Efficacy, Safety, and Quality of Life (QoL) Data from the EORTC 18071 Phase III Trial of Ipilimumab (Ipi) Versus Placebo After Complete Resection of Stage III Melanoma

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The future of cancer therapy

Disclosures

Prof. Alexander M.M. Eggermont, MD, PhD

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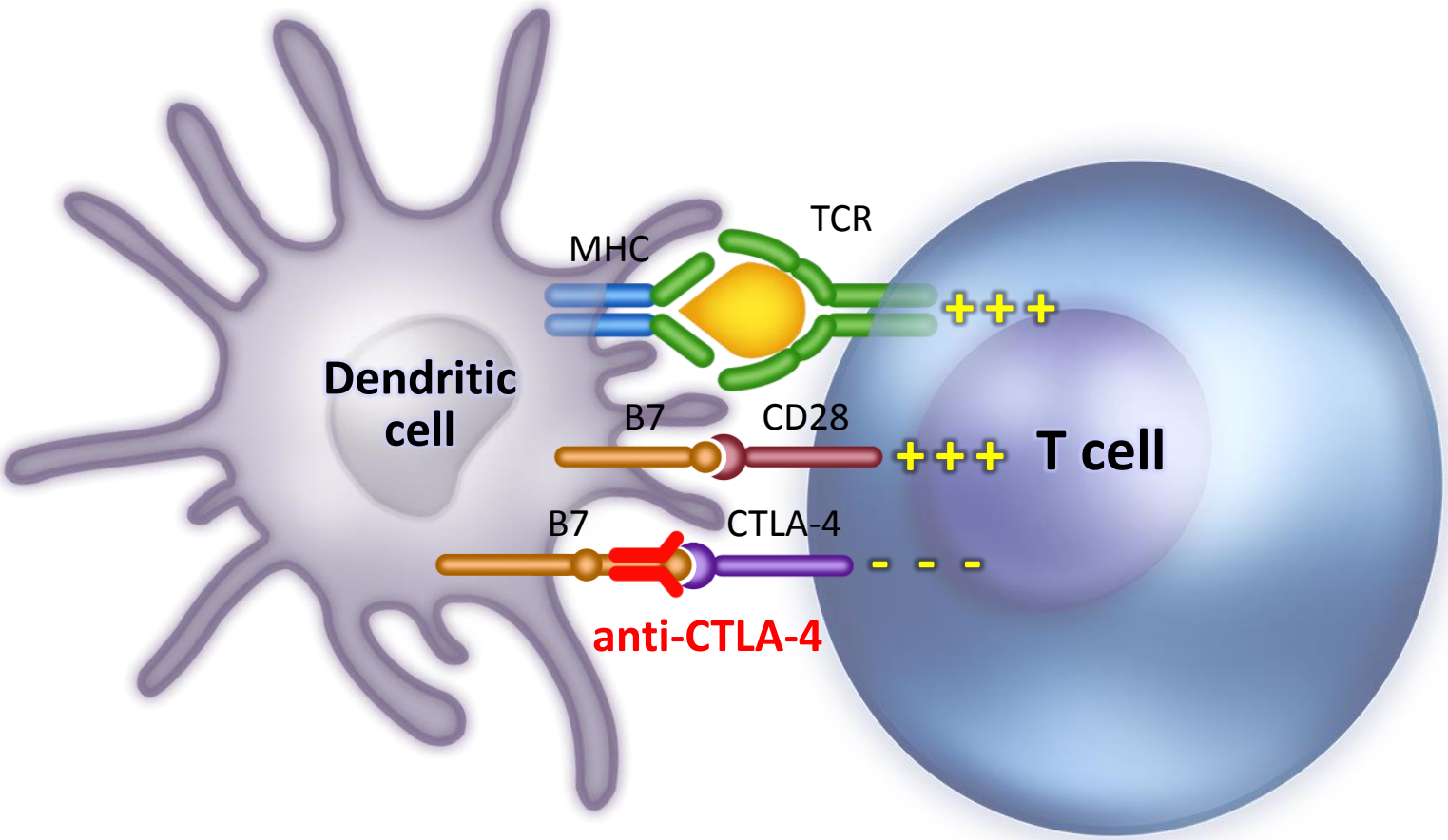
  - Amgen
  - Bristol-Myers Squibb
  - GlaxoSmithKline
  - MedImmune
  - Merck

Introduction

- Approved drugs for the adjuvant therapy of stage III melanoma are interferon (IFN)-α2b (US, EU) and pegylated IFN-α2b (US)[1]
- Unmet need: HR RFS for adjuvant HDI=0.83, IDI=0.84, LDI=0.85[2]
- IFN-α and pegylated IFN-α2b have a significant negative impact on health-related quality of life (HRQoL)[3,4]
- EORTC 18071 was performed in a patient population at high risk of relapse; five-year relapse rates: stage IIIA, 37%; stage IIIB, 68%; stage IIIC, 89%[5]
- EORTC 18071 is the first adjuvant trial with a drug, Ipi, that has demonstrated an overall survival benefit in advanced melanoma[6]

[1]Eggermont AM, et al. *Lancet* 2014;383:816–27. [2]Suciu S, et al. *J Clin Oncol* 2014;32(5s):abstract 9067. [3]Brandberg Y, et al. *Eur J Cancer* 2012;48: 2012–9. [4]Bottomley A, et al. *J Clin Oncol* 2009;27:2916–23. [5]Romano E, et al. *J Clin Oncol* 2010;28:3042–7. [6]Wolchok JD, et al. *Ann NY Acad Sci* 2013;1291:1–13.

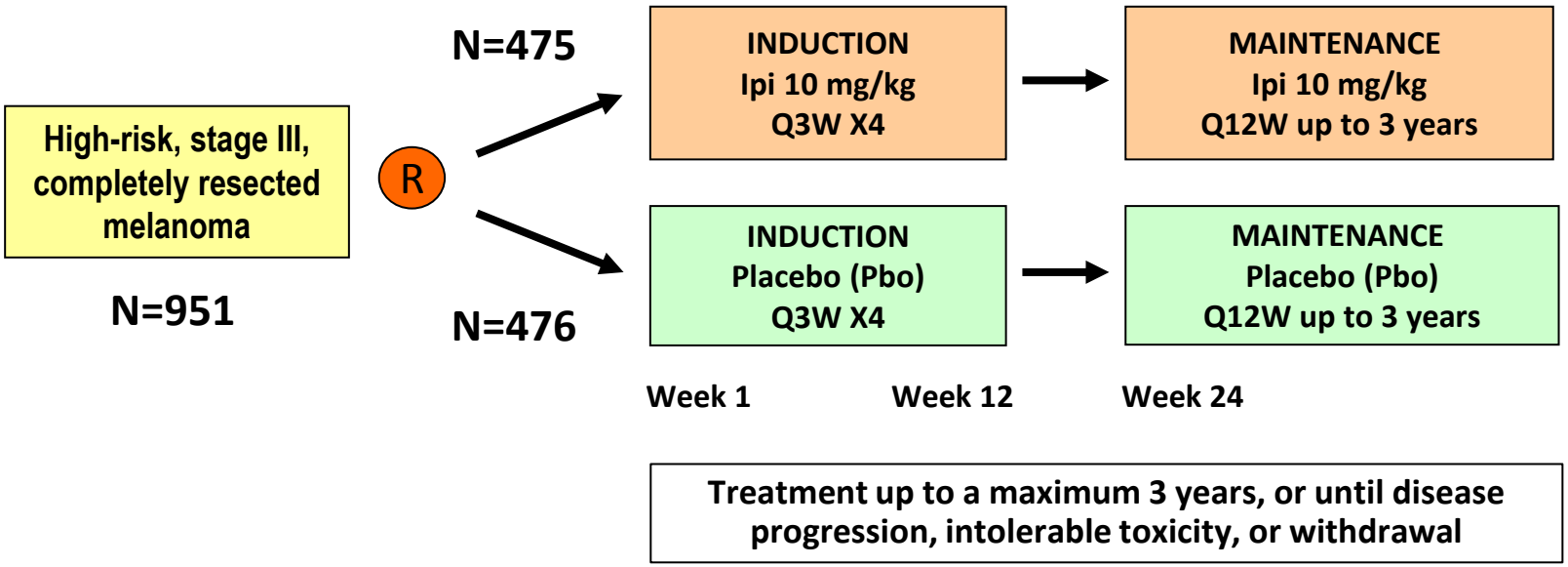
Immune Checkpoint Inhibitor Ipilimumab



Ipi: fully human, monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) to augment antitumor immunity[1]

[1]Fong L, Small EJ. *J Clin Oncol* 2008;26:5275–83.

EORTC 18071/CA184-029: Study Design



Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Key Eligibility Criteria

- At least 18 years of age
- Complete and adequate resection of stage III melanoma
- Histologically confirmed melanoma metastatic to lymph node
- Stage **IIIA (if N1a, at least 1 metastasis >1 mm);** stage **IIIB** or **IIIC** (no in-transit metastasis)
- No prior systemic therapy for melanoma
- Documented disease-free following surgery
- Randomization within 12 weeks of surgery
- No autoimmune disease

Study Overview

Primary endpoint

- **Recurrence-free survival (RFS)** by Independent Review Committee (IRC): time to local, regional, distant metastasis, or death
  - Stratified log-rank test; 2-sided α=0.05
  - 512 events required to provide 90% power (target HR=0.75)
  - Analyzed on intent-to-treat (ITT) population

Secondary endpoints

- OS, distant metastasis-free survival (DMFS), AE profile, and HRQoL

Enrollment Period: June 2008 – July 2011

Current analysis

- Primary efficacy endpoint (RFS), safety, and HRQoL
- Duration of follow-up: median 2.7 years; 528 events per IRC/56% of overall patients
- DMC recommendation: Study ongoing for OS and DMFS

Baseline Patient Characteristics

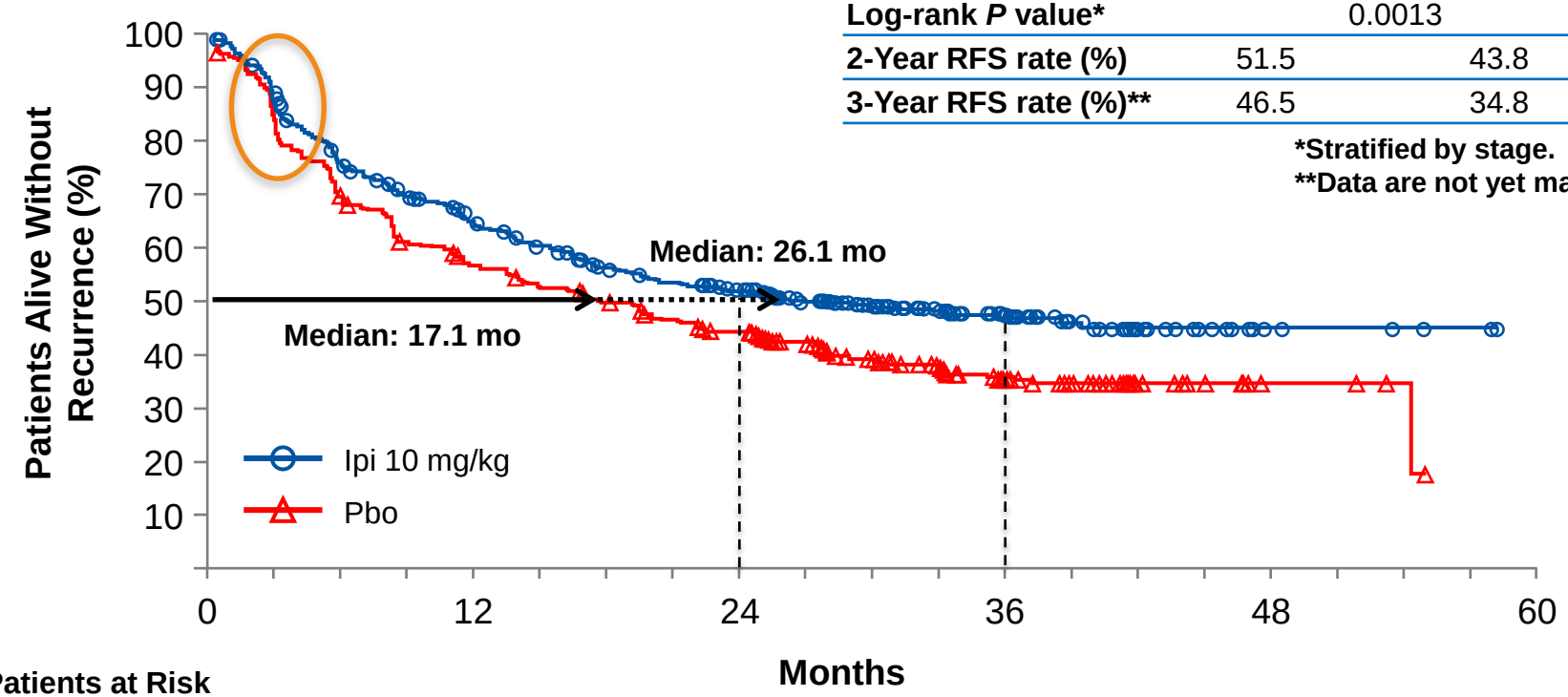
	Ipi (N=475)	Pbo (N=476)
Median age (years)	51	52
Male (%)	62	62
ECOG PS 0/1 (%)	94/6	94/6
Stage (%)		
IIIA	21	18
IIIB	45	43
IIIC with 1-3 positive LN	15	17
IIIC with ≥4 positive LN	20	21
Ulceration of primary (%)		
Present	41	43
1 vs 2-3 vs ≥4 positive LN (%)	46 vs 34 vs 20	46 vs 33 vs 21
Microscopic LN involvement (%)	44	41
Macroscopic LN involvement (%)	56	59

LN=lymph node.

Primary Endpoint: Recurrence-free Survival (IRC)

	Ipi	Pbo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

***Stratified by stage.**
****Data are not yet mature.**

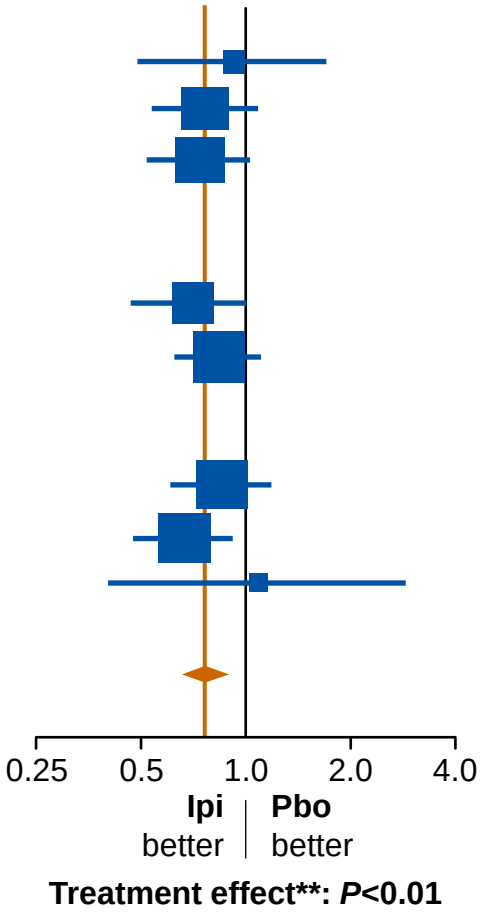


Patients at Risk

	O	N					
Ipi	234	475	276	205	67	5	0
Pbo	294	476	260	193	62	4	0

Recurrence-free Survival: Prespecified Subgroups

	Events/Patients Ipi	Events/Patients Pbo	HR & CI* (Ipi : Pbo)
AJCC 2002 (CRF)			
Stage IIIA	34/98	36/88	0.91 (0.49–1.68)
Stage IIIB	99/213	121/207	0.77 (0.54–1.08)
Stage IIIC	101/164	137/181	0.73 (0.52–1.02)
Type of LN+			
Microscopic	83/210	108/193	0.68 (0.47–0.99)
Macroscopic	151/265	186/283	0.83 (0.63–1.10)
Ulceration			
No	116/257	131/244	0.84 (0.61–1.17)
Yes	106/197	146/203	0.67 (0.48–0.93)
Unknown	12/21	17/29	1.08 (0.40–2.87)
Total	**234/475 (49.3%)**	**294/476 (61.8%)**	**0.76 (0.64–0.91)****



*95% CI for total, 99% CI elsewhere.
**Unstratified analysis.

POST HOC ANALYSES

MICROSCOPIC

VS

MACROSCOPIC/PALPABLE NODES

RFS Analyses Adjusted for Prognostic Factors

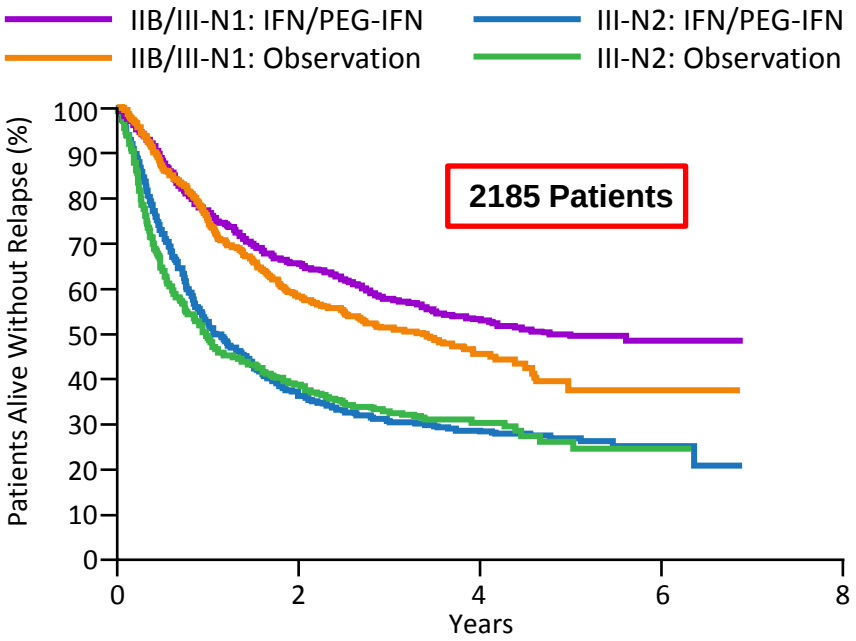
	All patients		Microscopic Stage III* (positive sentinel nodes)		Macroscopic Stage III* (palpable nodes)	
	Ipi (N=475)	Pbo (N=476)	Ipi (N=210)	Pbo (N=193)	Ipi (N=265)	Pbo (N=283)
3-yr rate (SE), %	46.5 (2.5)	34.8 (2.4)	57.6 (3.7)	39.2 (4.0)	37.8 (3.3)	31.7 (3.0)
HR (CI)**	0.75 (0.64-0.90)		0.65 (0.45-0.96)		0.81 (0.61-1.08)	
*P-value***	*0.0013*		*0.004*		*0.06*	
HR (CI)	0.74 (0.62-0.88)†		0.64 (0.44-0.93)‡		0.80 (0.60-1.06)‡	
P-value	*<0.001†*		*0.002‡*		*0.04‡*	

HR: hazard ratio for Ipi versus Pbo. CI: confidence interval at 95% (all patients) or at 99% (subgroups).

*Post hoc analyses.
**Cox model stratified by stage at randomization (primary analysis).
†Cox model: treatment effect adjusted by type of lymph node (LN) involvement (micro vs macroscopic), no. of LN+ (1, 2-3, ≥4), ulceration (No /Unknown, Yes), Breslow thickness (≤2, >2-4 or Unknown, >4 mm).
‡Cox model: as above, but without type of LN involvement.

Subgroup Analyses of RFS: Microscopic (N1) vs Clinically Palpable (N2) Lymph Nodes

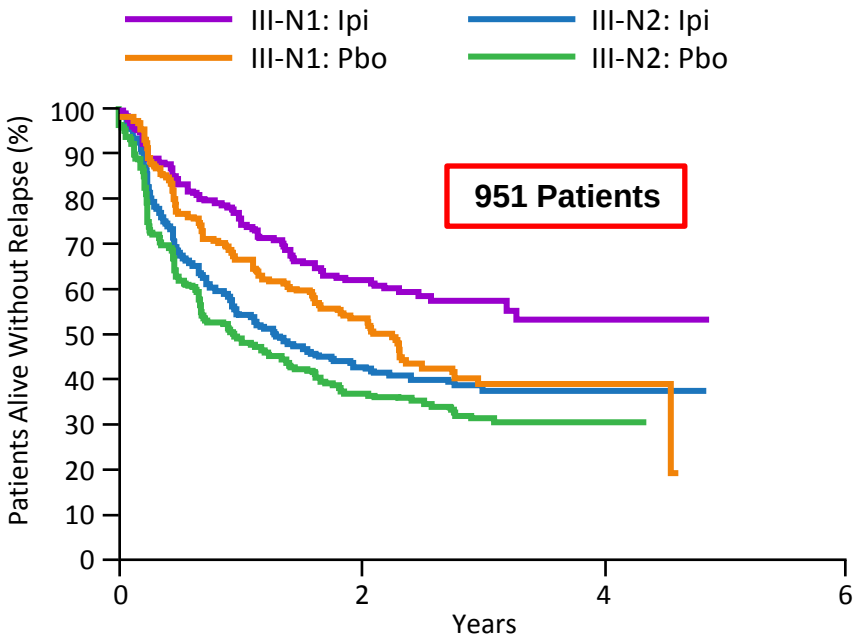
Interferon (IFN)/PEG-IFN
EORTC 18952/EORTC 18991[1]



O	N	Number of Patients at Risk		
357	770	501	234	26
204	384	221	79	7
467	655	241	108	13
261	376	144	52	2

Stage IIB/III-N1: **HR 0.78** (99% CI: 0.61–0.99)
Stage III-N2: **HR 0.91** (99% CI: 0.74–1.12)

Ipi
EORTC 18071



O	N	Number of Patients at Risk	
83	210	108	2
108	193	98	3
151	265	97	3
186	283	95	1

Stage III-N1: **HR 0.68** (99% CI: 0.47–0.99)
Stage III-N2: **HR 0.83** (99% CI: 0.63–1.10)

[1]Eggermont AM, et al. *Eur J Cancer* 2012;48:218–25.

POST HOC ANALYSES

ULCERATED PRIMARY

VS

NON-ULCERATED PRIMARY

Predictive importance of ulceration on the efficacy of adjuvant interferon-a (IFN): An individual patient data (IPD) meta-analysis of 15 randomised trials in > 7500 melanoma patients (pts)

Stefan Suciu1, Natalie Ives2, Alexander M. Eggermont3, John M. Kirkwood4, Paul Lorigan5, Svetomir Markovic6, Claus Garbe7, Keith Wheatley2

on behalf of the International Malignant Melanoma Collaborative Group

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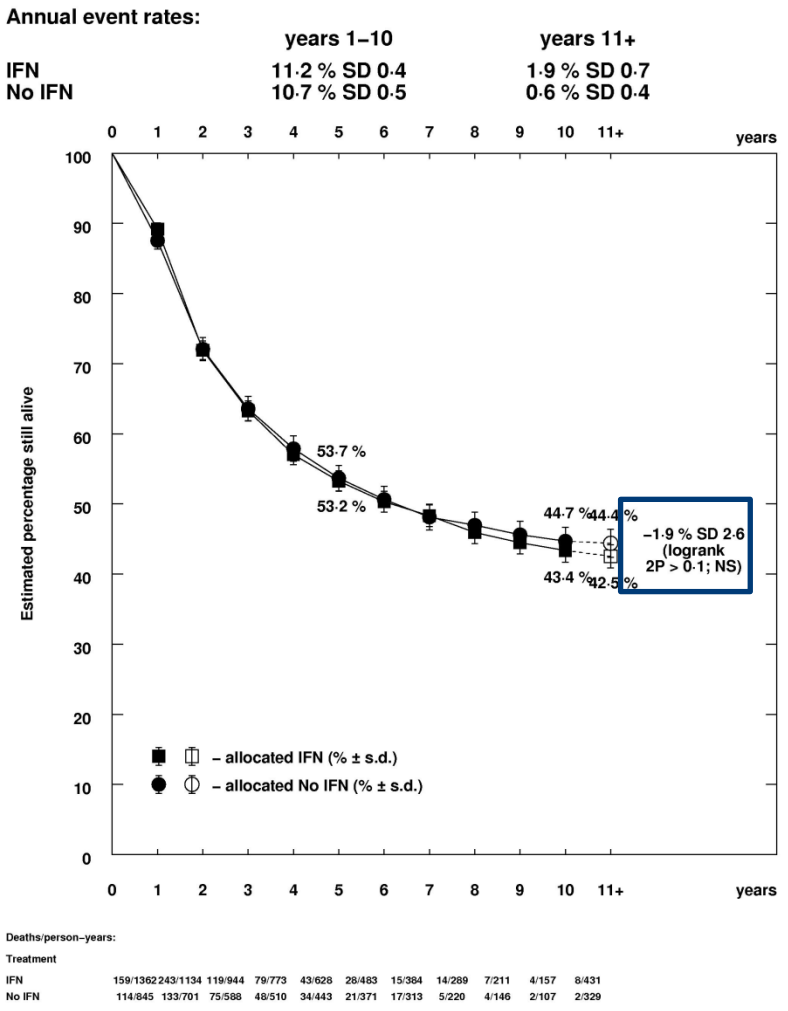
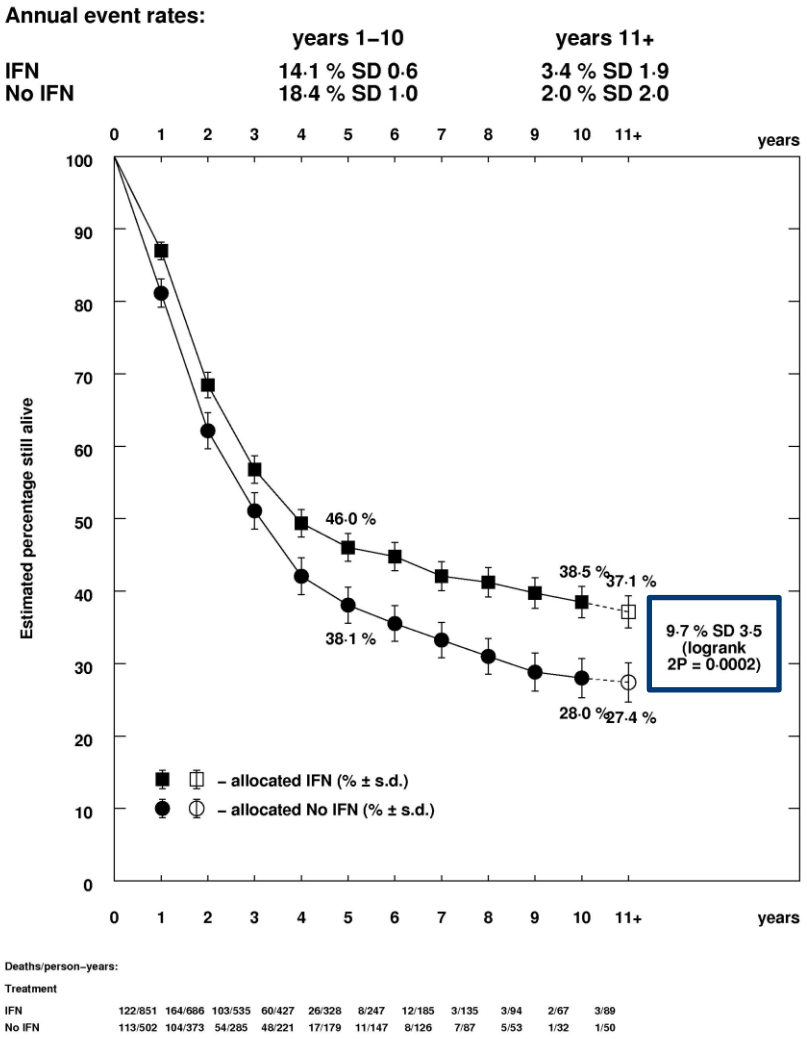
ASCO 2014:abstract 9067

ULCERATION AND IFN-SENSITIVITY
OVERALL SURVIVAL

Non-ulcerated primary



Ulcerated primary



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Suciu S, et al. ASCO 2014:abstract 9067

The future of cancer therapy

EORTC 18071: Importance of ULCERATION for RFS

	Microscopic or macroscopic Stage III		Microscopic Stage III* (sentinel nodes positive)		Macroscopic Stage III* (palpable nodes)	
Primary tumor	**Ulcerated (N=400)**	**Non-ulcer (N=501)**	**Ulcerated (N=187)**	**Non-ulcer (N=201)**	**Ulcerated (N=213)**	**Non-ulcer (N=300)**
HR (CI)[(1)]	**0.64 (0.46-0.90)**	0.84 (0.60-1.17)	**0.58 (0.34-0.97)**	0.75 (0.41-1.37)	**0.70 (0.45-1.08)**	0.86 (0.57-1.27)
HR (CI)	**0.63 (0.45-0.88)†**	0.82 (0.59-1.14)†	**0.53 (0.31-0.90)‡**	0.72 (0.40-1.31)‡	**0.68 (0.44-1.05)‡**	0.85 (0.57-1.28)‡

HR: hazard ratio for Ipi versus Pbo. CI: confidence interval at 95% (all patients)
or **CI at 99% (subgroups *Post hoc analyses).**
(1): Cox model stratified by stage at randomization (primary analysis).
†Cox model: treatment effect adjusted by type of lymph node (LN) involvement (micro vs macroscopic), no. of LN+ (1, 2-3, ≥4), ulceration (No, Yes), Breslow thickness (≤2, >2-4 or Unknown, >4 mm).
‡Cox model: as above, but without type of LN involvement.

Patient Disposition and Treatment

	Ipi (n=471)	Pbo (n=474)
Discontinuation, %*	91.7%	83.1%
Reasons for discontinuation, %		
Normal completion*	7.0	16.2
Disease progression	28.0	57.6
AE related to study drug	48.8	1.7
Other reasons**	7.9	7.6
Median doses, per patient	4.0	8.0
Mean doses, per patient	5.7	8.8
% Receiving ≥1 maintenance dose	42.0	70.0
% Receiving ≥7 doses (1 yr of therapy)	28.9	56.8

*1.9% of patients in the Ipi group and 3.0% in the Pbo group had 16 cycles reported as per protocol without a documented reason for discontinuation.

**Less than 1% difference between groups; includes AE unrelated to study drug, both (related and unrelated to study drug), patient request, poor/non-compliance, death, pregnancy, patient no longer eligible, other.

Safety: Immune-related Adverse Events

	% Patients					
	Ipi (n=471)			Pbo (n=474)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any irAE	90.4	36.5	5.5	38.6	2.3	0.2
Dermatologic	63.3	4.5	0	20.9	0	0
Rash	34.4	1.3	0	11.0	0	0
Gastrointestinal	46.3	14.9	1.1	17.7	0.6	0.2
Diarrhea	41.4	9.6	0	16.7	0.4	0
Colitis*	15.9	6.8	0.8	1.3	0.2	0
Endocrine	37.6	7.9	0.6	6.5	0	0
Hypophysitis	18.3	4.7	0.4	0.4	0	0
Hypothyroidism	8.9	0.2	0	0.8	0	0
Hepatic	25.1	7.9	2.8	4.4	0.2	0
LFT increase	19.7	3.8	1.5	4.0	0	0
Neurologic	4.5	1.1	0.8	1.9	0	0
Other	23.6	7.4	0.4	4.4	1.7	0

LFT=liver function test.*Gastrointestinal perforations: Ipi, 6 related (1.3%); Pbo, 3 unrelated (0.6%).

Deaths Related to Study Drug

- Five patients (1.1%) died due to drug-related AEs in the Ipi group:
  - Three patients with colitis (2 with gastrointestinal perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths related to study drug were reported in the Pbo group

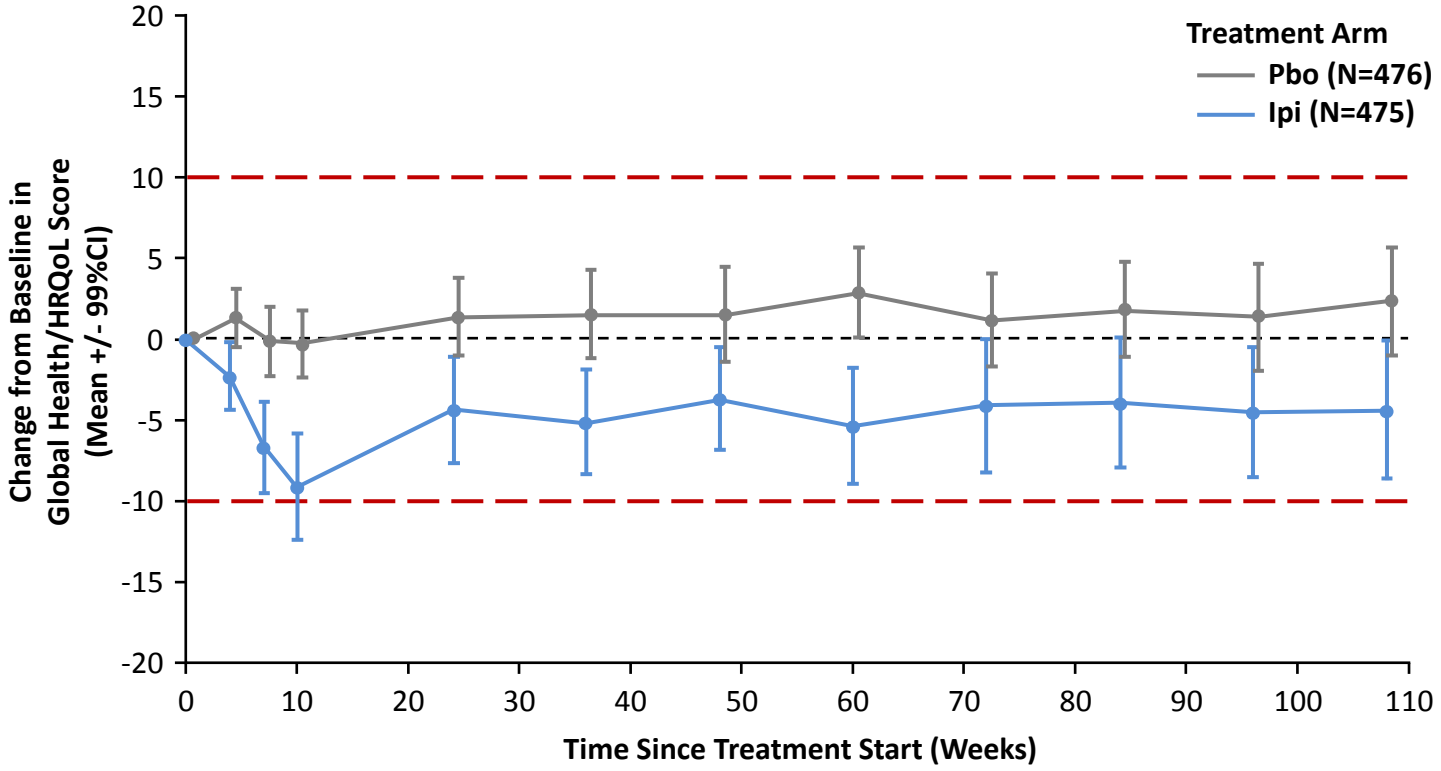
Health-Related QoL Assessment

- Includes all randomized patients (ITT population)
- Instrument: EORTC QLQ-C30[1]
  - Primary (prespecified): Global health status/HRQoL scale
  - Secondary: all other scales (e.g., functioning and symptom scales)
- Timing:
  - Baseline (i.e., within one week prior to first treatment)
  - Weeks 4, 7, 10, and 24, and every 12 weeks up to 2 years regardless of disease recurrence and last day of treatment administration
- Methods:
  - Treatment differences for the scales were assessed via a longitudinal mixed model
  - ≥10 point change between treatment arms = clinically relevant difference[2]
  - No corrections were made for multiplicity testing

[1]Aaronson NK, et al. *J Natl Cancer Inst.* 1993;85:365–76. [2]Osoba D, et al. *J Clin Oncol* 1998;16:139–44.

Change from Baseline in Global Health Status

- No clinically relevant difference (≥10 points) between treatment arms in mean score was observed at any time point, although there was a trend toward a negative effect with Ipi, particularly at week 10 (7.89)



- *There were significant differences in average scores for global health status during and after induction (P<0.001), yet the study was over powered for 10-point HRQoL differences*

Secondary Scales

- Clinically significant differences were observed for diarrhea and insomnia
  - Both occurred at week 10, with worse symptoms in the Ipi group, but there were no differences from week 24 and beyond
- No clinically significant differences were observed for all other scales

Mean scores	Diarrhea			Insomnia		
Assessment time	Pbo	Ipi	Diff (Pbo-Ipi)	Pbo	Ipi	Diff (Pbo-Ipi)
Baseline	5.64	6.22	-0.57	18.99	17.82	1.18
Week 4	7.23	12.59	-5.36	17.49	19.54	-2.06
Week 7	7.37	16.49	-9.13	17.08	23.92	-6.84
Week 10	7.67	18.17	-10.50	15.17	25.60	-10.43
Week 24	6.51	8.04	-1.54	17.96	18.04	-0.08
Week 36	5.91	11.15	-5.24	17.31	16.07	1.24
Week 48	6.38	9.90	-3.52	18.39	20.07	-1.67
…….						

Summary/Conclusions

- Study EORTC 18071/CA184-029 met its primary endpoint of a significant improvement in RFS with 10 mg/kg Ipi versus Pbo: HR 0.75, p=.0013
- Results are consistent across prespecified subgroups
- Post hoc analyses show:
  - All subgroups benefitted but the benefit appears greater in patients with microscopic disease but was greatest in patients with ulceration of the primary
- No clinically significant impact of Ipi treatment on global health status was observed, although Ipi scores were consistently below Pbo scores
- Safety profile was generally consistent with that observed in advanced melanoma, although the incidence of some irAEs (e.g., endocrinopathies) was higher in this study
- Data remain blinded for OS and DMFS and will be reported in the future
- Ongoing second phase III study in adjuvant setting (E1609), evaluating Ipi at 3 or 10 mg/kg vs high-dose IFN

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