Interferon
Indications and Clinical Management in Melanoma

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Disclosures

- **Dr. Sondak is a compensated consultant for Merck, GSK, Amgen, Provectus and Navidea**

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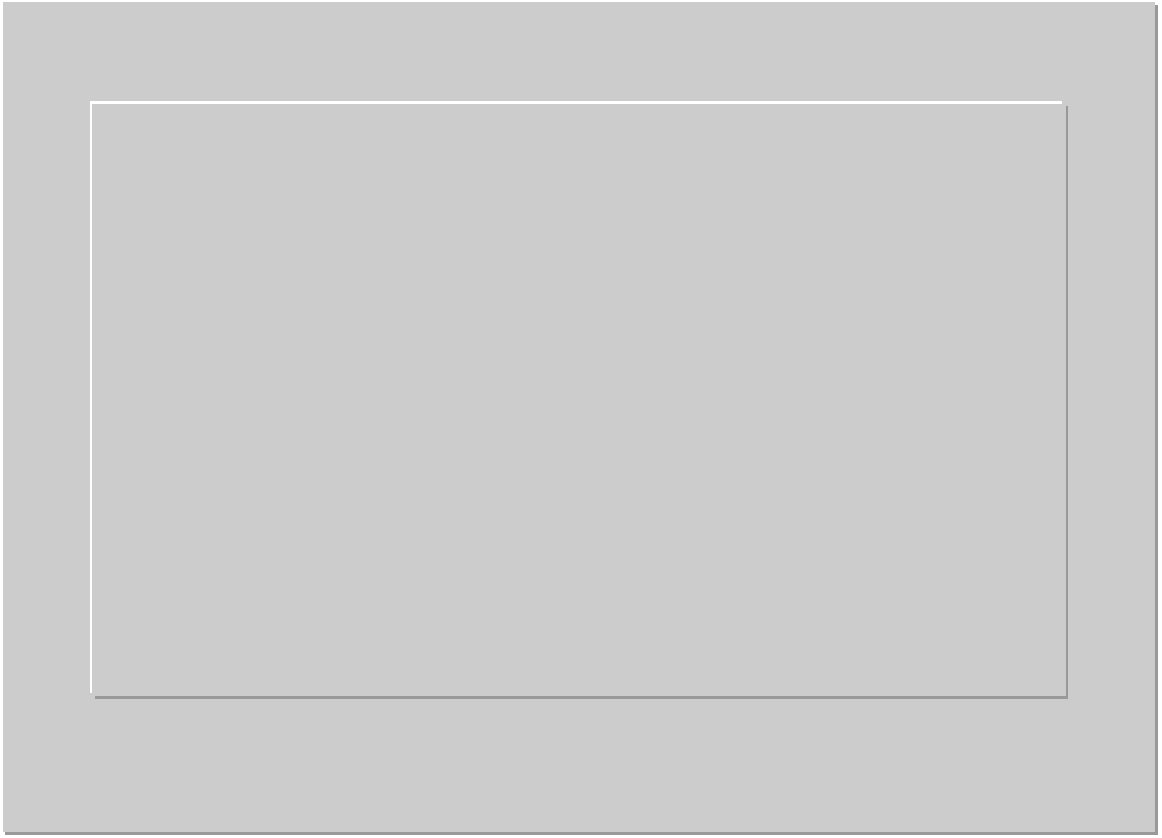
Stage II immunotherapy algorithm

Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for cutaneous melanoma



Kaufman et al, Nat Rev Clin Oncol 2013;10:588

Stage III immunotherapy algorithm

Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for cutaneous melanoma

(1) Limited data on adjuvant therapy without lymphadenectomy for sentinel node positive cases

(3) Level A data for RFS benefit for high-dose IFN for one year

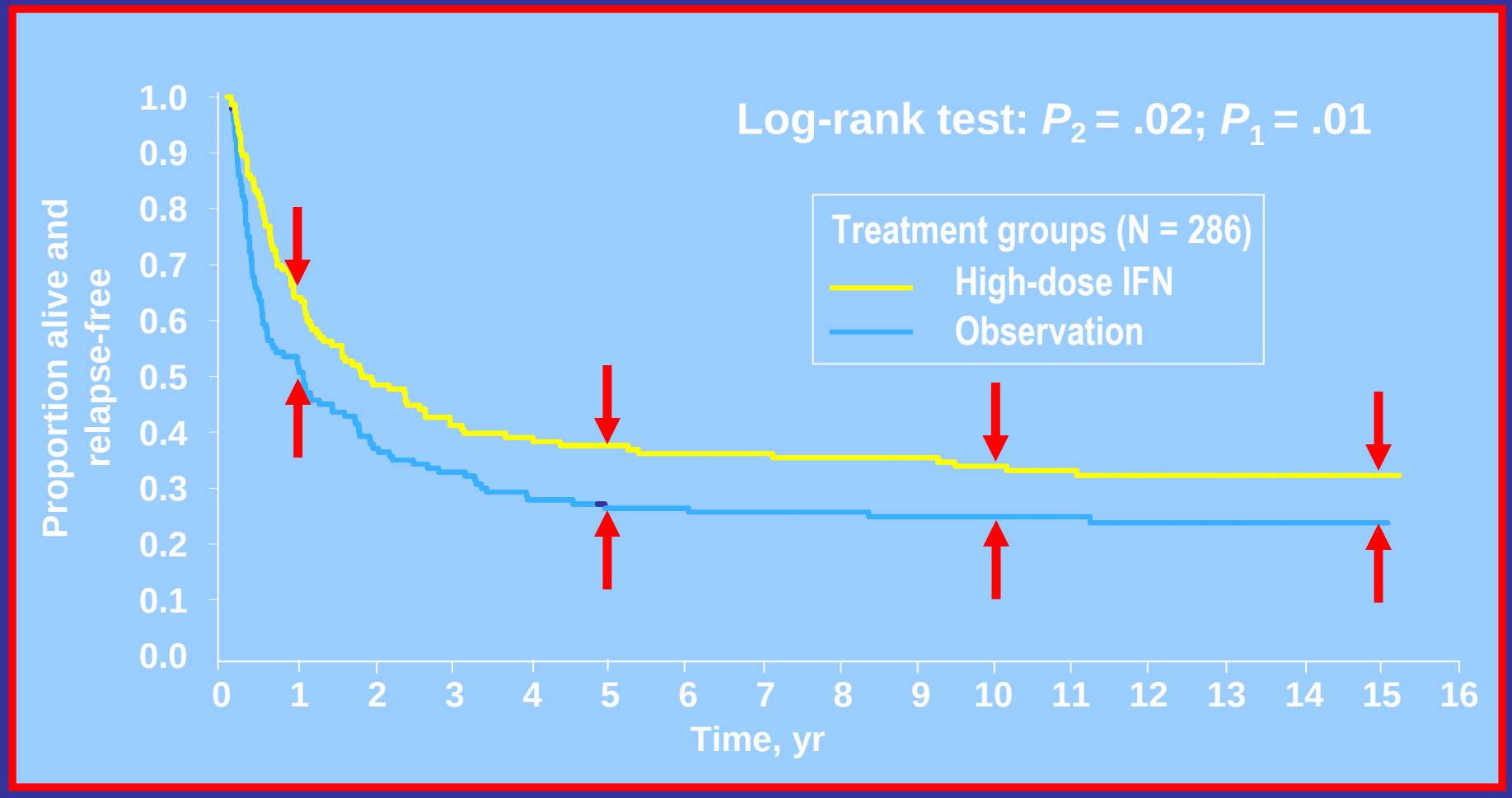
with ulceration of the primary

Kaufman et al, Nat Rev Clin Oncol 2013;10:588

E1684

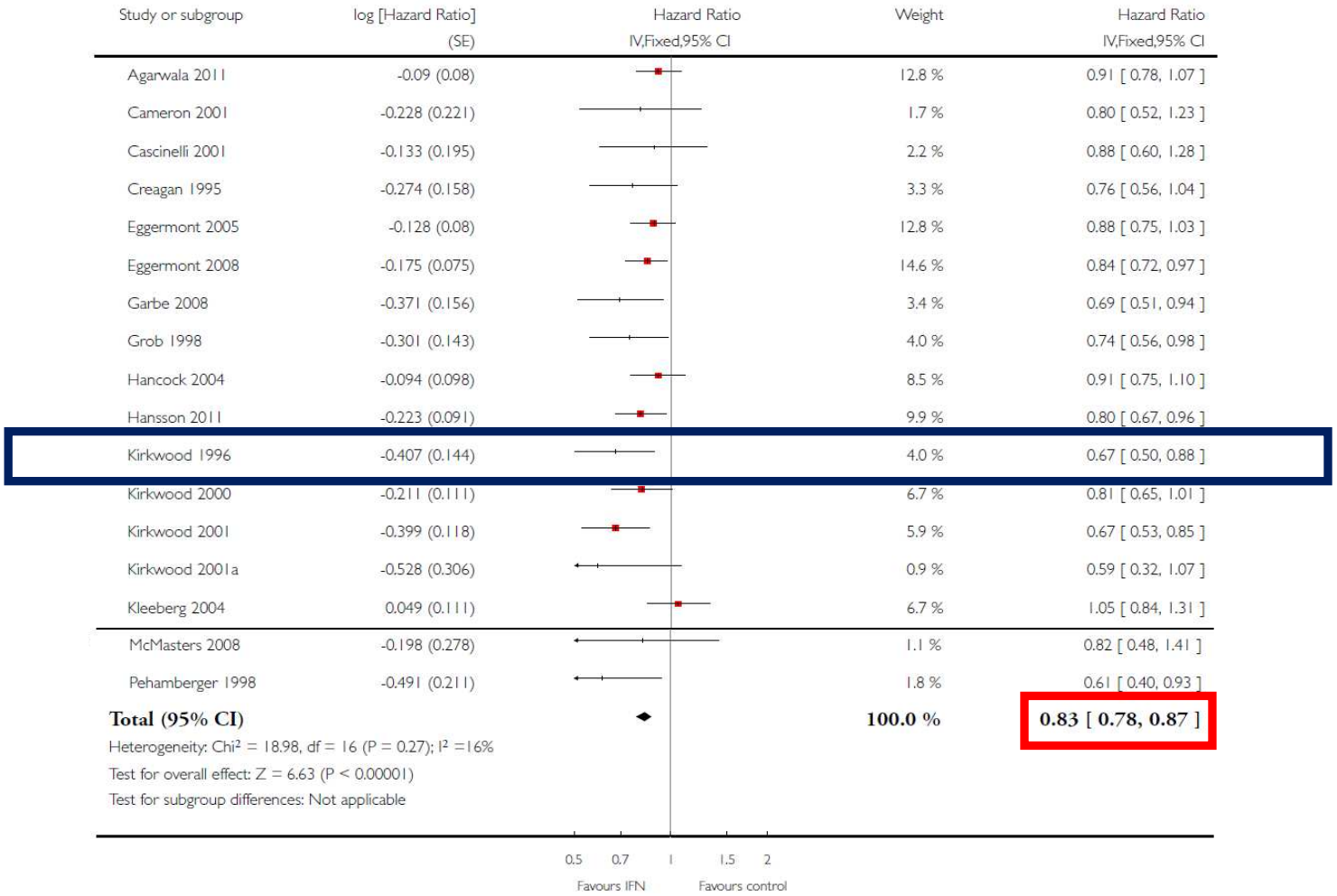
Relapse-free survival

Extended follow-up



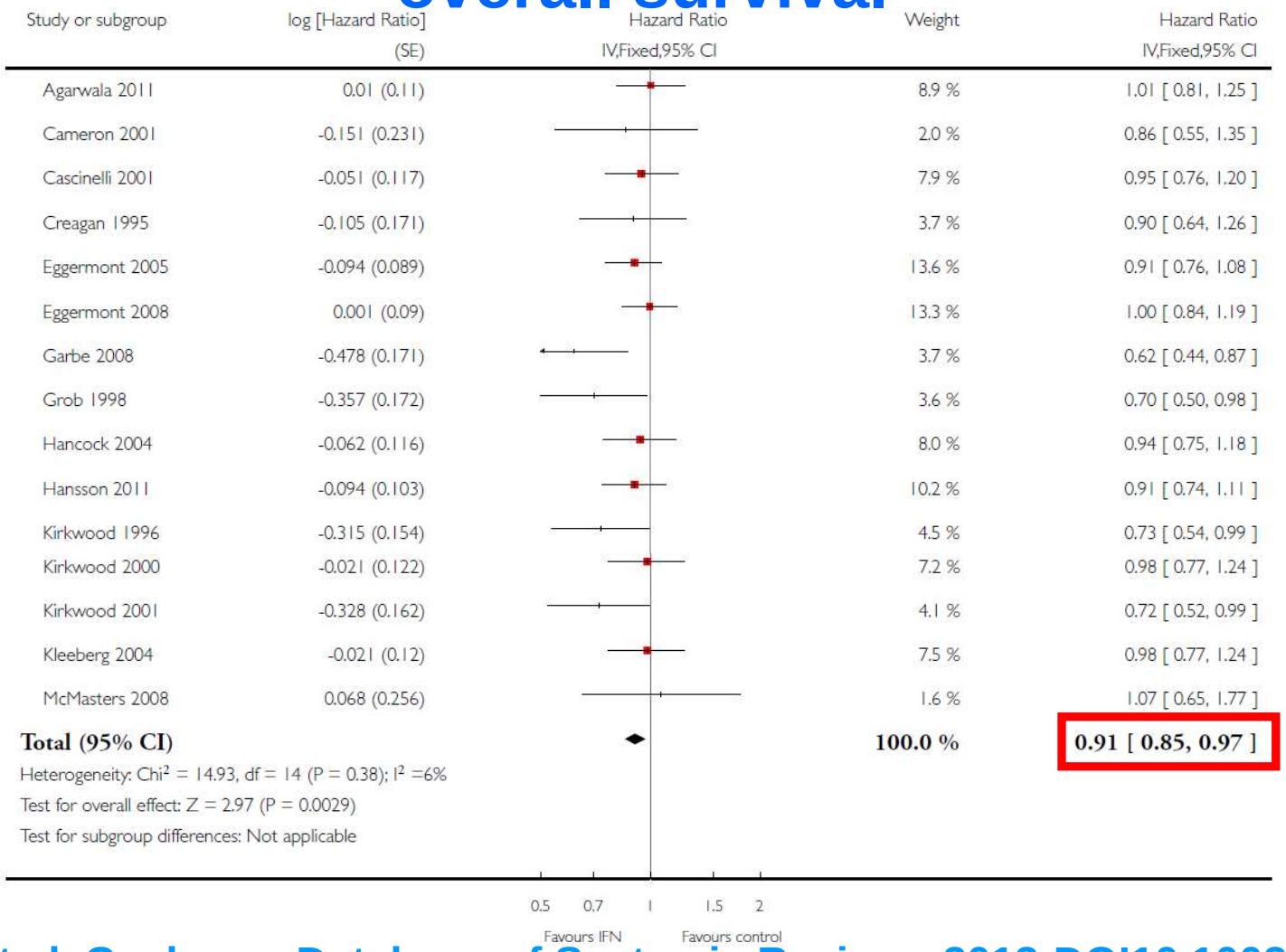
Kirkwood et al Clin Cancer Res 2004;10:1670

Meta-analysis of interferon impact on relapse-free survival



Mocellin et al, Cochrane Database of Systemic Reviews 2013;DOI10.1002/14651858

Meta-analysis of interferon impact on overall survival



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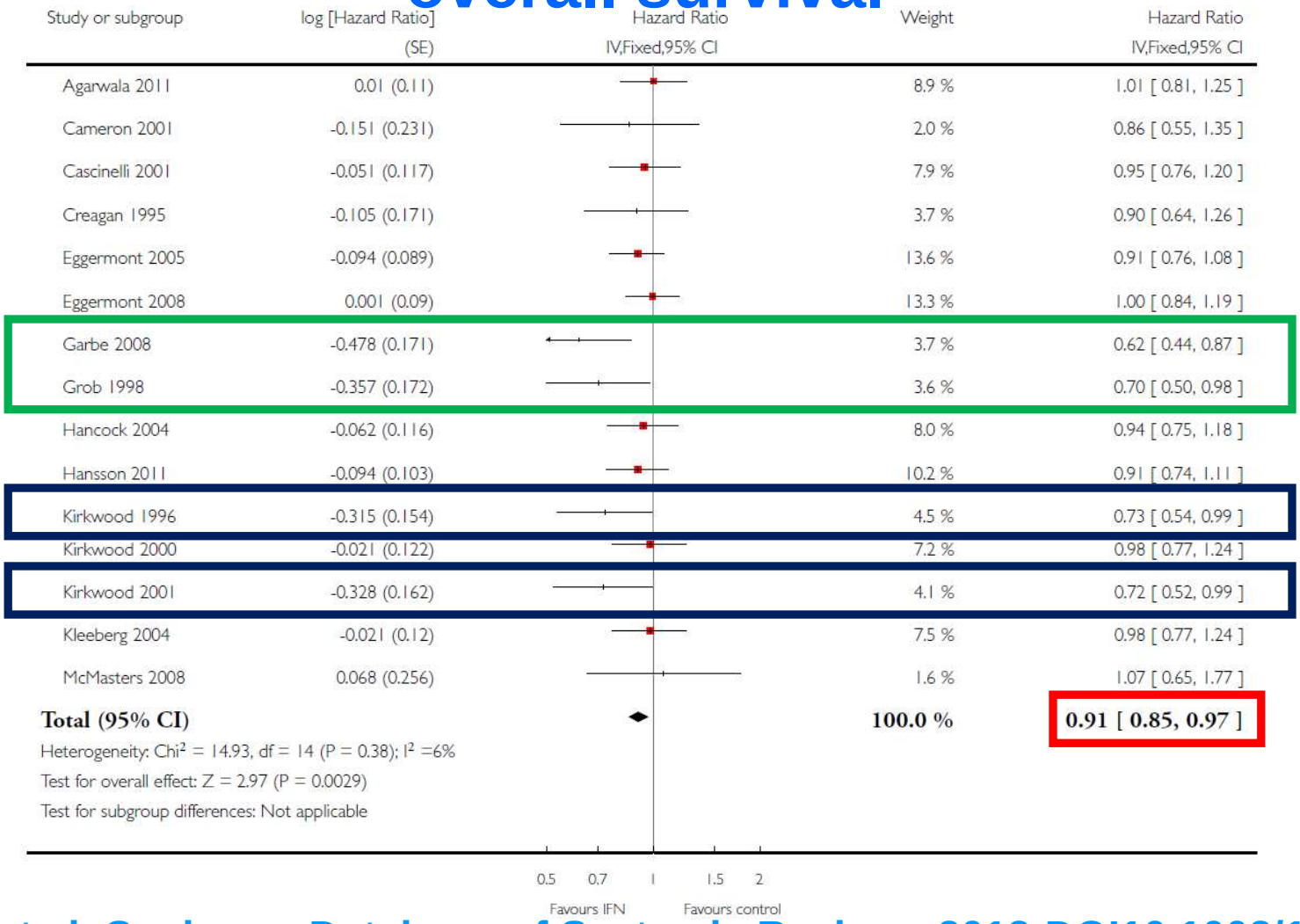
Meta-analysis of interferon impact on overall survival



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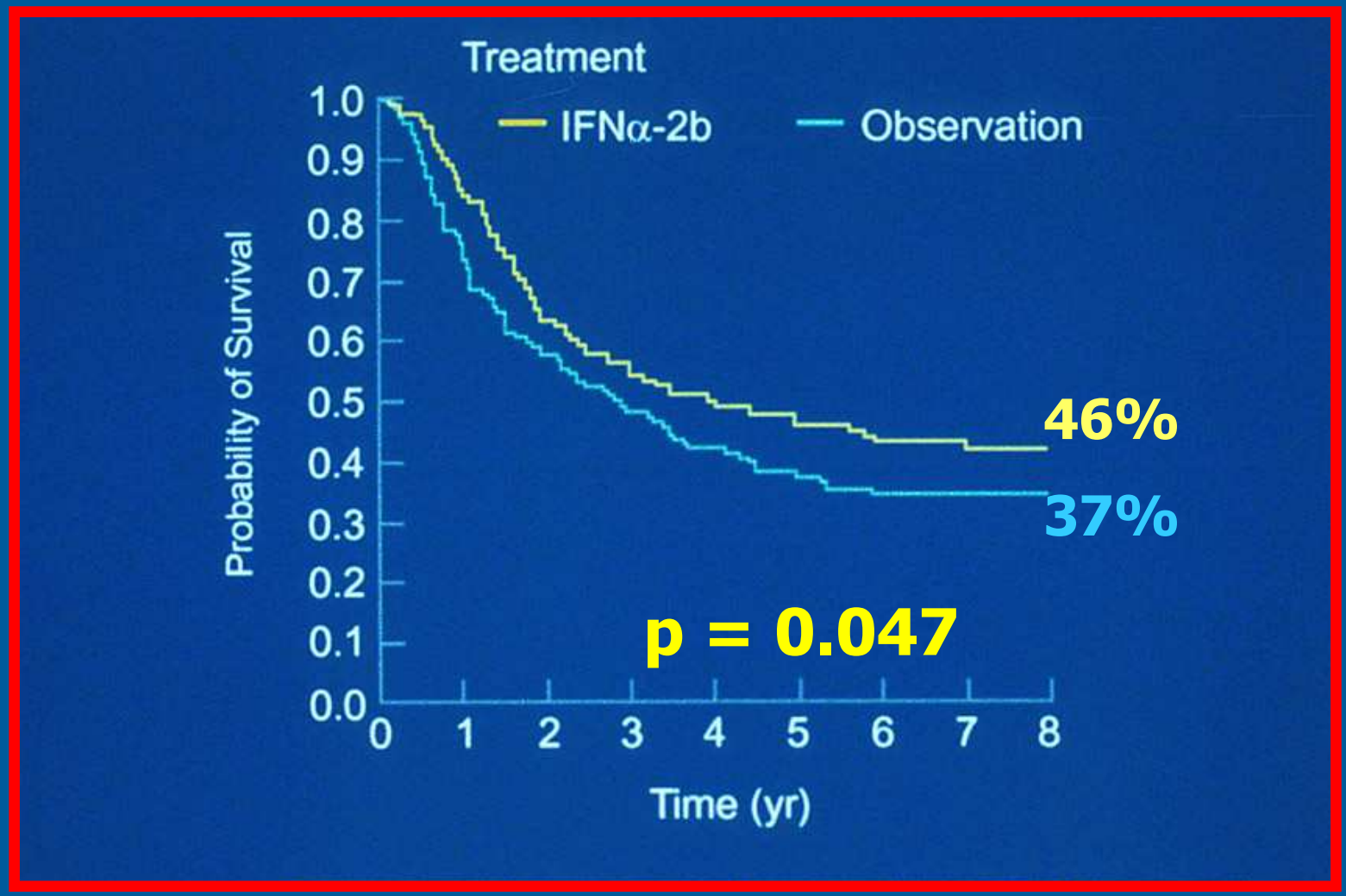
E1684
Overall survival



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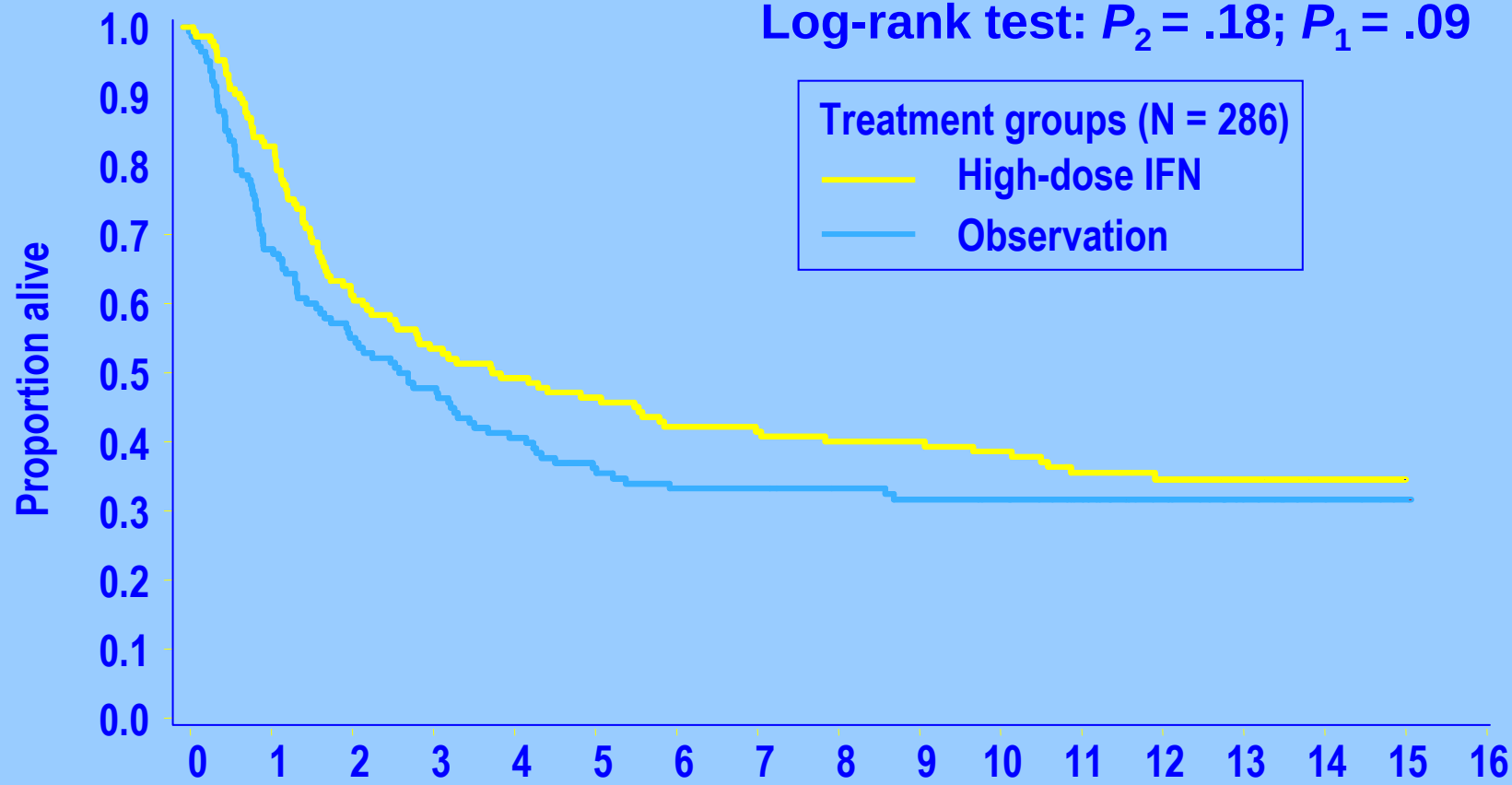
Overall survival

Extended follow-up



	Total	Dead	Alive	Median
Observation	140	95	45	2.7
High-dose IFN	146	93	53	3.8

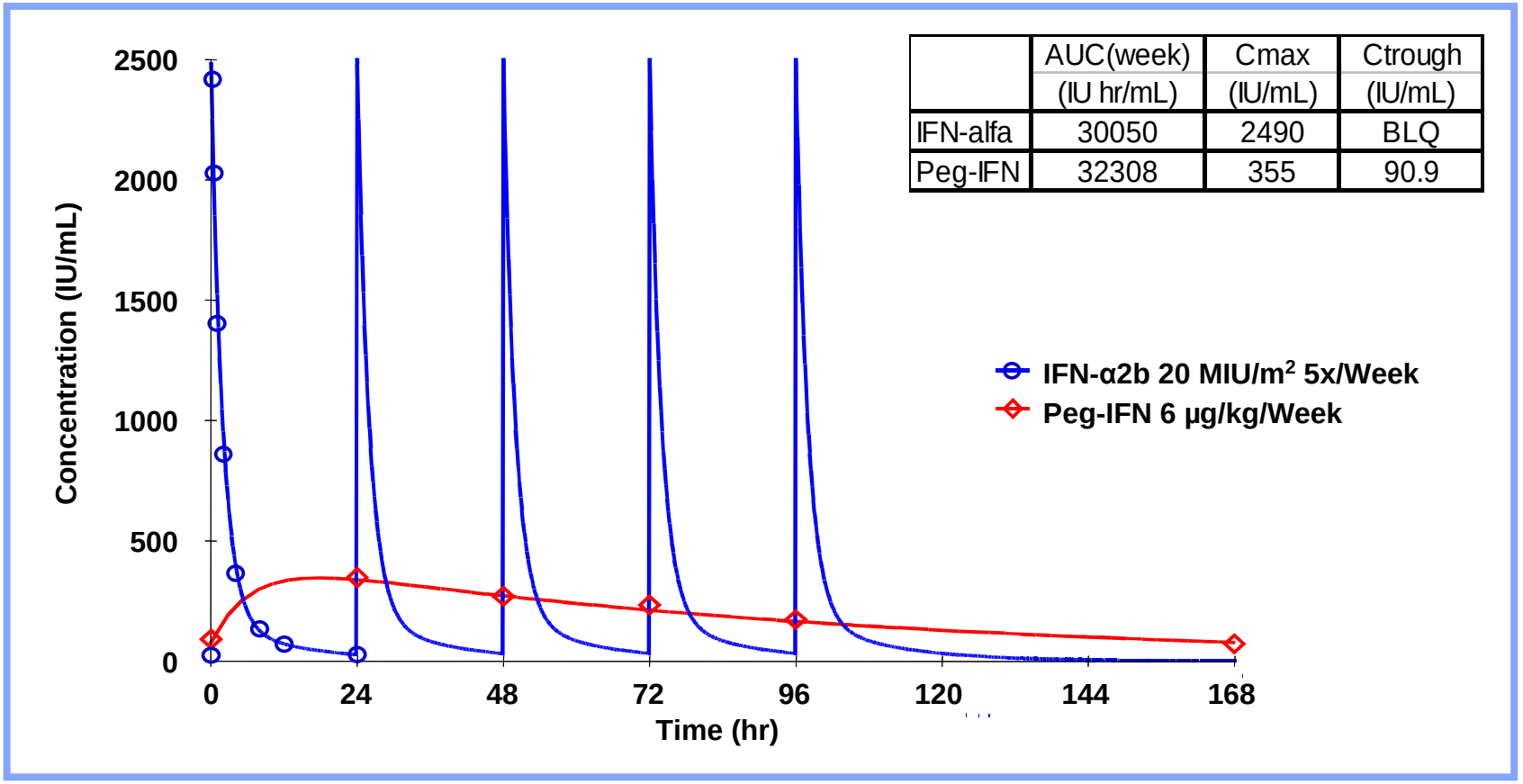
What are the most critical components?

- **Peak plasma level**
  - **IV interferon achieves highest peak plasma levels**
- **Exposure**
  - **Pegylated interferon provides superior exposure to drug over the course of a week**
- **Duration of therapy**
  - **Both lower dose standard interferon and pegylated interferon regimens allow treatment beyond one year**

What do we know about peginterferon?

- Pegylated interferon has essentially replaced native interferon in the management of hepatitis
- Available data supports that compared to native interferon, equitoxic doses of peginterferon are more effective and equieffective doses are less toxic
- **Adjuvant peginterferon in the FDA approved dose and schedule appears to be associated with fewer grade 3-4 adverse effects than high dose interferon, and can be given long-term in at least some patients with proper dose modification**

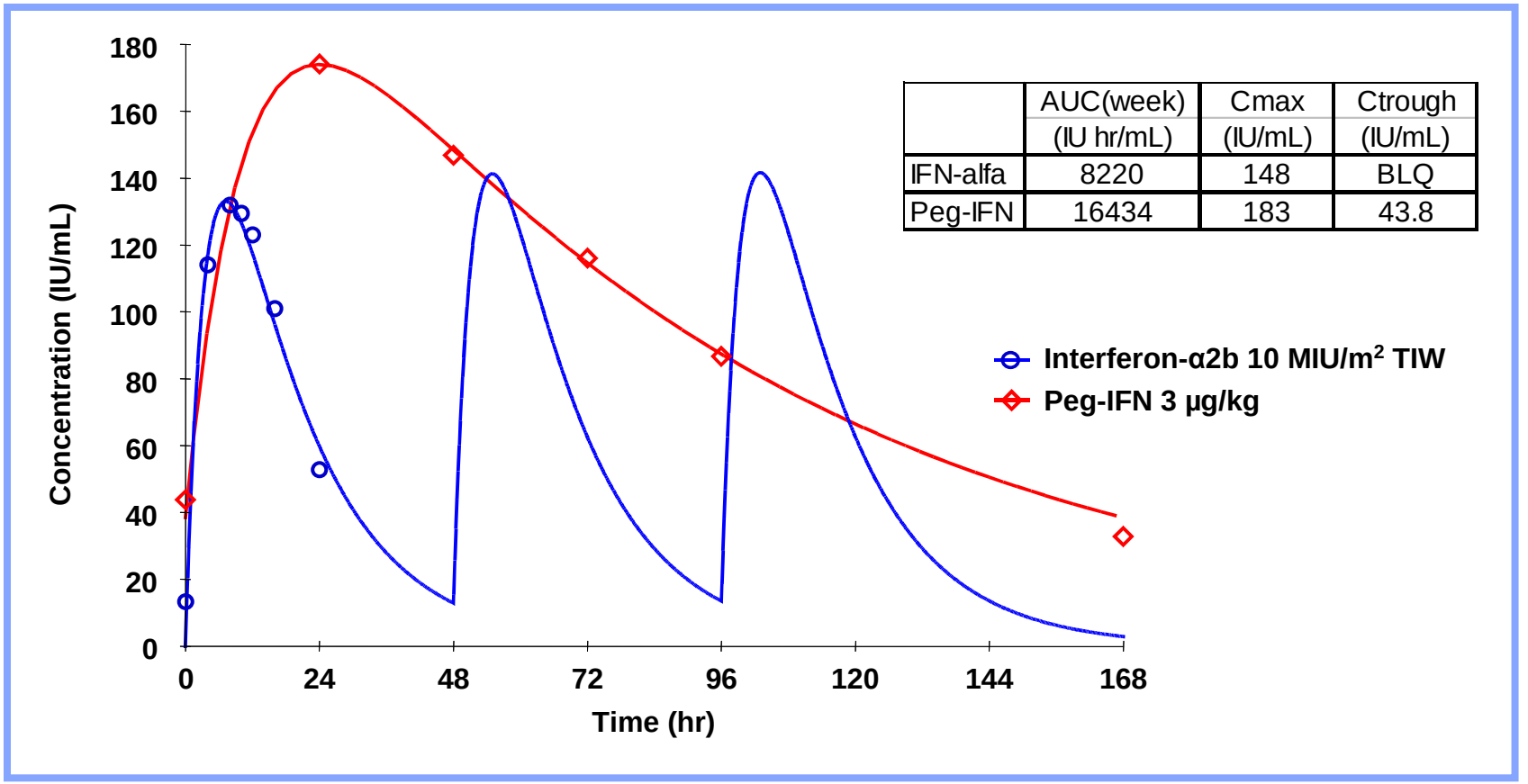
Pharmacodynamics of IFN-α2b IV 20 MIU/m^2 5 Days/Week vs Pegylated IFN-α2b SC 6 μg/kg/Week



	AUC(week) (IU hr/mL)	Cmax (IU/mL)	Ctrough (IU/mL)
IFN-alfa	30050	2490	BLQ
Peg-IFN	32308	355	90.9

Daud et al, Cancer Chemother Pharmacol 2011;67:657

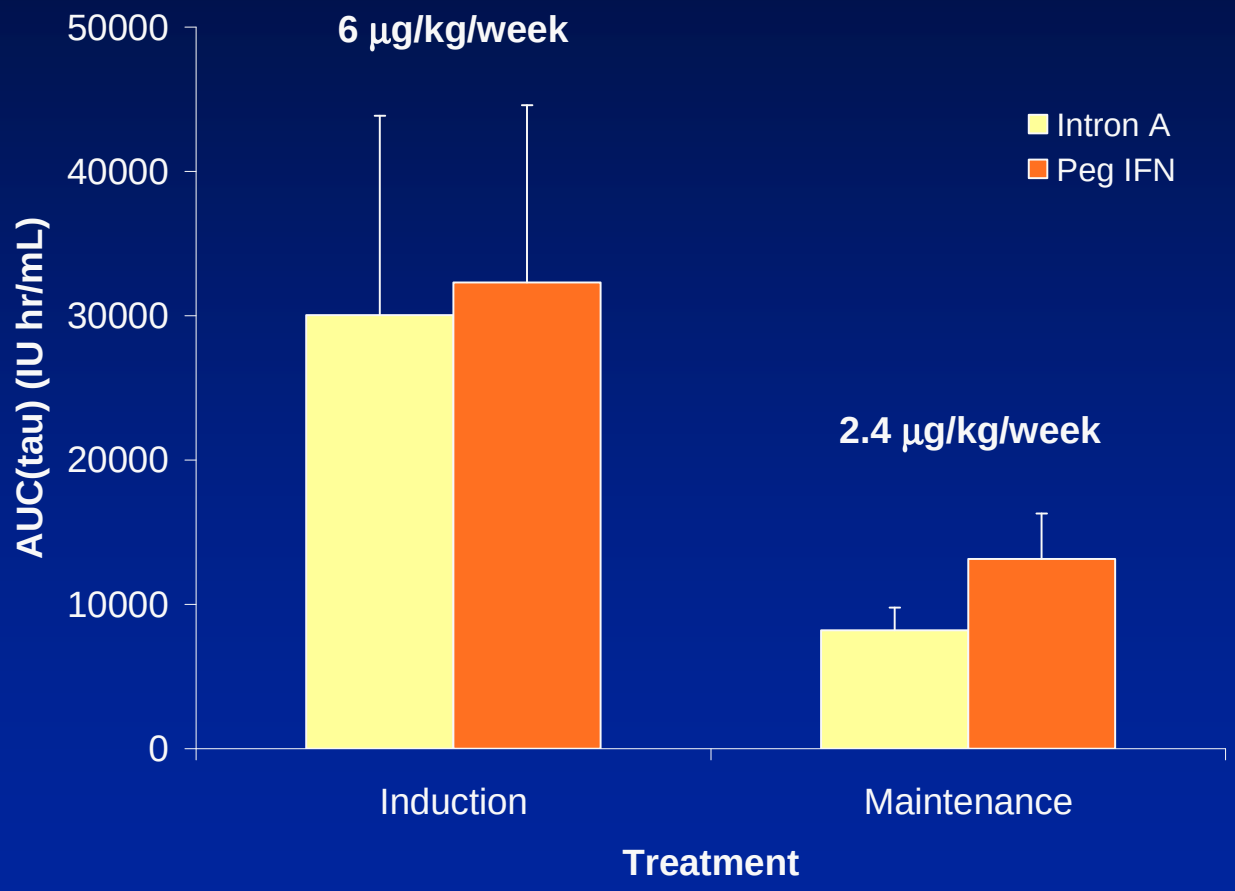
Pharmacodynamics of IFN-α2b SC 10 MIU/m² 3 Days/Week vs Pegylated IFN-α2b SC 3 μg/kg/Week



	AUC(week) (IU hr/mL)	Cmax (IU/mL)	Ctrough (IU/mL)
IFN-alfa	8220	148	BLQ
Peg-IFN	16434	183	43.8

Daud et al, Cancer Chemother Pharmacol 2011;67:657

Pharmacodynamics of IFN-α2b IV and SC vs Pegylated IFN-α2b SC



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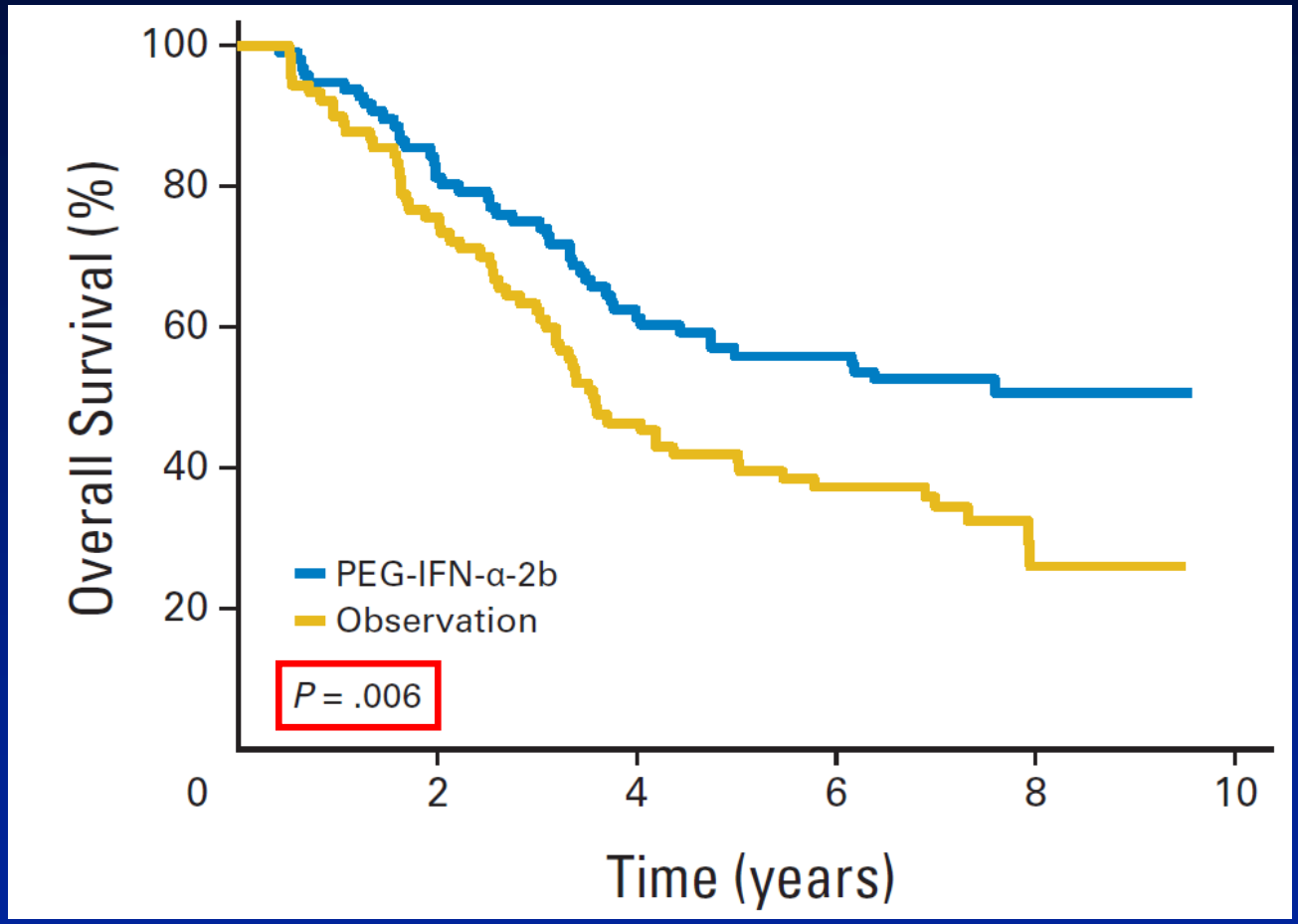
EORTC 18991 Phase III Trial of Peg-IFNα in Stage III Melanoma

OS in the SLN+, Ulcerated Primary Population

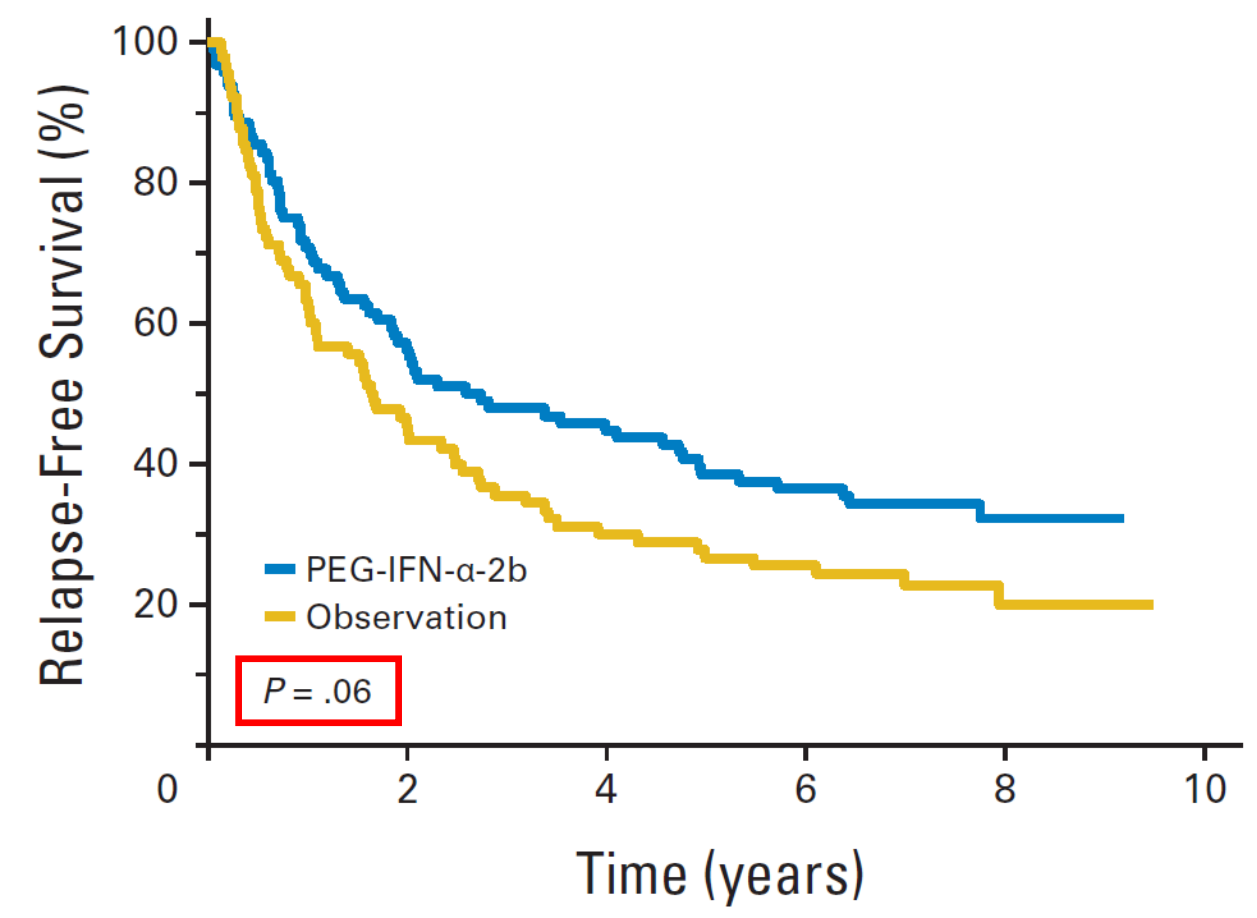


Hazard Ratio 0.59 (99% CI 0.35, 0.97)
Median OS not reached vs 3.6 years

Eggermont et al, J Clin Oncol 2012;30:3810

EORTC 18991 Phase III Trial of Peg-IFNα in Stage III Melanoma

RFS in the SLN+, Ulcerated Primary Population

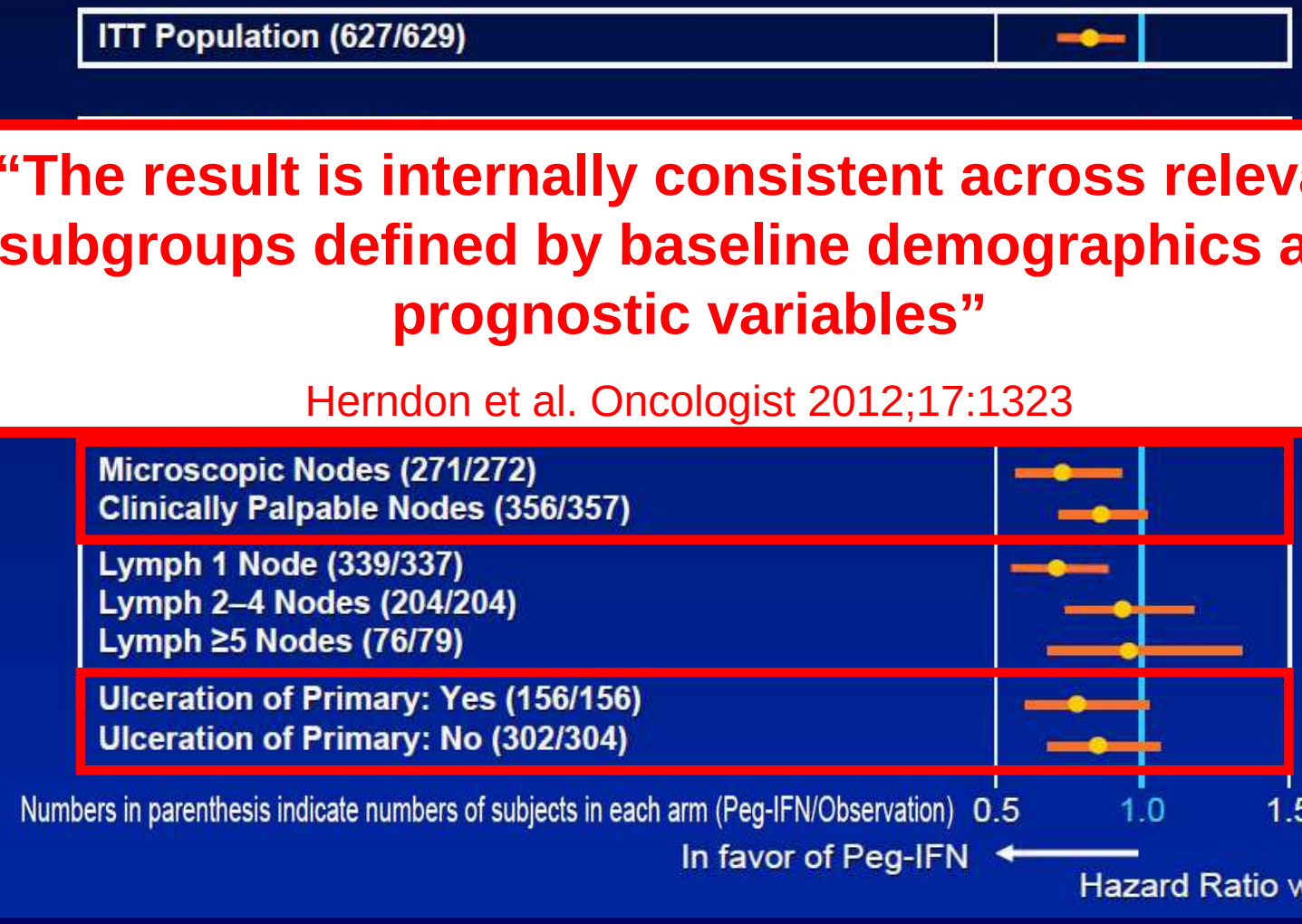


Hazard Ratio 0.72 (99% CI 0.46, 1.13)

Median RFS 2.7 years vs 1.7 years

Eggermont et al, J Clin Oncol 2012;30:3810

EORTC 18991: RFS in Stratified Subsets



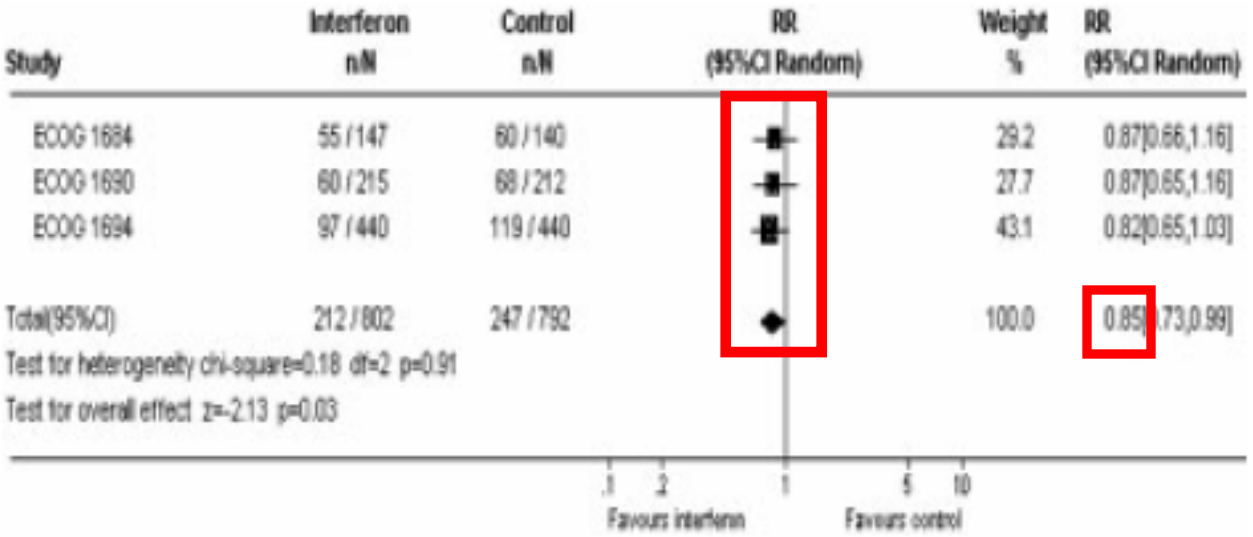
"The result is internally consistent across relevant subgroups defined by baseline demographics and prognostic variables"

Herndon et al. Oncologist 2012;17:1323

Unpublished data presented to FDA ODAC, October 5, 2009

The “Adjuvant Therapy Bridge”

Meta-analysis of high-dose interferon impact on survival at 2 years



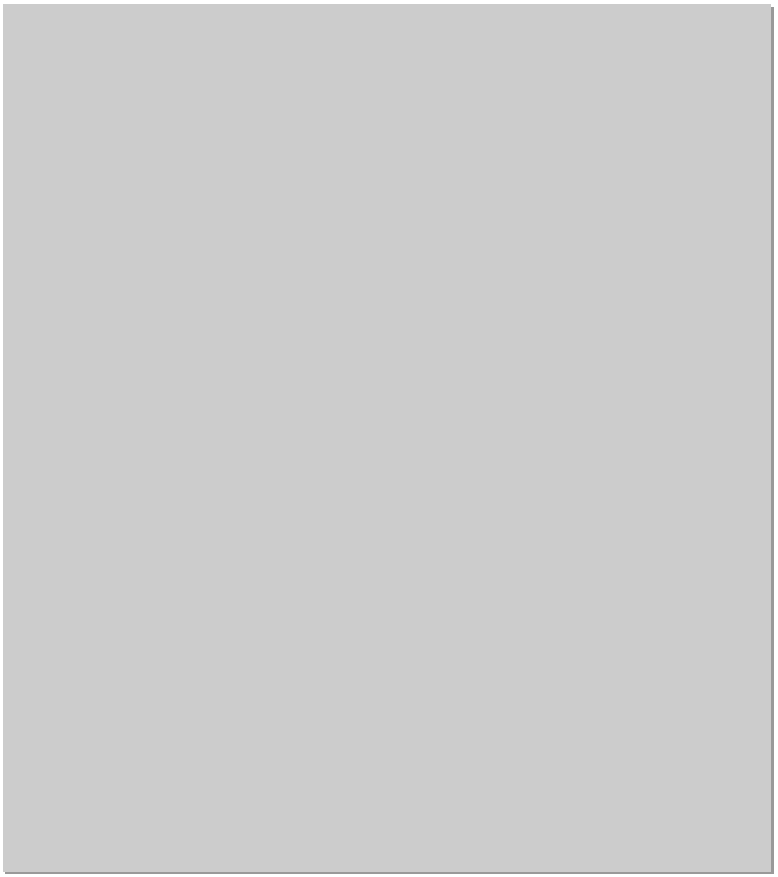
High dose interferon for one year significantly improved survival at two years

(15% increase, p=0.03)

Verma et al Cancer 2006;106:1431

Interferon management recommendations

Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for cutaneous melanoma



Kaufman et al, Nat Rev Clin Oncol 2013;10:588

How much does interferon help?

Interferon alpha compared with treatment other than interferon (including observation) for the adjuvant treatment of melanoma

Patient o
Settings:
Intervent
Comparis

Outcome

evidence

First recu

Death

Until better selection methods or more effective therapies are available, the findings of the present meta-analysis lend support to the use of interferon in the routine clinical setting to provide patients with the best chance of survival. Moreover, we must remember that other well-established adjuvant treatments, such as those routinely administered to people with breast, colorectal, and ovarian carcinomas, are associated with risk reductions very similar to those found in this meta-analysis for those with high-risk melanoma treated with interferon (Ascierto 2008). Therefore, the need for better therapeutic strategies is an urgent issue for virtually all tumour types.

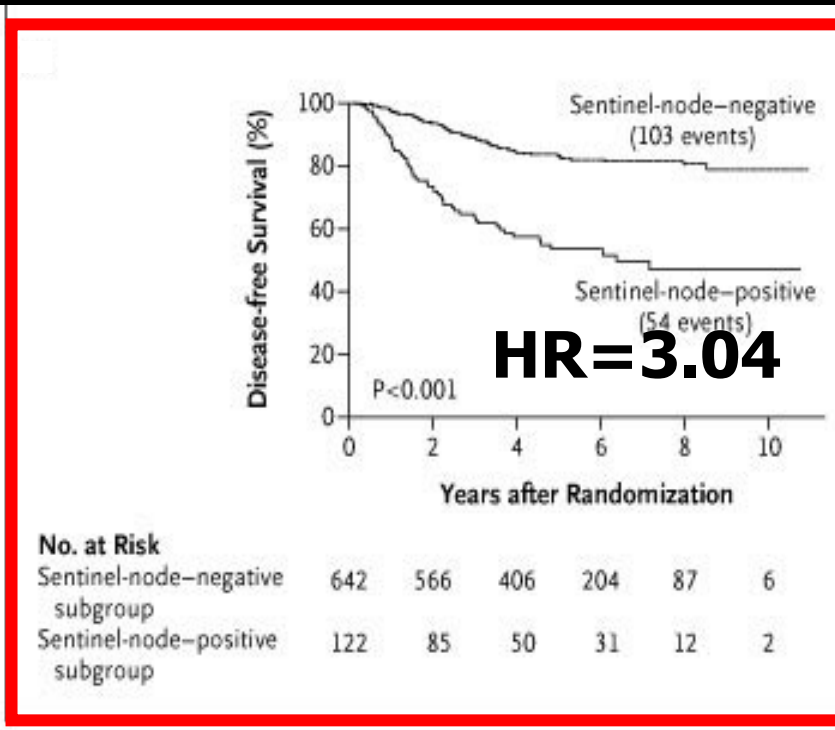
Mocellin et al, Cochrane Database of Systemic Reviews 2013;DOI10.1002/14651858

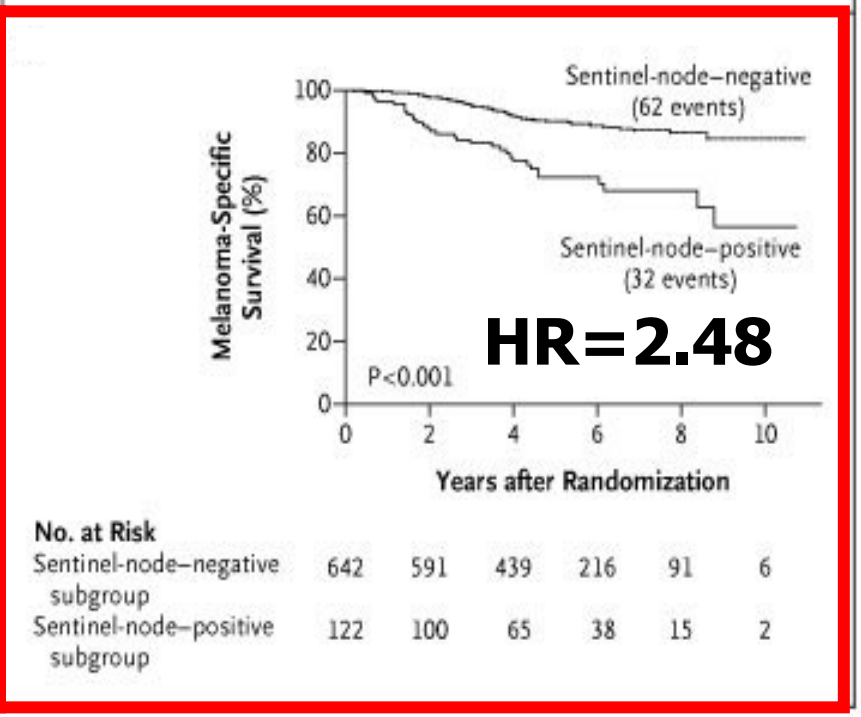
What are the most critical components?

- **Peak plasma level?**
  - **IV for one month not enough by itself, even for lower risk patients**
- **Exposure?**
  - **Pegylated interferon may be most useful in sentinel node positive patients with ulcerated primaries, but this observation needs to be directly validated**
- **Duration of therapy?**
  - **No trial has yet proven an advantage for continuing interferon therapy beyond one year**

ADJUVANT THERAPY OF MELANOMA

Let's Not Forget The "Low Risk" Groups





Morton D et al. N Engl J Med 2006;355:1307-1317

Sentinel node negative patients outnumber sentinel node positive patients by about 5 to 1

The NEW ENGLAND JOURNAL of MEDICINE

Where will we be three years from now?

- Multiple new inhibitors will be available, and likely used in combination for BRAF mutant metastatic melanoma
- New approaches for NRAS mutant metastatic melanoma may be available
- Optimum dose/schedule of ipilimumab will be defined, toxicity management may be improved, new immunomodulatory antibodies with more activity and fewer side effects may be available
- **Shouldn't our stage III patients today have the best possible chance to get these drugs?**

ADJUVANT THERAPY OF MELANOMA

What Do We Need Most?

- **We still need better prognostic markers to identify patients at risk of relapse, especially in the sentinel node negative population**
- **As more potential adjuvant therapy options become available, predictors of efficacy or resistance will become increasingly important**
- **We also need improved understanding of adjuvant therapy's efficacy in molecularly defined subsets**