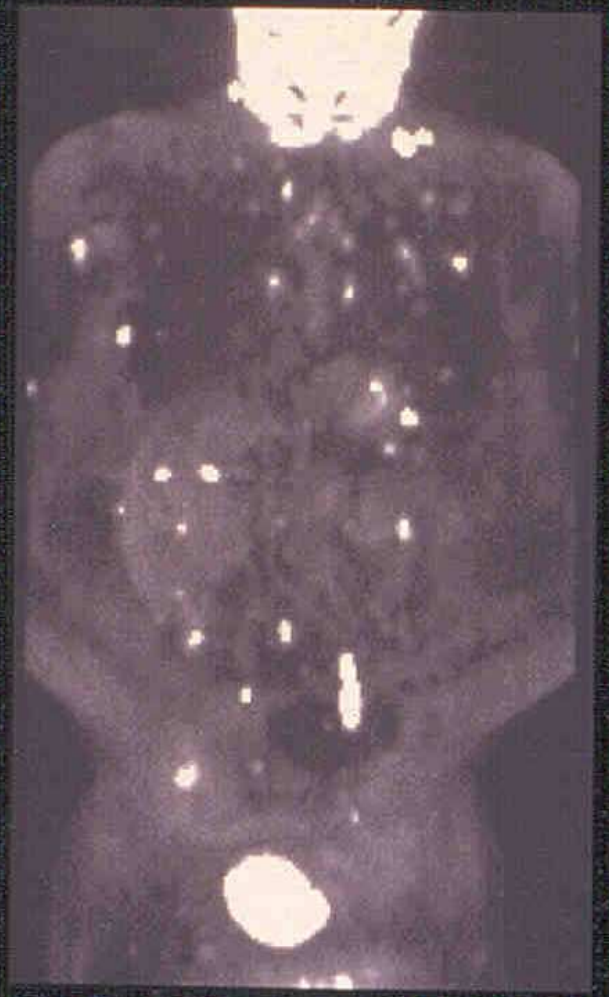
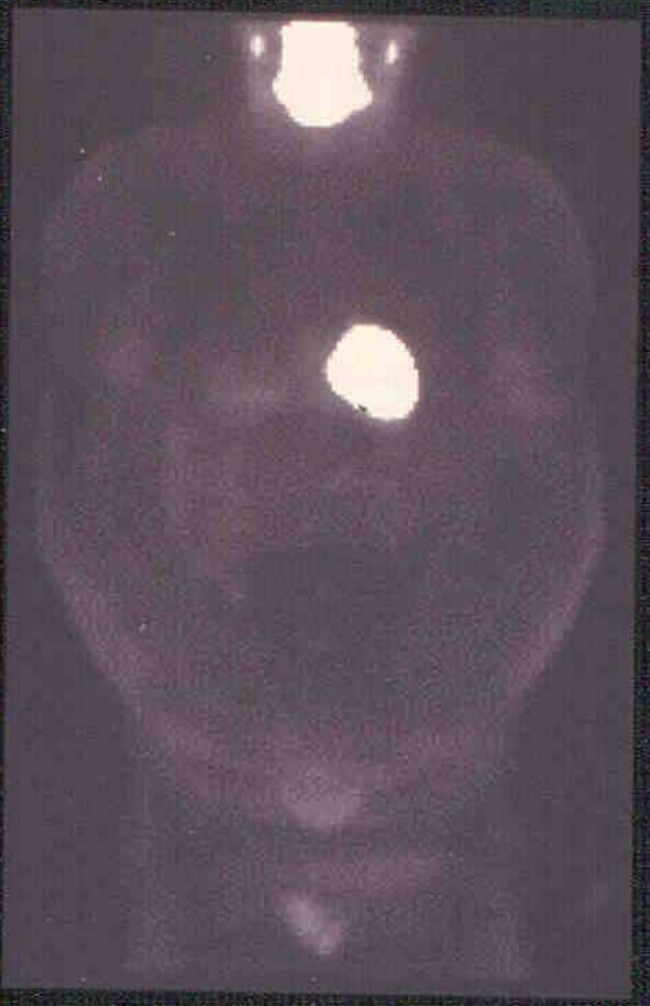
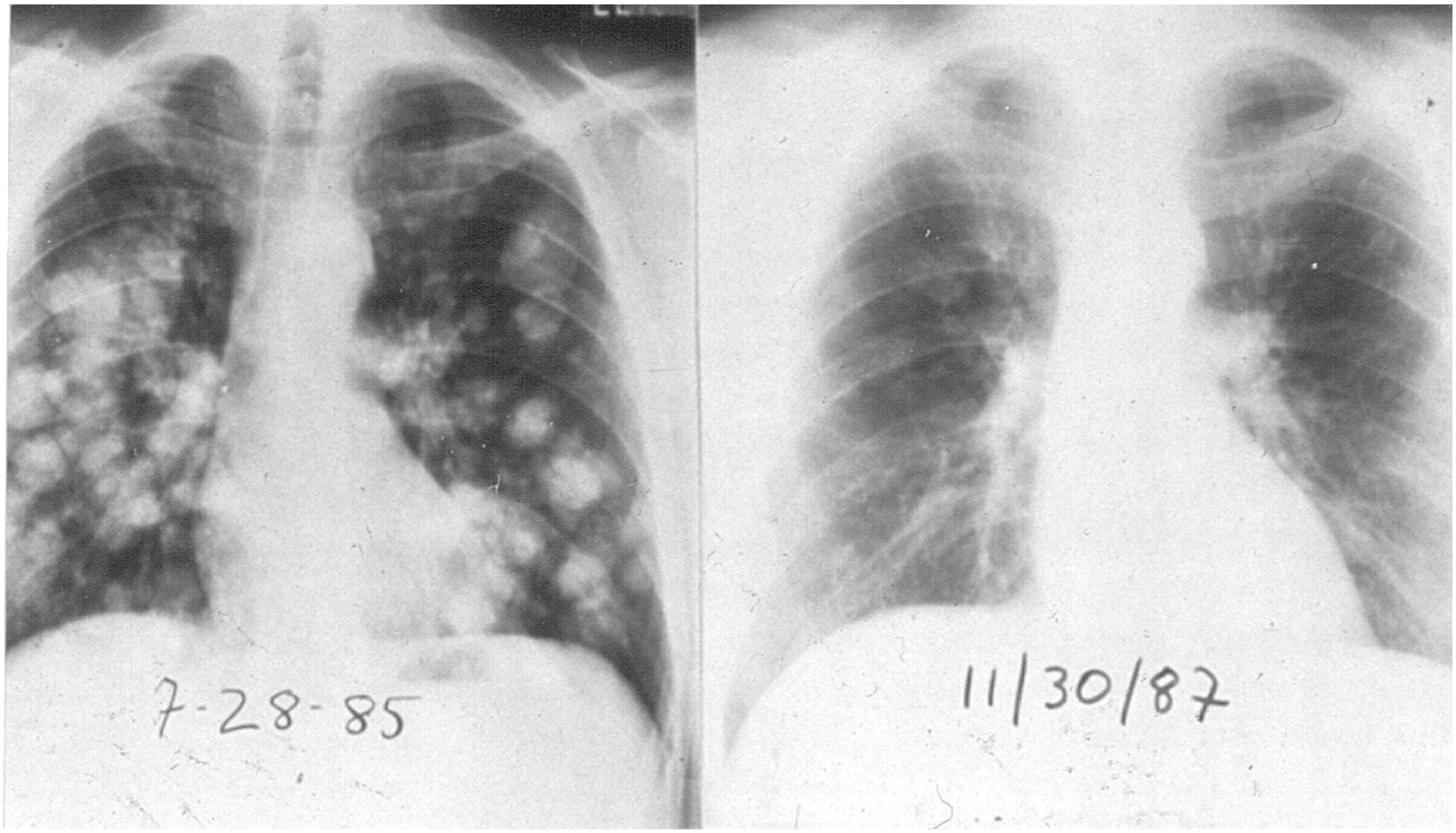
Metastatic Melanoma



Staging FDG PET Scan



Post Interleukin-II Therapy



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Response of Patients with Metastatic Cancer Treated Using High-dose Bolus Interleukin-2: NCI Experience

Diagnosis	Total	CR	PR	CR + PR
		Number of patients (%)		
Melanoma	182	12 (7%)	16 (9%)	28 (15%)
Renal Cell Cancer	227	21 (9%)	22 (10%)	43 (19%)
Total	409	33 (8%)	38 (9%)	71 (17%)

Patients accrued between Sept. 1985 and Nov. 1996.
Follow-up as of April 1, 1999 (median follow-up 8.2 yrs)

Duration of Response in Patients with Metastatic Cancer Treated Using High-dose Bolus Interleukin-2: NCI Experience

Diagnosis	CR	PR
	Months	
Melanoma	161+, 109+, 108+ ,106+, 104+, 97+, 93+, 84+, 84+, 83+, 16, 12	35, 31, 19, 10, 10 8, 8, 7, 7, 6, 5, 5, 5, 4, 4, 2
Renal Cell Cancer	147+, 139+, 136+, 107+, 107+, 103+, 99+, 99+, 92+, 87+, 83+, 77+, 76+, 73+, 62+, 52+, 46+, 35, 23, 19, 19	52, 30, 30, 22, 20, 17, 16, 15, 14, 14, 13, 11, 9, 8, 8, 7, 7, 6, 4, 4, 4, 4

"+" indicates ongoing response, as of April 1, 1999.
Of 33 patients with complete response, 27 remain in CR at 46 to 161 months

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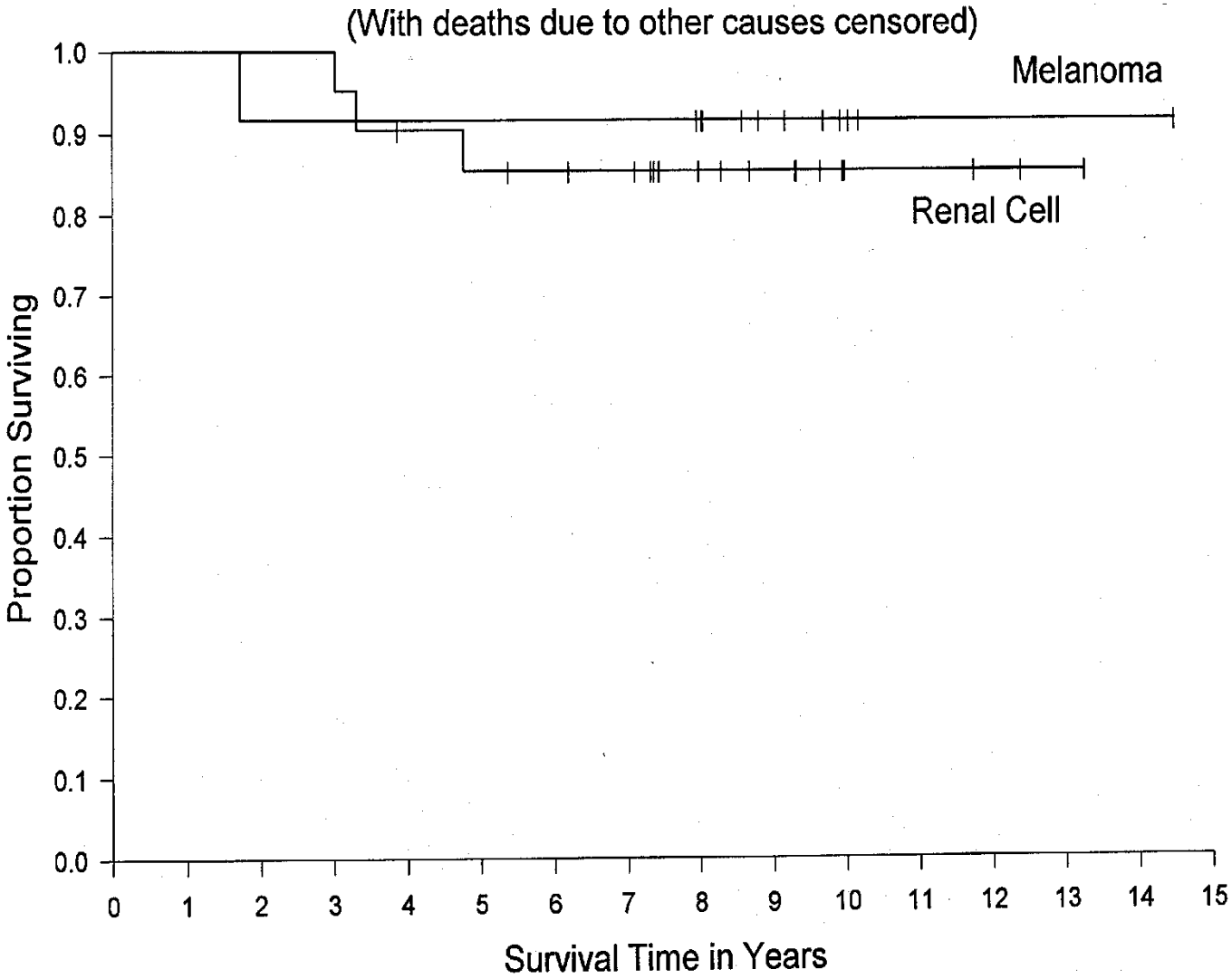
Complete and partial responses to high dose IL-2 treatment, Carolinas Medical Center

	Renal cell cancer			Melanoma		
Treatment date	Number of patients treated	Response rate (CR+PR) No. (%)	Duration of all responses (months)*	Number of patients treated	Response rate (CR+PR) No. (%)	Duration of all responses (months)*
1998 through 2011	104	**27 (26)** [CR=8 (7.7%) PR=19 (18.3%)]	CR: 122+, 106+, 70, 37+, 23, 20+, 19+, 15 PR: 84+, 47+, 24, 22, 19, 18, 14, 17, 16, 13, 11, 11, 10, 9, 8, 7, 6, 5, 3	117	**16 (13.7)** [CR=7 (6%) PR=9 (7.7%)]	CR: 114+, 54+, 48+, 43, 41+, 19+, 13+ PR: 99+, 74+, 52+, 12, 8, 8, 6, 5, 4,

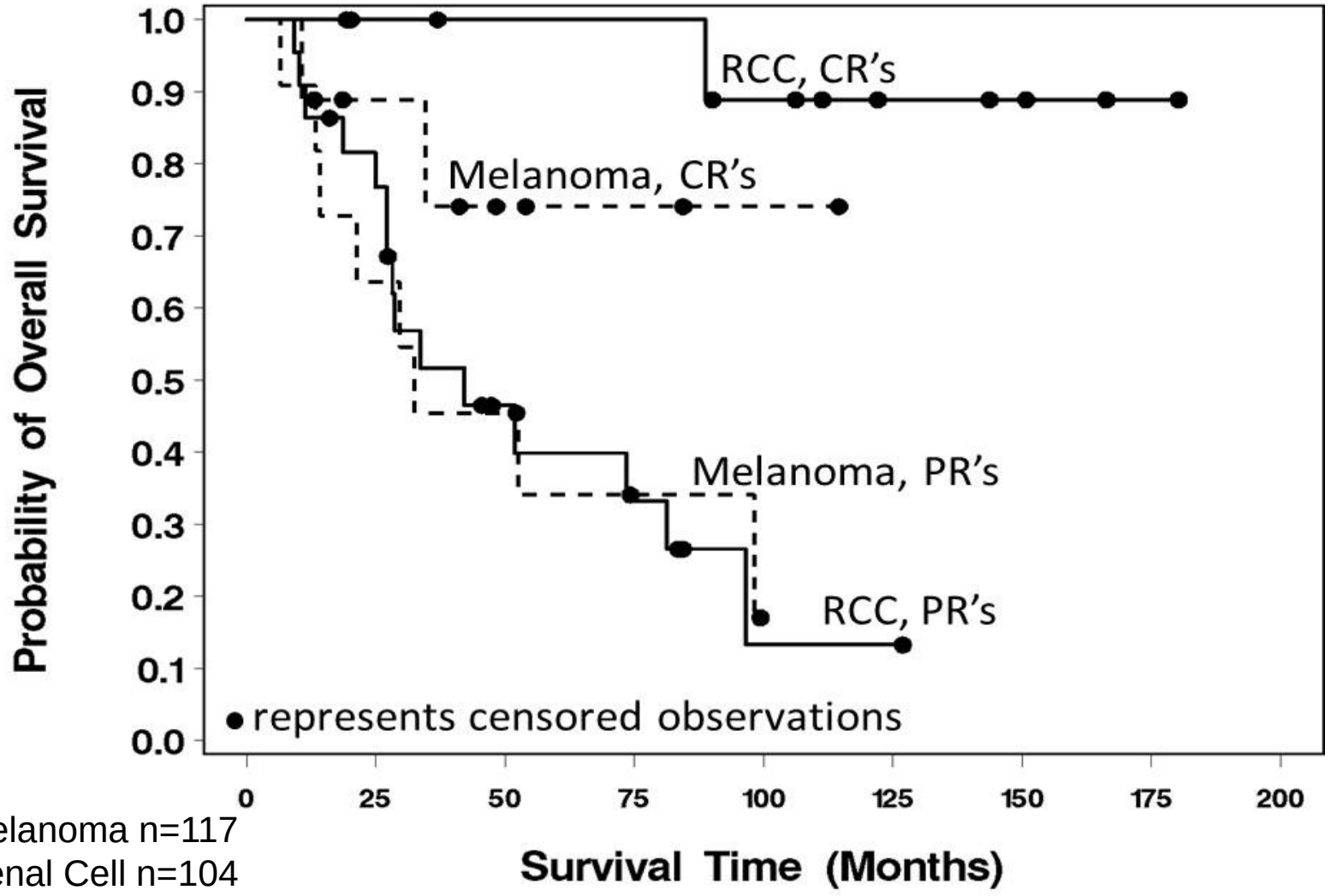
CR=complete response
PR=partial response
*Duration of response on 12/31/2011 for patients completing IL-2 treatment; + indicates ongoing response

Complete Response to Treatment with High-Dose IL-2



Courtesy Douglas Schwartzentruber - NCI Surgery Branch

Overall Survival Carolinas Medical Center High Dose IL2 Experience



Amin A, White R, *Oncology* 2013

Melanoma n=117
Renal Cell n=104

Expected toxicities with IL-2 treatment

System	Toxicities	Percent IL-2 Courses in which Grade 3 or 4 Toxicity Occurred N=354
Cardiovascular	Atrial or ventricular arrhythmias	10.2
	Hypotension requiring pressors	35.6
Fatigue	Difficulty performing some activities	13.6
GI	Nausea and vomiting (severe)	1.7
	Diarrhea (severe)	3.1
Hematologic	Low platelet count (<50,000)	9.6
	Low white blood count (<1,000)	0.8
Neurological	Anxiety or depression (severe)	1.4
	Confusion	2.0
Pulmonary	Shortness of breath (severe)	1.7
Renal	Elevated creatinine	0.3
	Peripheral edema	0.6
	Poor urine output	7.3

Data from Carolinas Medical Center, Charlotte, NC

Sites of Melanoma vs Response

Site of Metastases		No. of Patients	Responders		P_2
			No.	%	
SQ and/or cutaneous alone					
	Yes	28	15	53.6	.000001*
	No	346	43	12.4	
SQ/cutaneous + LN alone					
	Yes	23	5	27.7	.38
	No	351	53	15.1	
LN alone					
	Yes	29	6	20.7	.42
	No	345	52	15.1	
Visceral alone					
	Yes	69	8	11.6	.32
	No	305	50	16.4	
Visceral + SQ/cutaneous alone					
	Yes	61	9	14.8	.86
	No	313	49	15.7	
Visceral + LN alone					
	Yes	56	5	8.9	.14
	No	318	53	16.7	
Bone + any other site(s)					
	Yes	30	5	16.7	.80
	No	344	53	15.4	
Brain + any other site(s)					
	Yes	21	1	0.05	.056
	No	353	57	16.1	

*Odds ratio, 8.13; 95% confidence interval, 3.33 to 19.81.
Abbreviations: SQ, subcutaneous; LN, lymph node(s).

Phan GQ *JCO* 2001

Safety of High-dose IV Bolus rIL-2 Therapy (720,000 IU/kg q.8h)

With patient selection and experience managing side effects, high-dose rIL-2 is safe.

- **The NCI experience**
- **No treatment-related deaths in 809 consecutive patients treated at the NCI.**

At CMC 2 deaths in 1002 cycles in 337 patients since 1995*

* all IV dose regimens through 2013

Levine Cancer Institute

Table 1 High-Dose Interleukin-2 (IL-2) in Advanced Renal Cell Carcinoma

Study	N	Dose	Overall Response Range	Response Duration
7 Phase II studies[10]	255	600,000–720,000 IU/kg	15% CR = 7% PR = 8%	Overall median: 54 mos (3 to 131+) Median in CRs: 80+ mos (7 to 131+) Median in PRs: 20 mos (3 to 126+)
Randomized phase II (two-arm)[21]	155	720,000 IU/kg	21% (CR = 11, PR = 22)	8/11 ongoing CRs at 9.3 yrs
	149	72,000 IU/kg	13% (CR = 6, PR = 13)	3/6 ongoing CRs at 10.1 yrs
Randomized phase II (three-arm)[21]	96	720,000 IU/kg	21%	8/11 ongoing CRs at 9.3 yrs
	93	72,000 IU/kg	11%	3/6 ongoing CRs at 10.1 yrs
	94	SQ low-dose	10%	1 CR, 78+ mos
Phase III[11]	91	SQ low-dose IL2 + IFN	10% (CR = 3)	15 mos
	95	600,000 IU/kg	23% (CR = 8)	24 mos
NCI experience (single institution)[12]	259	720,000 IU/kg	20% (CR = 23, PR = 30)	In 21 pts with CR, median survival not reached at 221+ mos
Phase II "SELECT" study[65]	120	600,000 IU/kg	29%	20 responders (4 to 35+ mos)
LCI experience (single institution)[a]	104	720,000 IU/kg	26% (CR = 8, PR = 19)	5/8 CRs: ongoing response at 122+ mos 2/19 PRs: ongoing response at 84+ mos

[a]White RL, Amin A, et al (unpublished data).
CR = complete response; IFN = interferon; LCI = Levine Cancer Institute; NCI = National Cancer Institute; PR = partial response; SQ = subcutaneous.

Amin A, White R, Oncology 2013;July:680-696

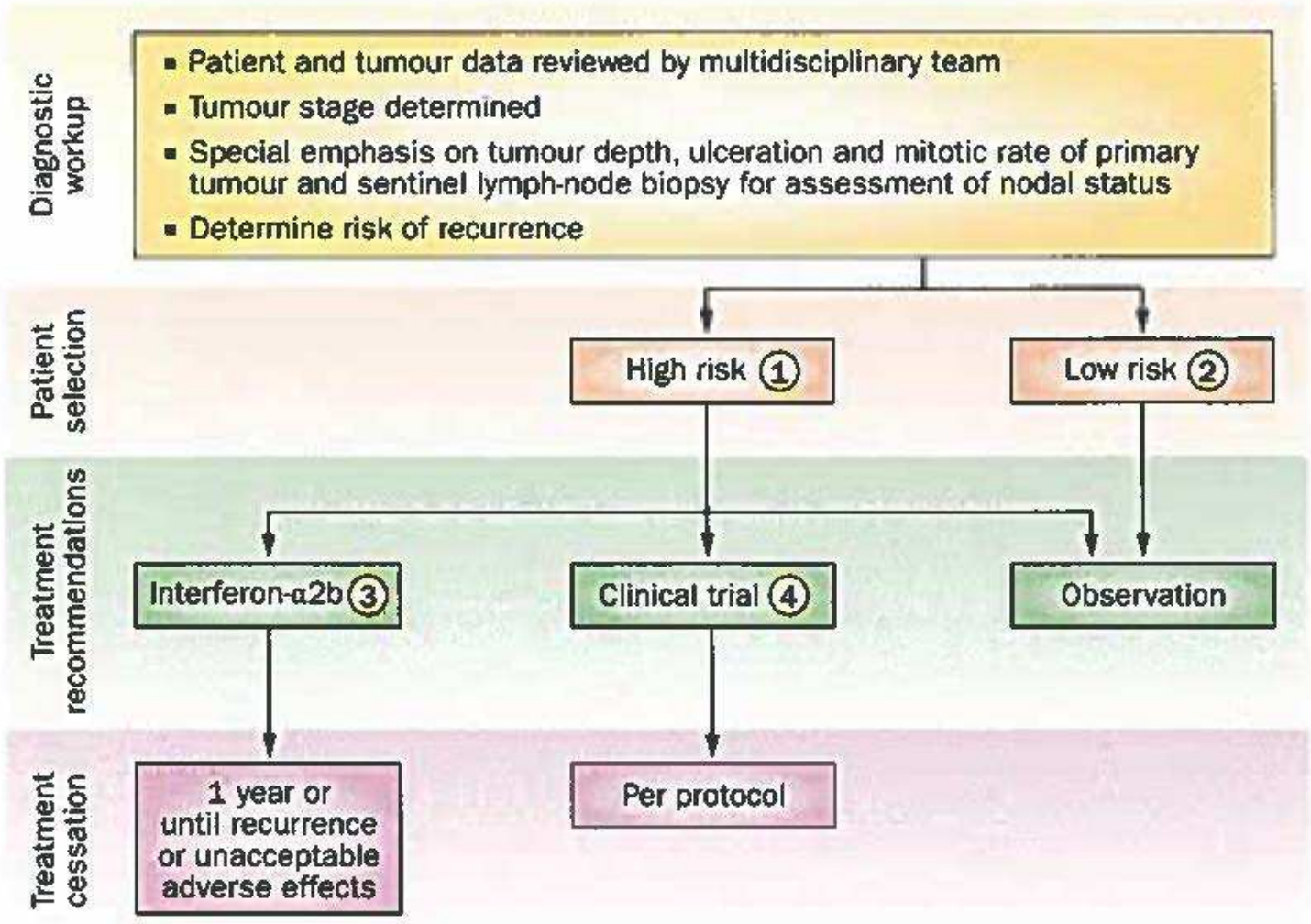
Table 2 High-Dose Interleukin-2 (IL-2) in Advanced Melanoma

Study	N	Dose	Overall Response Range	Response Duration
8 Phase II studies[13]	147	4 Studies 720,000 IU/kg		Median response duration not reached
	118	3 Studies 600,000 IU/kg		
	5	1 Study 360,000/540,000 IU/kg		
	Total: 270		16% CR = 6% PR = 10%	Overall median: 9 mos (1 to 122+) Median in CRs: NR (3 to 122+) Median in PRs: 6 mos (1 to 111+)
3 Phase II studies[14]	121	600,000 IU/kg + gp100 vaccine	16% CR = 9% (n = 11) PR = 7%	9/11 CRs maintained 30+ to 73+ mos
NCI experience (single institution)[15]	305	720,000 IU/kg	13% CR = 4% (CR = 13, PR = 26)	11/13 CRs: ongoing response at 253+ mos
	379	720,000 IU/kg + vaccine	16% CR=3% (CR = 13, PR = 46)	4/13 CRs: ongoing response at 120+ mos
Phase III[16]	185	720,000 IU/kg vs 720,000 IU/kg + gp100 vaccine	6% 16%	Not reported
LCI experience (single institution)[a]	117	720,000 IU/kg	13.7% (CR = 7, PR = 9)	6/7 CRs: ongoing responses at 114+ mos 3/9 PRs: ongoing responses at 99+ mos

[a]White RL, Amin A, et al (unpublished data).
CR = complete response; gp100 vaccine = glycoprotein 100 peptide vaccine; LCI = Levine Cancer Institute; NCI = National Cancer Institute; PR = partial response.

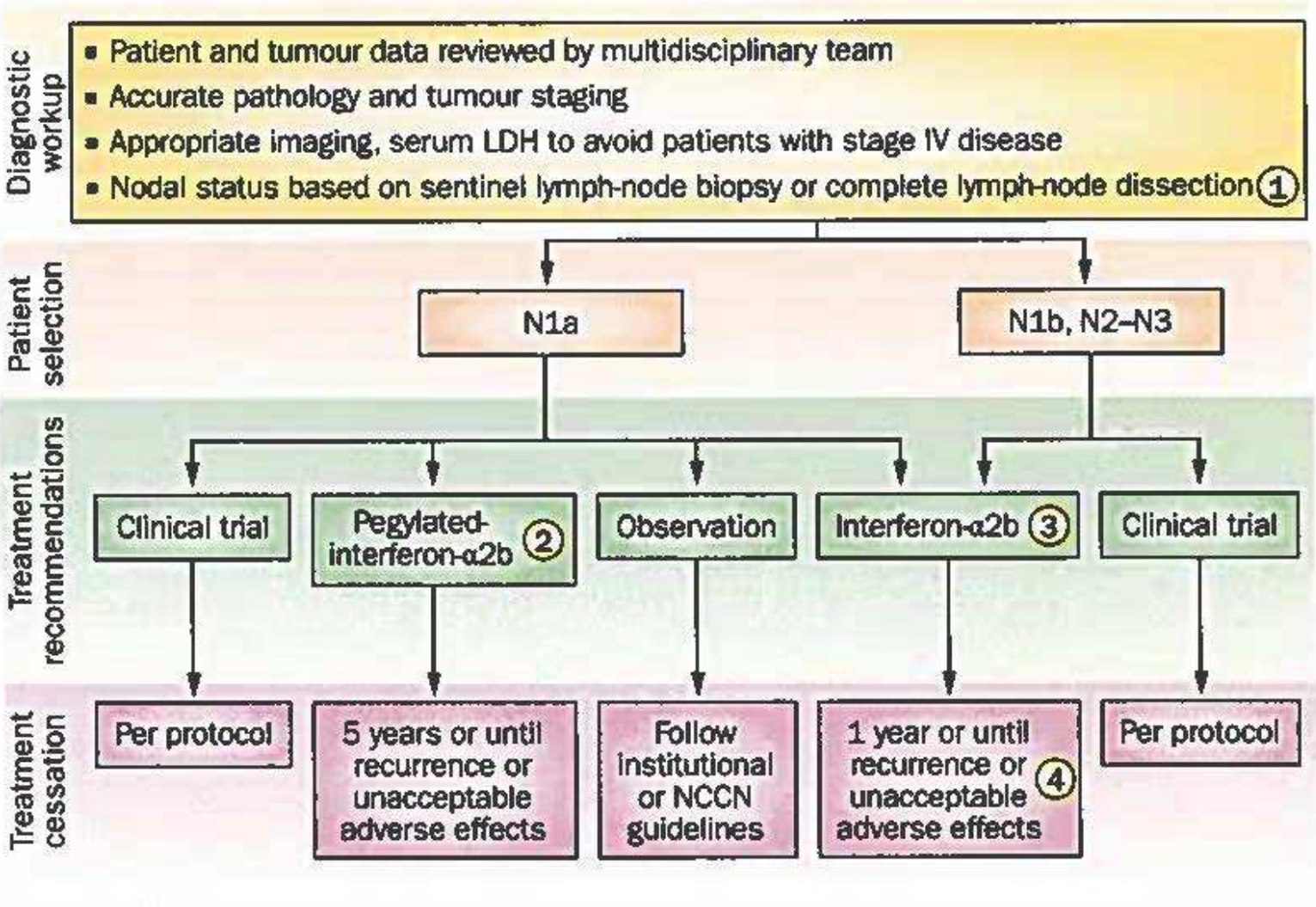
Amin A, White R, Oncology 2013;July:680-696

Stage II melanoma treatment algorithm

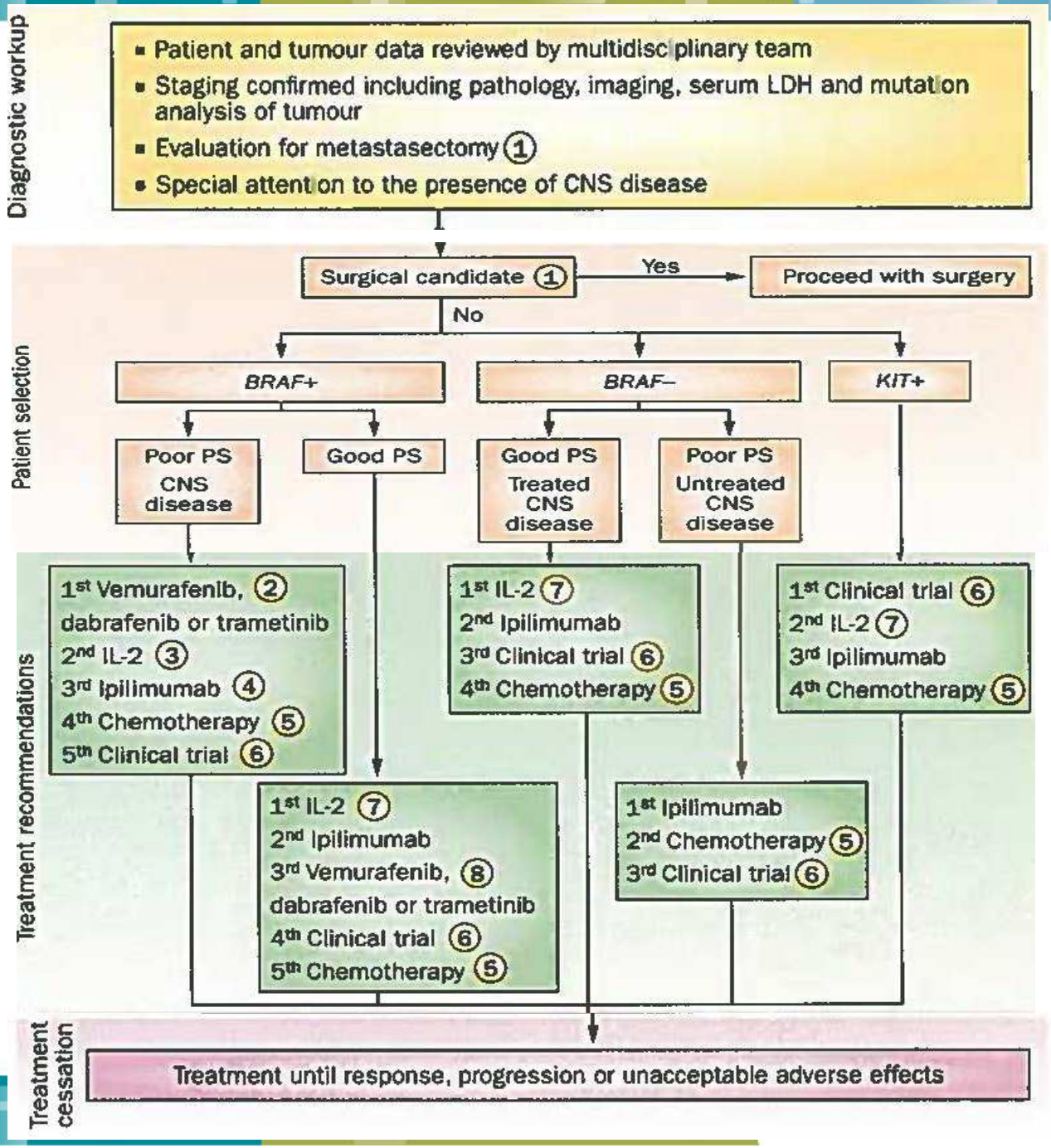


Kauffman HL, et al. Nature Reviews 2013;10:588-598

Stage III Treatment Algorithm



Kauffman HL, et al. Nature Reviews 2013;10:588-598


Diagnostic workup
Patient and tumour data reviewed by multidisciplinary team
Staging confirmed including pathology, imaging, serum LDH and mutation analysis of tumour
Evaluation for metastasectomy (1)
Special attention to the presence of CNS disease
Patient selection
Surgical candidate (1)
Yes
Proceed with surgery
No
BRAF+
BRAF–
KIT+
Poor PS CNS disease
Good PS
Good PS Treated CNS disease
Poor PS Untreated CNS disease
Treatment recommendations
1st Vemurafenib, (2) dabrafenib or trametinib
2nd IL-2 (3)
3rd Ipilimumab (4)
4th Chemotherapy (5)
5th Clinical trial (6)
1st IL-2 (7)
2nd Ipilimumab
3rd Clinical trial (6)
4th Chemotherapy (5)
1st Clinical trial (6)
2nd IL-2 (7)
3rd Ipilimumab
4th Chemotherapy (5)
1st IL-2 (7)
2nd Ipilimumab
3rd Vemurafenib, (8) dabrafenib or trametinib
4th Clinical trial (6)
5th Chemotherapy (5)
1st Ipilimumab
2nd Chemotherapy (5)
3rd Clinical trial (6)
Treatment cessation
Treatment until response, progression or unacceptable adverse effects

titute

Which of the below is true regarding Interleukin 2 treatment

A. Mortality is 20% with 20% percent response rate

B. Interleukin 2 has no role in the current treatment of melanoma or renal cell cancer

C. In patients with melanoma those with bone and brain lesions are the most likely to benefit

D. Long term durable complete responses are the hallmark of IL2 therapy

Answer: D