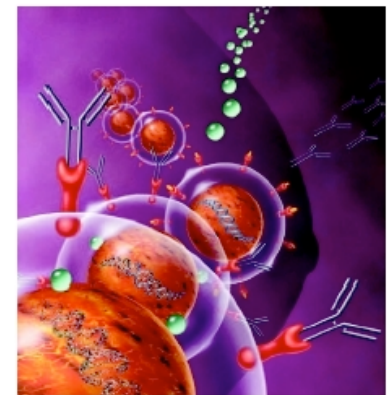


Journal Club Medecine- Science

Session V: Cancer immunology



David PUYRAIMOND-ZEMMOUR, TCEM1 Oncology Paris VI
Eimad SHOTAR, TCEM1 Radiology Paris V
CRI, 12/A6/2010

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IFN γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

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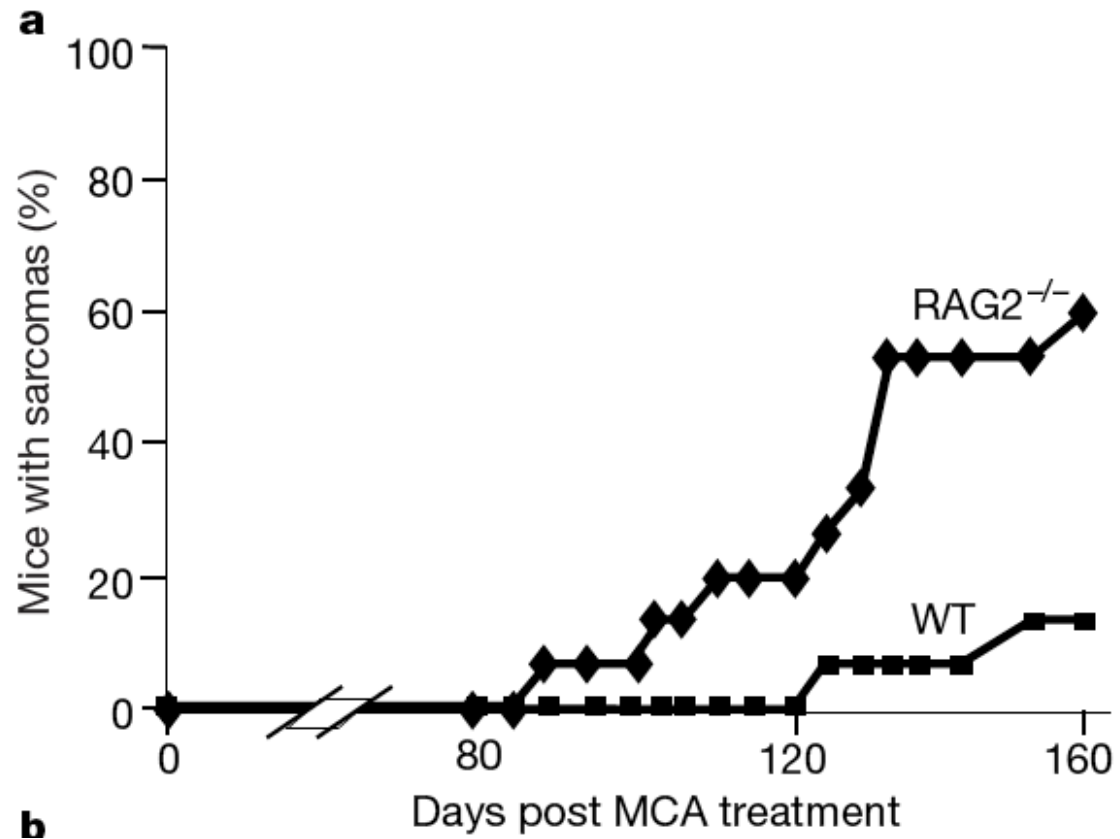
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Introduction

- Cancer immunosurveillance: process that protect immunocompetent hosts against primary tumor development
- but no difference between nude and wt syngenic mice in primary development tumor...
- But discovery that some lymphocytes are present in nude mice.
- So...?

Results

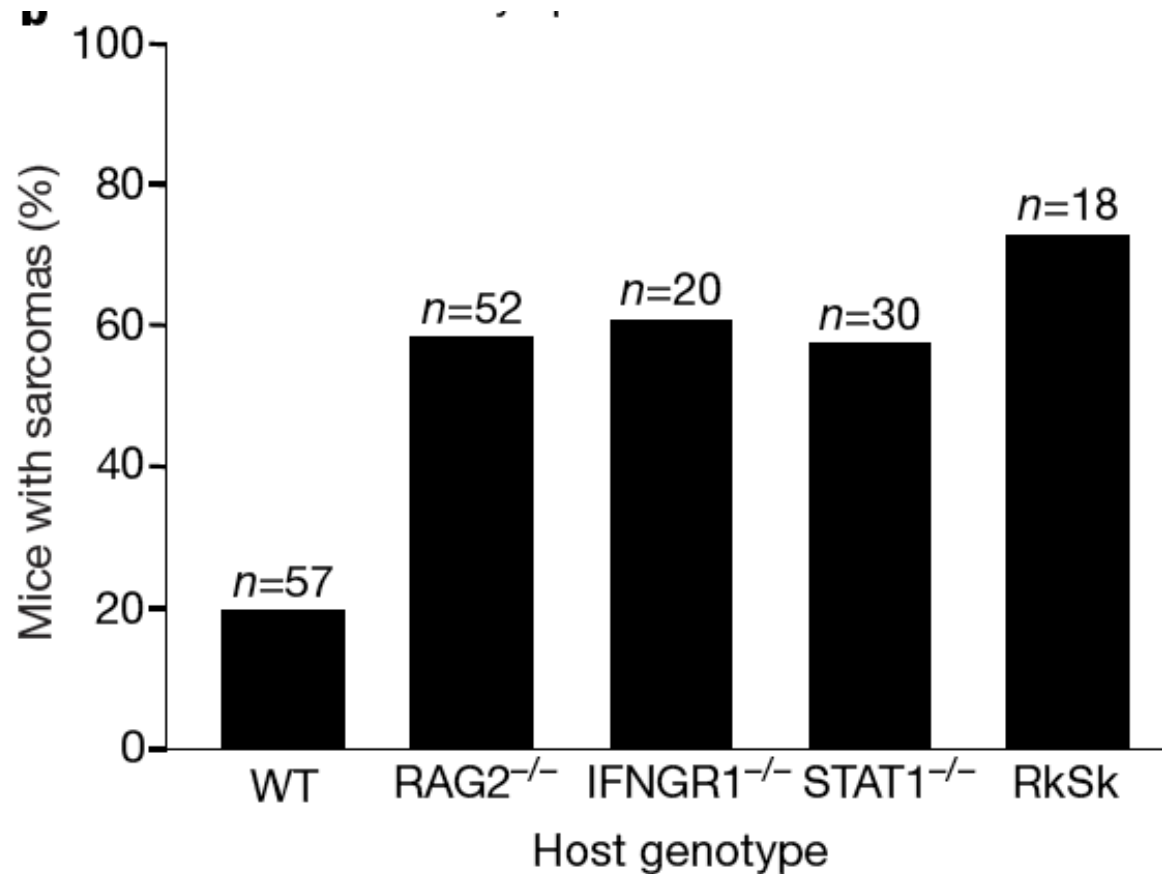
Sarcoma induction in wt and RAG2 KO mice



-earlier and greater frequency in RAG 2KO mice

Results

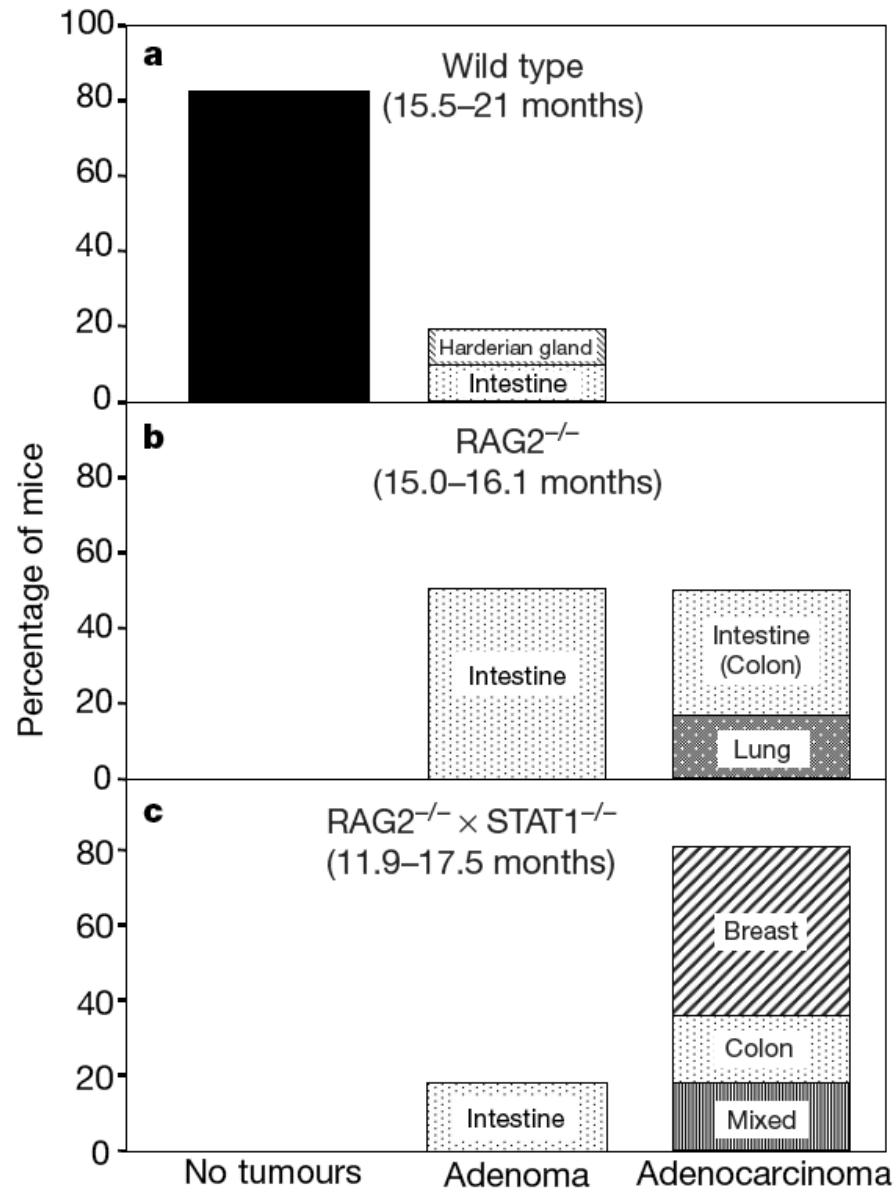
Sarcoma induction in wt and RAG2, IFNGR1, STAT1, IFNGR1 and RAG2 KO mice



- greater frequency in RAG2, IFNGR1, STAT1, IFNGR1 and RAG2 KO mice
- no difference in histology analysis
- no frequency difference between RAG2 and/or IFNGR1 → overlap?

Results

Spontaneous cancer formation in wt and RAG2, IFNGR1 and RAG2 KO mice



-wt: 2/11 tumors (1 adenoma, 1 harderian gland cystadenoma) → no cancer

-RAG2KO: 12/12 tumors, 6 cancers and 6 adenoma

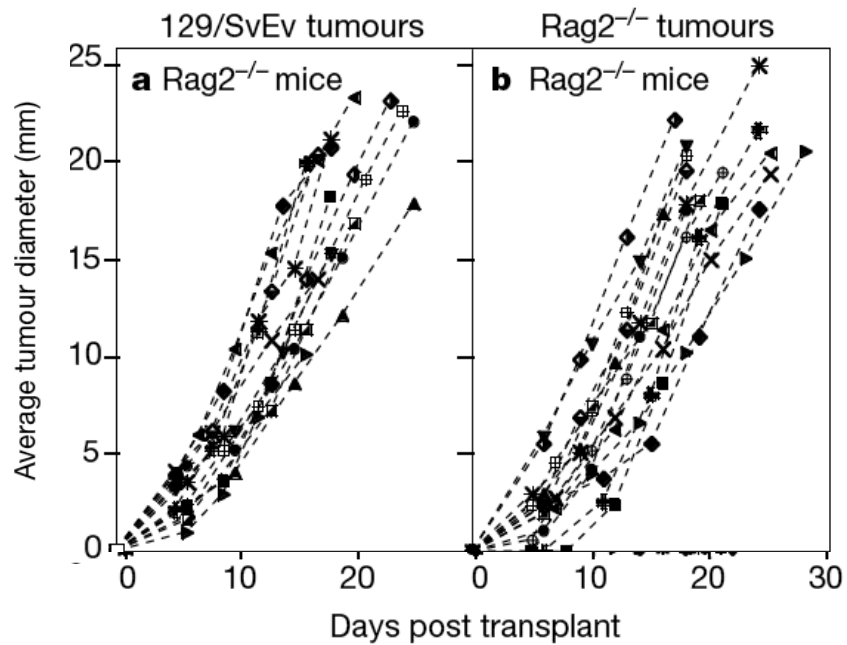
-RAG2/IFNGR1 KO: 11/11 tumors, earlier formation, more cancer

→ Partial overlap?

-NB: control: growth of the tumors after transplantation in naïve RAG2/IFNGR1 mice

Results

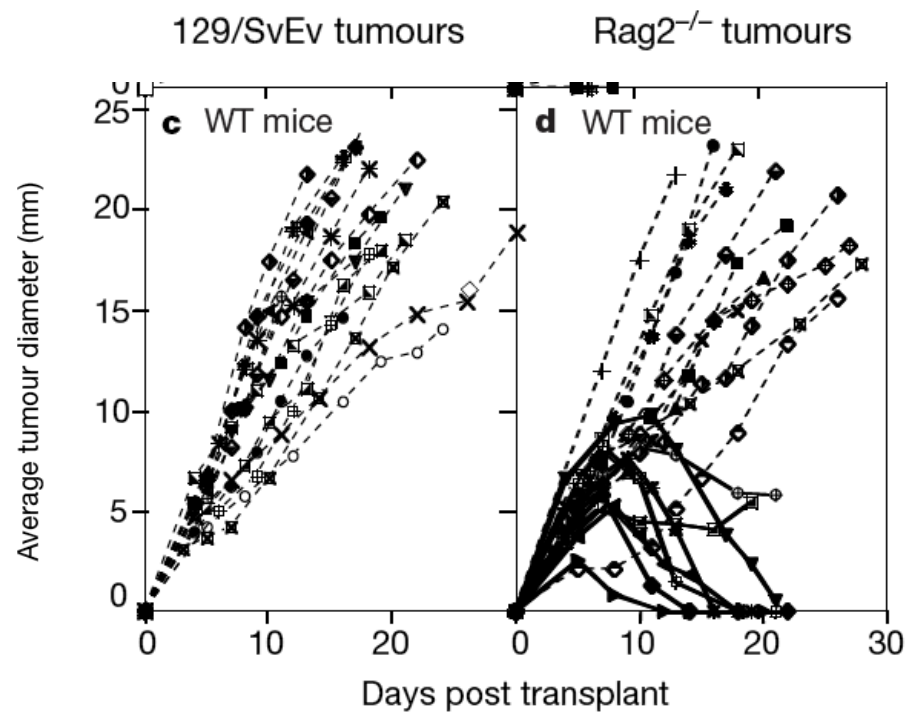
Does the immune system influences the immunogenic phenotype of tumors formed during chemical carcinogenesis?
→ Tumor transplantation assay



-Both wt and rag2KO sarcomas grow with the same kinetics in RAG2KO mice

Results

Does the immune system influence the immunogenic phenotype of tumors formed during chemical carcinogenesis?
→ Tumor transplantation assay



- rejection of tumor from RAG2KO mice in wt mice !

-Not due to:

- Genetic differences between KO and wt mice since still rejection in wtXRAG2 F1 mice
- Retrovirus related Ag since not isolated, no expression of gp70 or MuLV

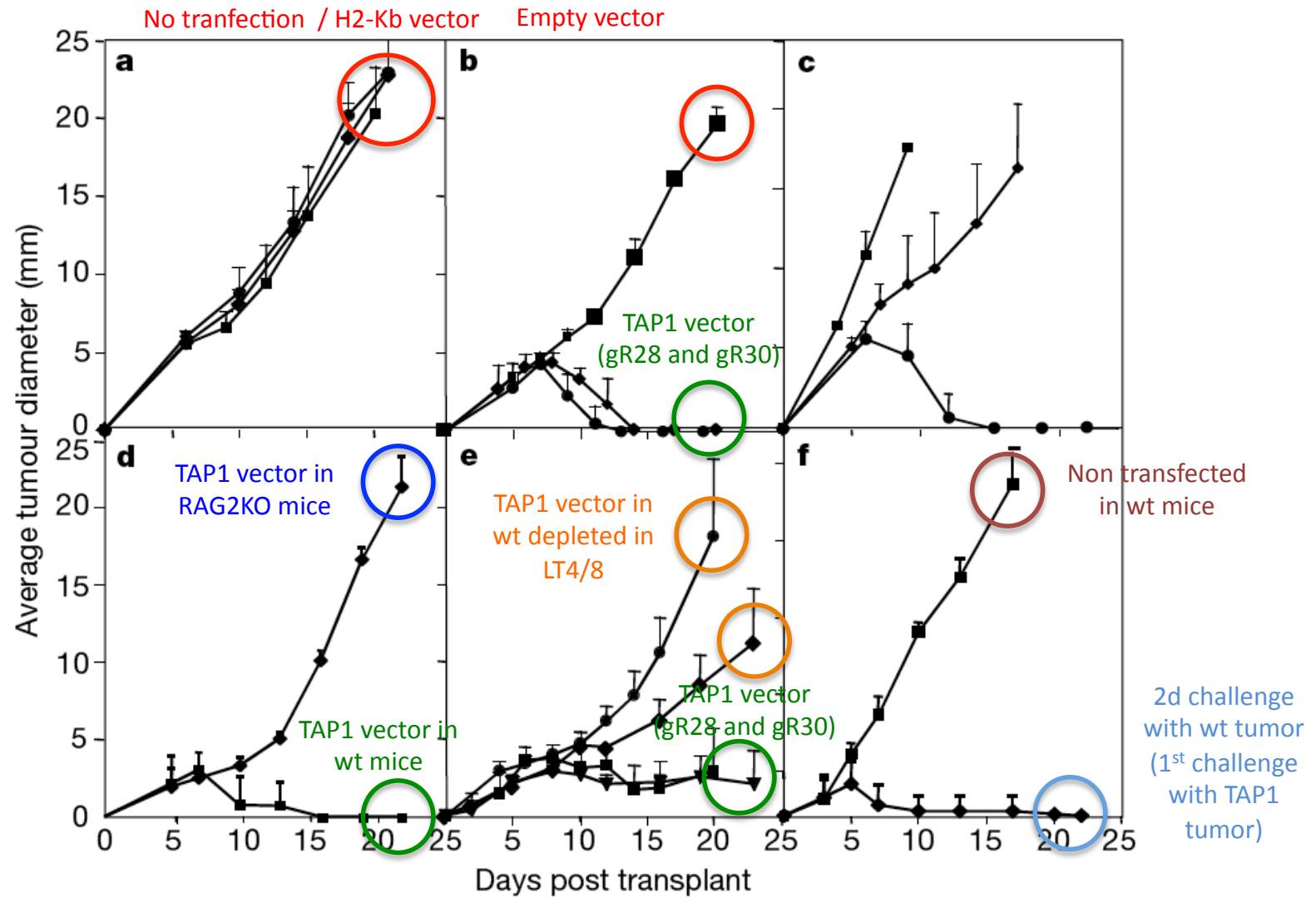
Results

Link between lymphocyte dependent and IFN/STAT1 dependent tumour suppressor processes?

- Could the highly tumorigenic phenotype of IFN γ -insensitive tumour cells be eliminated by selectively expressing in them components of the MHC class I processing and presentation pathway that are known to be significantly upregulated by IFN γ ?
- Study of 2 pathway components: TAP1 and H2-Kb (mouse HMC1)
 - known to be upregulated by IFN
 - downregulated in immune escape of tumors
- Use of 2 IFN insensitive sarcomas (gR28 and gR30) derived from IFNGR1 mice
 - Transfection with TAP1/H2-Kb/empty plasmid
 - Transplantation in wt mice
 - Growth study

Results

Link between lymphocyte dependent and IFN/STAT1 dependent tumour suppressor processes?



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Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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Introduction

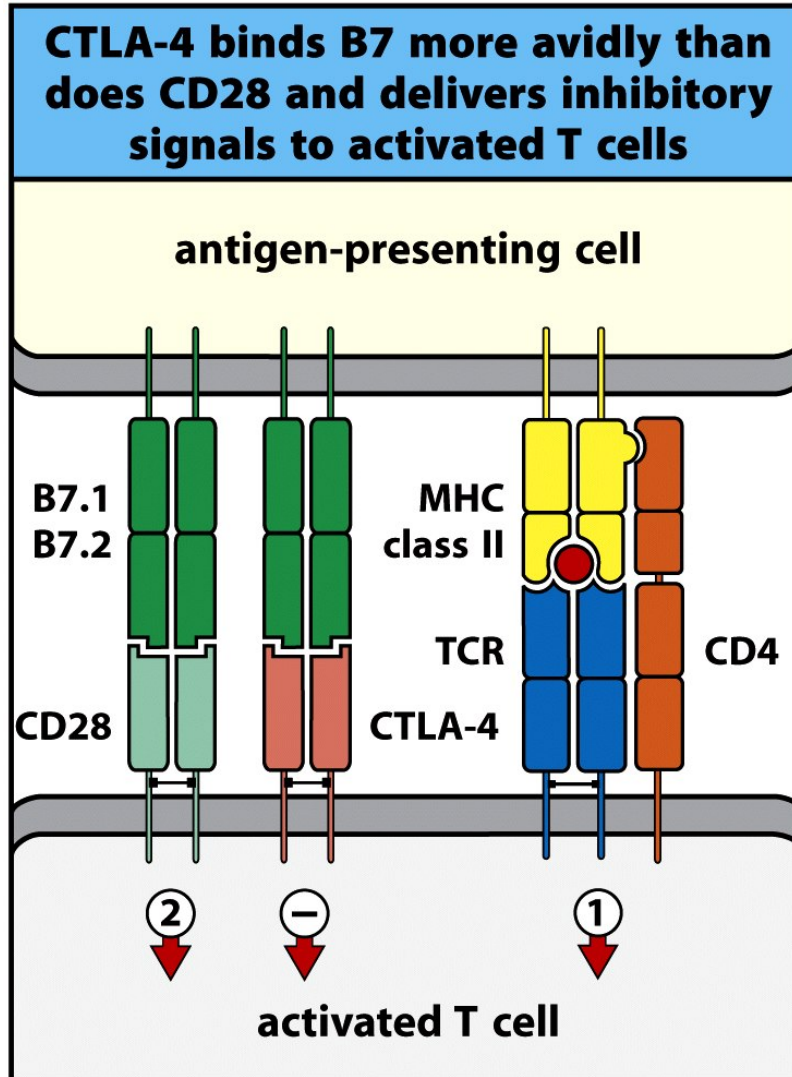


Figure 8-22 Immunobiology, 7ed. (© Garland Science 2008)

Introduction

- No therapy has been shown in a phase 3, randomized, controlled trial to improve overall survival in patients with metastatic melanoma.
- Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is an immune checkpoint molecule that down-regulates pathways of T-cell activation.
- Ipilimumab, a fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote antitumor immunity, has shown activity in patients with metastatic melanoma when it has been used as monotherapy in phase 2 studies.
- One well-studied cancer vaccine comprises HLA-A*0201–restricted peptides derived from the melanosomal protein, glycoprotein 100 (gp100). Monotherapy with this vaccine induces immune responses but has limited antitumor activity.
- With no accepted standard of care, gp100 was used as an active control for our phase 3 study.

Methods

Patients

Inclusion criteria

- unresectable stage III or IV melanoma
- had received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2.
- age of at least 18 years
- life expectancy of at least 4 months
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- **positive status for HLA-A*0201**
- normal hematologic, hepatic, and renal function; and no systemic treatment in the previous 28 days.

Exclusion criteria

- any other cancer from which the patient had been disease-free for less than 5 years (except treated and cured basal-cell or squamouscell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder)
- primary ocular melanoma
- previous receipt of anti-CTLA-4 antibody or cancer vaccine
- autoimmune disease
- active, untreated metastases in the central nervous system
- pregnancy or lactation
- concomitant treatment with any non study anticancer therapy or immunosuppressive agent
- long-term use of systemic corticosteroids

Study design

- randomized, double-blind, phase 3 study
- 125 centers in 13 countries in North America, South America, Europe, and Africa.
- between September 2004 and August 2008
- three study groups, with stratification according to baseline metastasis stage (M0, M1a, or M1b vs. M1c) and receipt or nonreceipt of previous interleukin-2 therapy.

Protocol

-3:1:1 ratio:

- ipilimumab, at a dose of 3 mg per kilogram of body weight + gp100 peptide vaccine;
- ipilimumab + gp100 placebo
- gp100 plus ipilimumab placebo

- all administered once every 3 weeks for four treatments

- in the vaccine groups: two modified HLA*0201-restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1 mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh. Peptide injections were given immediately after a 90-minute intravenous infusion of ipilimumab or placebo.

- Weeks 1, 4, 7, 12 and reinduction to their group if disease progression after this cycle

Primary endpoint

- Best overall response rate (i.e., the proportion of patients with a partial or complete response)
- between the ipilimumab-plus-gp100 group and the gp100-alone group
- amended to overall survival (with the amendment formally approved on January 15, 2009) in the ongoing blinded study, on the basis of phase 2 data and in alignment with another ongoing phase 3 trial of ipilimumab involving patients with metastatic melanoma.

Prespecified secondary endpoints

- comparison of overall survival between the ipilimumab-alone and the gp100-alone groups and between the two ipilimumab groups
- the best overall response rate
- the duration of response
- Progression free survival

Subgroup comparison

-across five prespecified categories:

- metastasis stage (M0, M1a, or M1b vs. M1c)

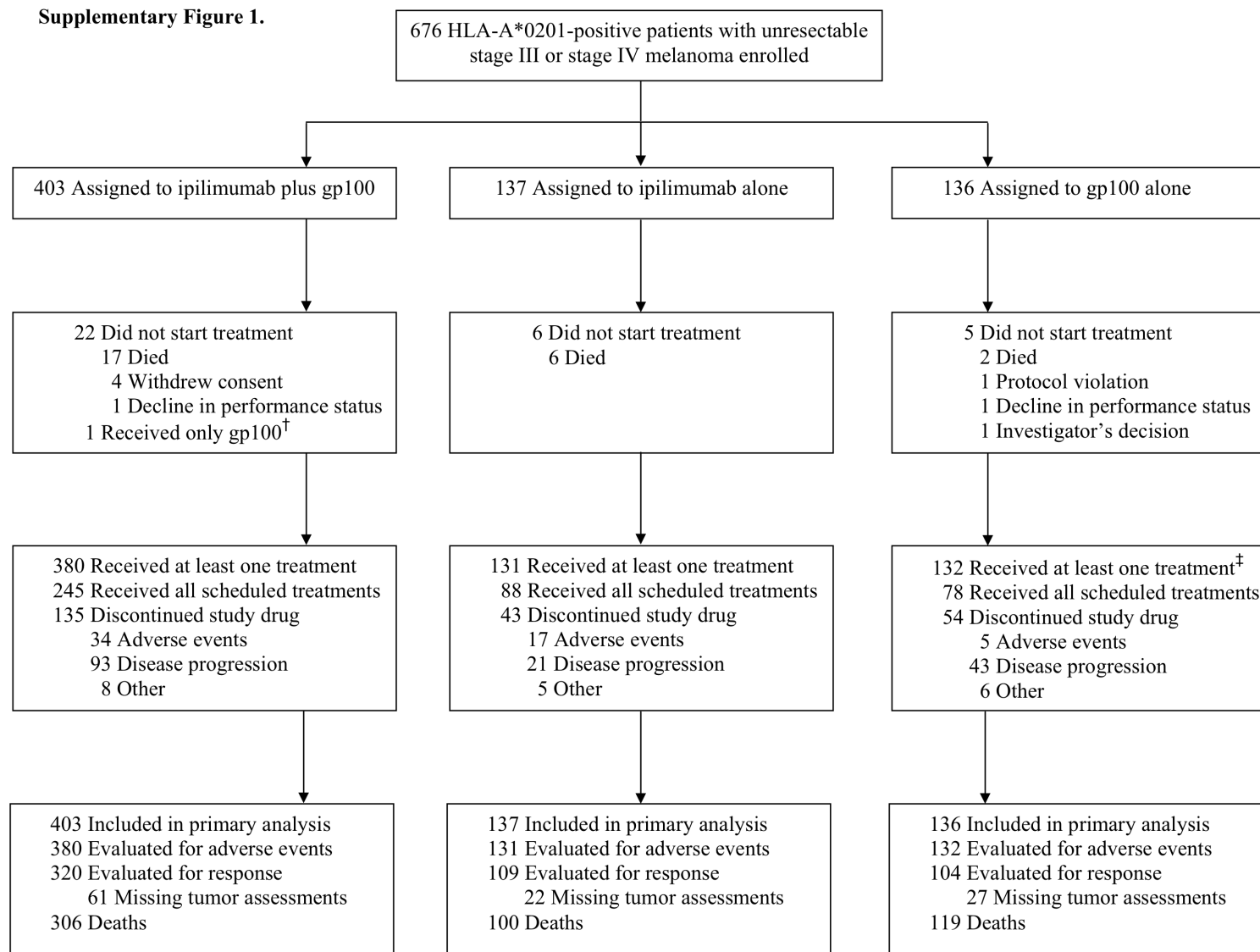
- receipt or nonreceipt of previous interleukin- 2 therapy

- baseline levels of serum LDH (less than or equal to the upper limit of the normal range vs. higher than the upper limit of the normal range)

- age (<65 years vs. ≥65 years)

- sex.

Supplementary Figure 1.



[†]This patient was included in the gp100-alone group for safety analyses. [‡]Includes 1 patient randomized to ipilimumab plus gp100 who received only gp100.

Results

Baseline characteristics of patients

Table 1. Baseline Characteristics of the Patients.*

Variable	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)	Total (N=676)
Mean age — yr	55.6	56.8	57.4	56.2
Sex — no. (%)				
Male	247 (61.3)	81 (59.1)	73 (53.7)	401 (59.3)
Female	156 (38.7)	56 (40.9)	63 (46.3)	275 (40.7)
ECOG performance status — no. (%)†				
0	232 (57.6)	72 (52.6)	70 (51.5)	374 (55.3)
1	166 (41.2)	64 (46.7)	61 (44.9)	291 (43.0)
2	4 (1.0)	1 (0.7)	4 (2.9)	9 (1.3)
3	1 (0.2)	0	0	1 (0.1)
Unknown	0	0	1 (0.7)	1 (0.1)
M stage — no. (%)‡				
M0	5 (1.2)	1 (0.7)	4 (2.9)	10 (1.5)
M1a	37 (9.2)	14 (10.2)	11 (8.1)	62 (9.2)
M1b	76 (18.9)	22 (16.1)	23 (16.9)	121 (17.9)
M1c	285 (70.7)	100 (73.0)	98 (72.1)	483 (71.4)
Lactate dehydrogenase level — no. (%)				
≤Upper limit of the normal range	252 (62.5)	84 (61.3)	81 (59.6)	417 (61.7)
>Upper limit of the normal range	149 (37.0)	53 (38.7)	52 (38.2)	254 (37.6)
Unknown	2 (0.5)	0	3 (2.2)	5 (0.7)
CNS metastases at baseline — no. (%)				
Received study drug	42 (10.4)	15 (10.9)	20 (14.7)	77 (11.4)
Had had previous treatment for CNS metastases	39 (9.7)	15 (10.9)	19 (14.0)	73 (10.8)
Previous systemic therapy for metastatic disease — no. (%)	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Previous interleukin-2 therapy — no. (%)	89 (22.1)	32 (23.4)	33 (24.3)	154 (22.8)

* Percentages may not total 100 because of rounding. CNS denotes central nervous system.

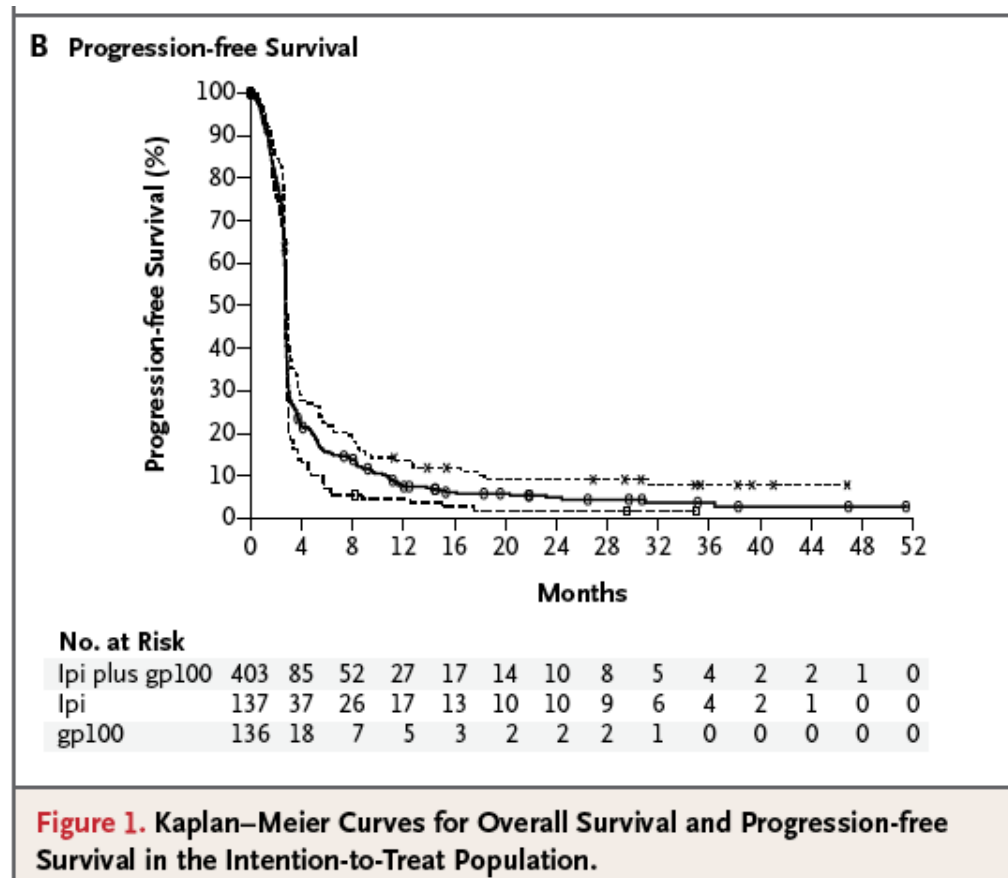
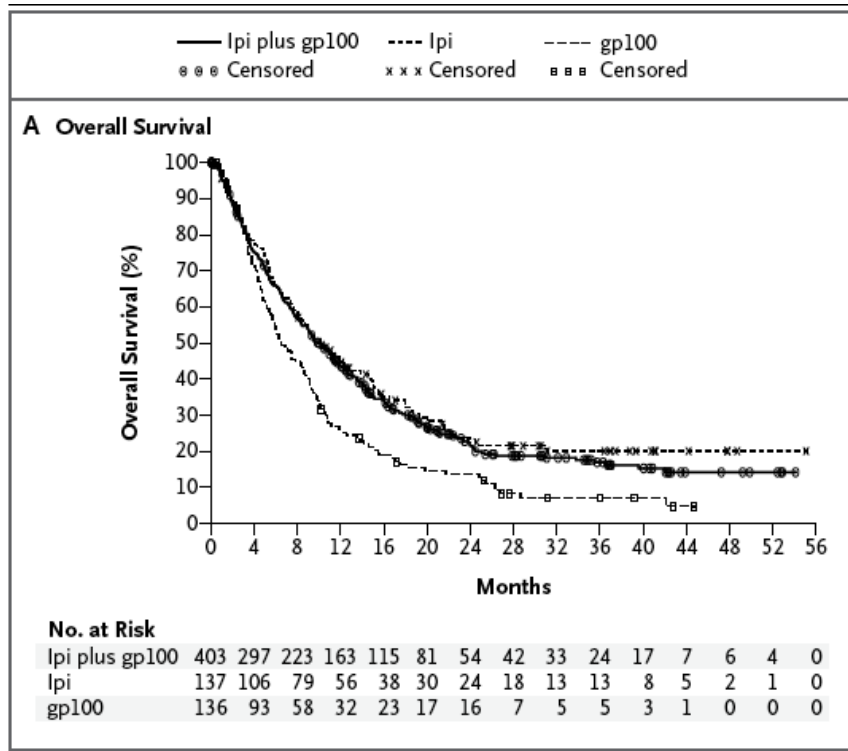
† The Eastern Cooperative Oncology Group (ECOG) status ranges from 0 to 5, with higher scores indicating greater impairment (5 indicates death).

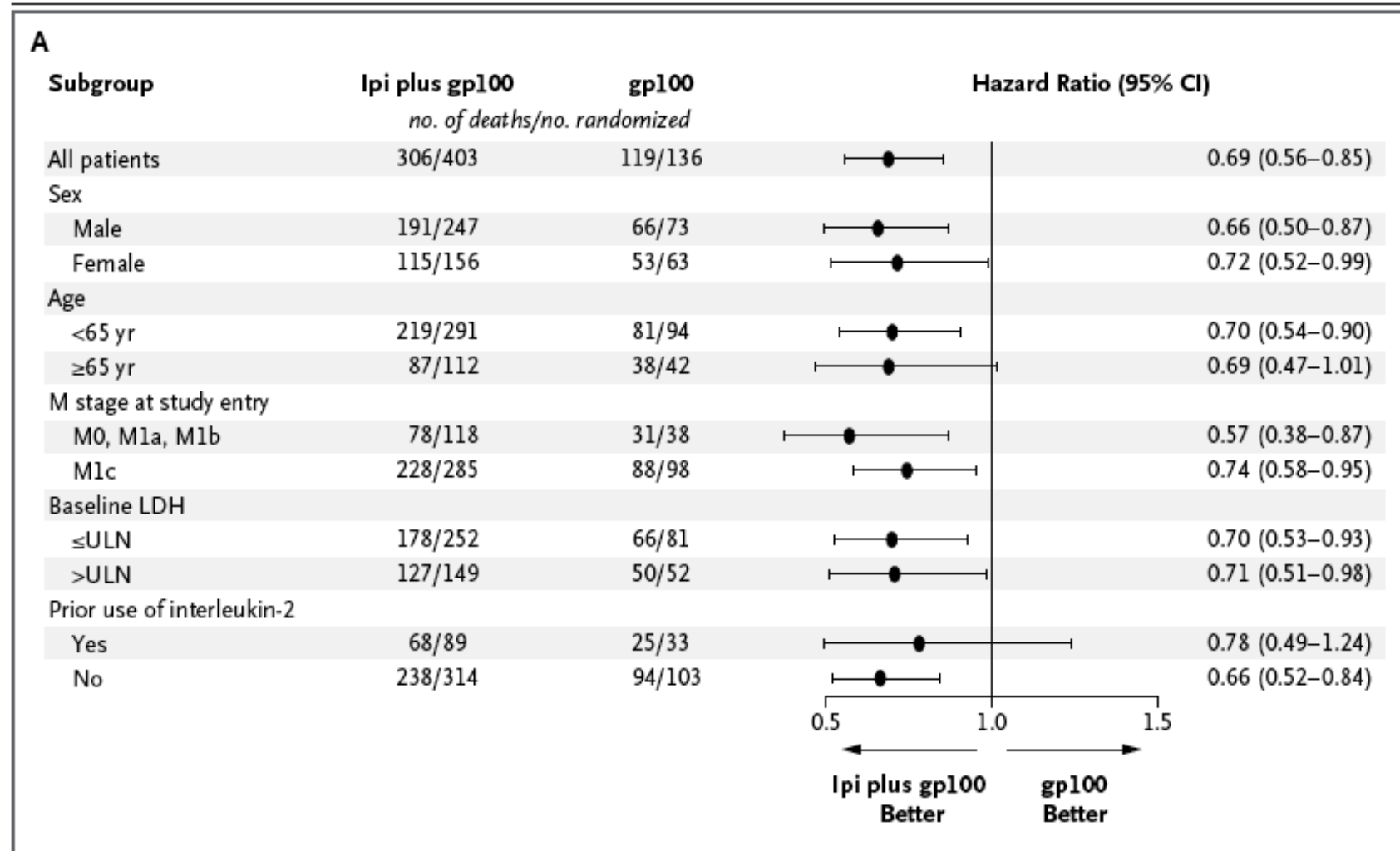
‡ The metastasis (M) stage was classified according to the tumor–node–metastasis (TNM) categorization for melanoma of the American Joint Committee on Cancer.

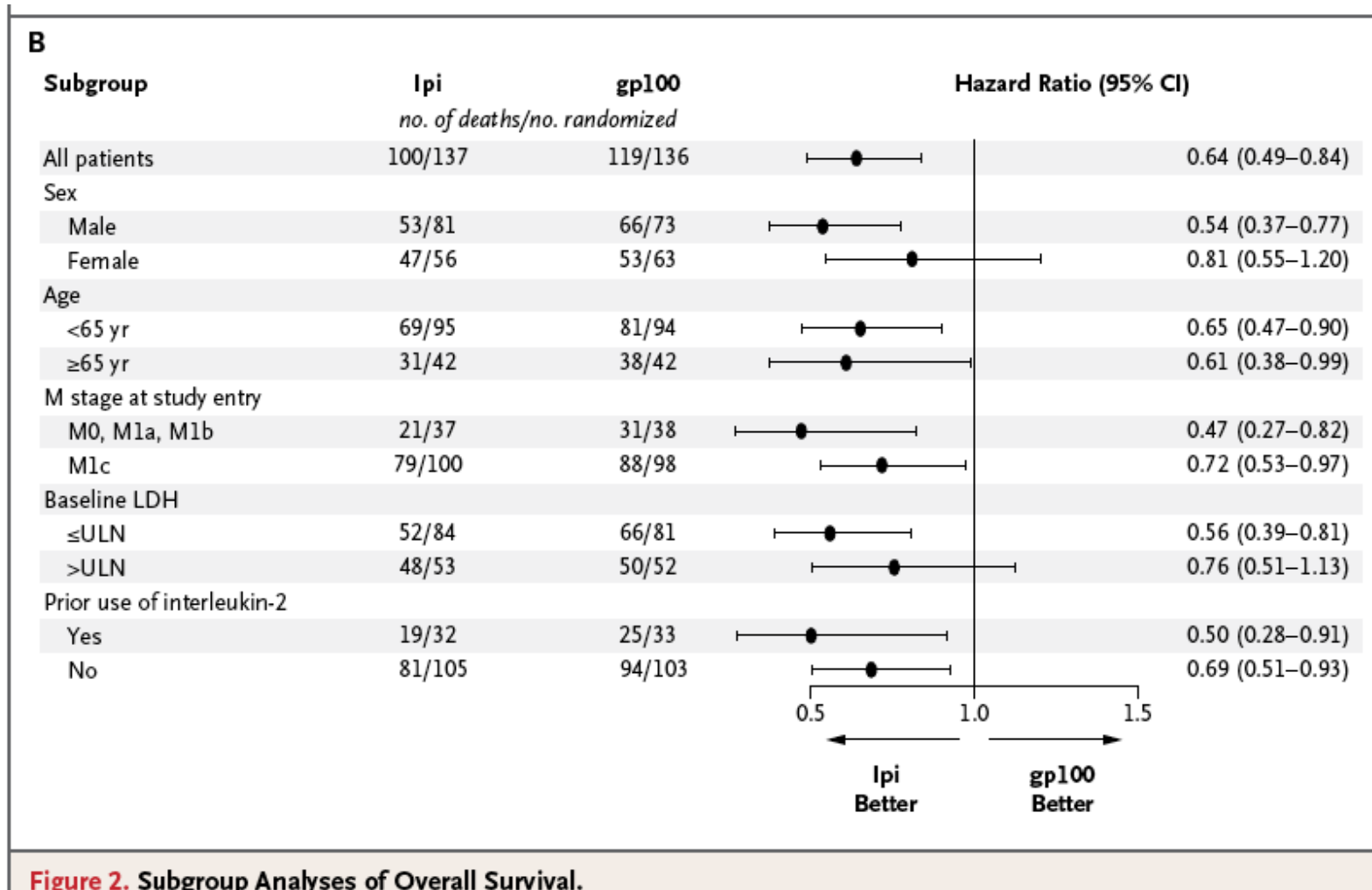
Results

Efficacy

Primary endpoint







Results

Efficacy

Secondary endpoints

Table 2. Best Response to Treatment and Time-to-Event Data.*

Response and Time to Event	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)
Overall survival			
Total no. of deaths	306	100	119
Comparison with gp100 alone			
Hazard ratio (95% CI)	0.68 (0.55–0.85)	0.66 (0.51–0.87)	—
P value by log-rank test	<0.001	0.003	—
Comparison with ipilimumab alone			
Hazard ratio (95% CI)	1.04 (0.83–1.30)	—	—
P value by log-rank test	0.76	—	—
Evaluation of therapy			
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Time to event — mo			
Time to progression — median (95% CI)	2.76 (2.73–2.79)	2.86 (2.76–3.02)	2.76 (2.73–2.83)
Time to response — mean (95% CI)	3.32 (2.91–3.74)	3.18 (2.75–3.60)	2.74 (2.12–3.37)
Duration of response — median (95% CI)	11.5 (5.4–NR)	NR (28.1–NR)	NR (2.0–NR)
Reinduction‡			
Best overall response — no./total no. (%)			
Complete response	0	1/8 (12.5)	0
Partial response	3/23 (13.0)	2/8 (25.0)	0
Stable disease	12/23 (52.2)	3/8 (37.5)	0
Progressive disease	8/23 (34.8)	2/8 (25.0)	1/1 (100.0)

Adverse events