All Activities for Cancer Patients

National Cancer Center Hospital
Tokyo, Japan

Development of Checkpoint Inhibitors for Cancer Therapy

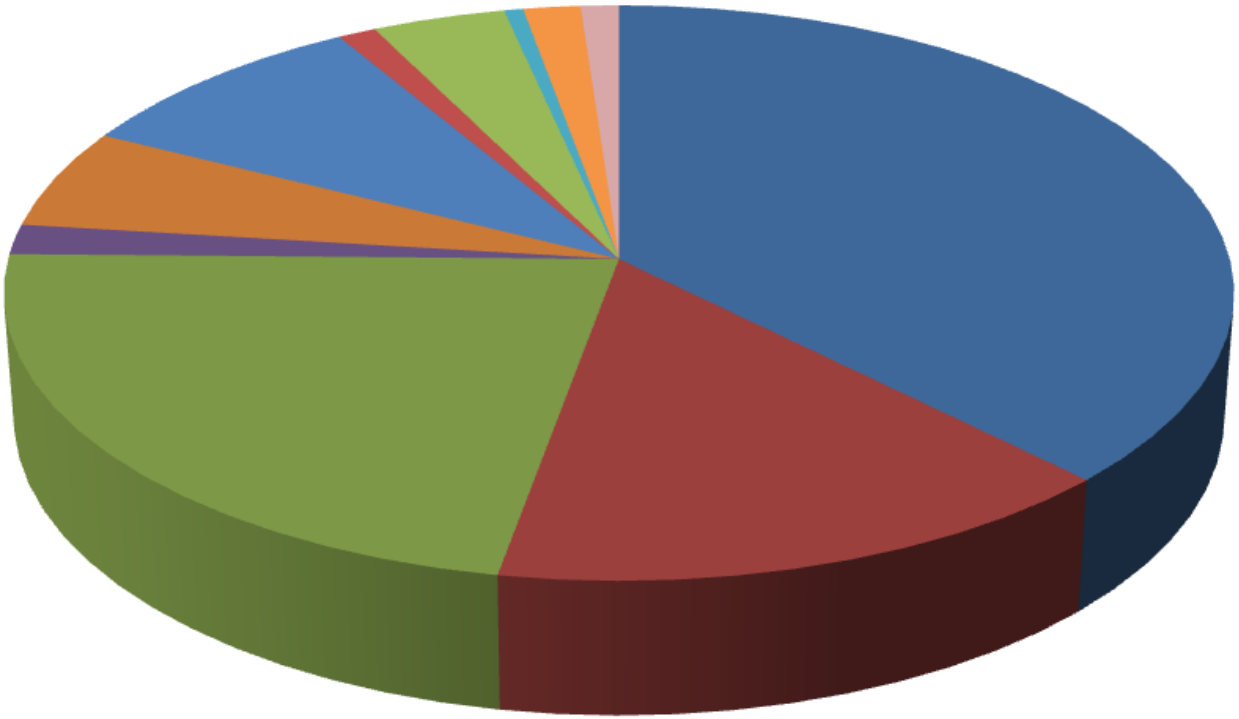
Naoya Yamazaki
National Cancer Center Hospital
Tokyo, JAPAN

Conflict of Interest Disclosure

- Naoya Yamazaki has received a speaker Fee from ONO, BMS, and Chugai.

All Activities for Cancer Patients

National Cancer Center Hospital
Tokyo, Japan

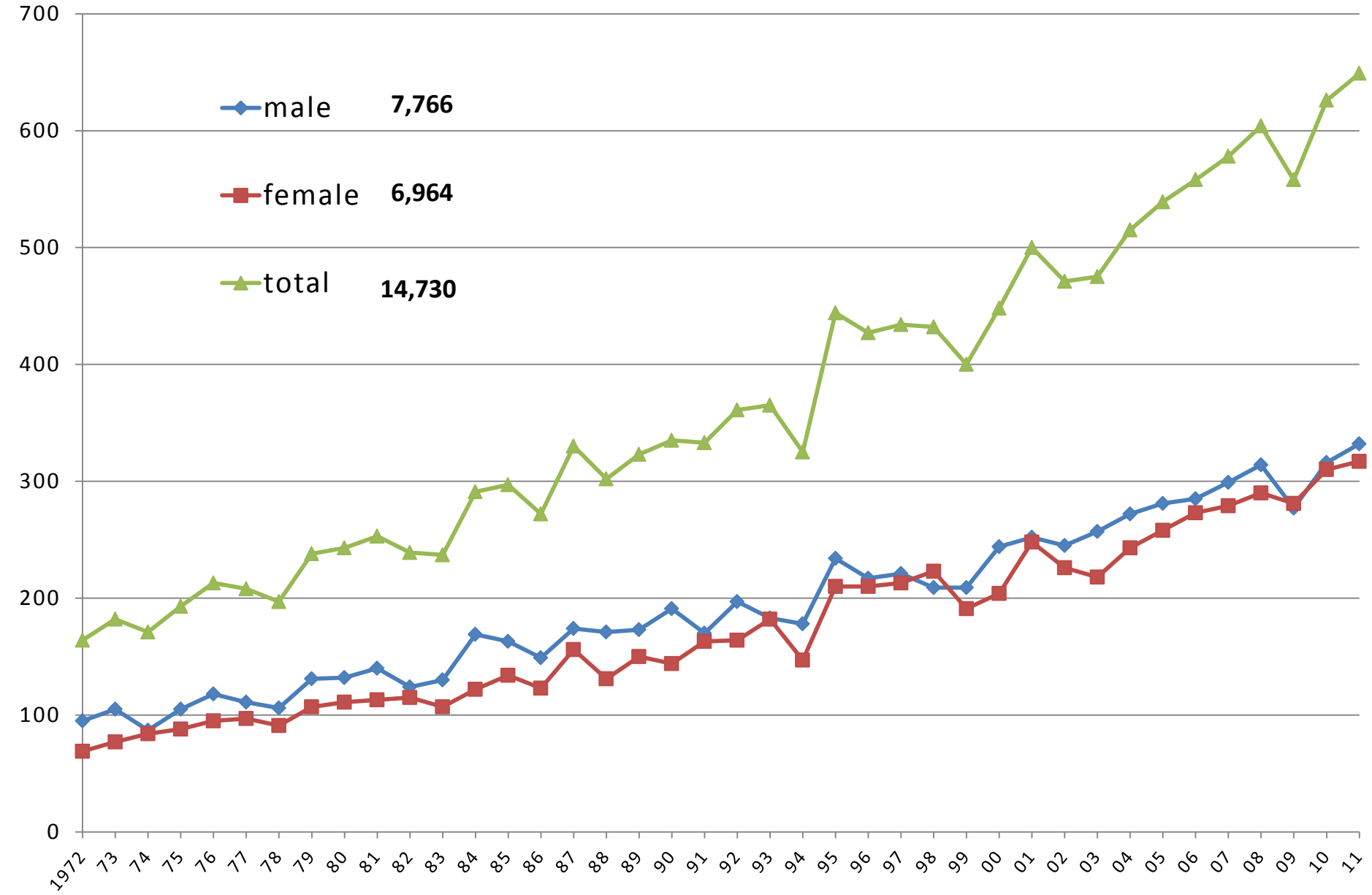


- Malignant melanoma
- Squamous cell carcinoma
- Basal cell carcinoma
- Sweat gland carcinoma
- Trichilemmal carcinoma
- Paget's disease
- Bowen's disease
- Dermatofibrosarcoma protuberans
- Angiosarcoma
- Malignant fibrous histiocytoma
- Epithelioid sarcoma
- Malignant lymphoma
- Merkel cell carcinoma
- others

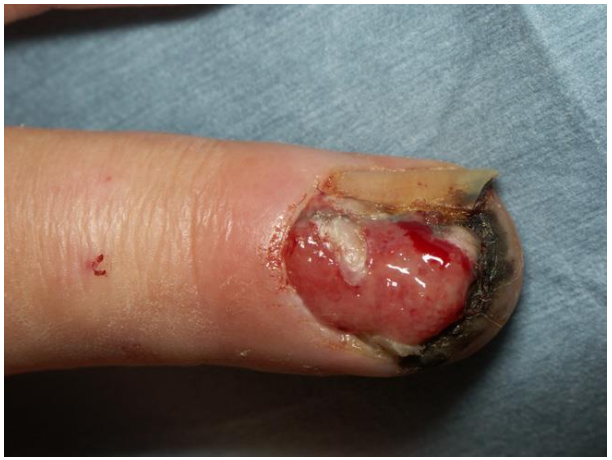
Incidence rates of representative skin cancers

Basal cell carcinoma	25%
Squamous cell carcinoma	17%
Melanoma	12%
Extramammary Paget's disease	6%
Angiosarcoma	1%

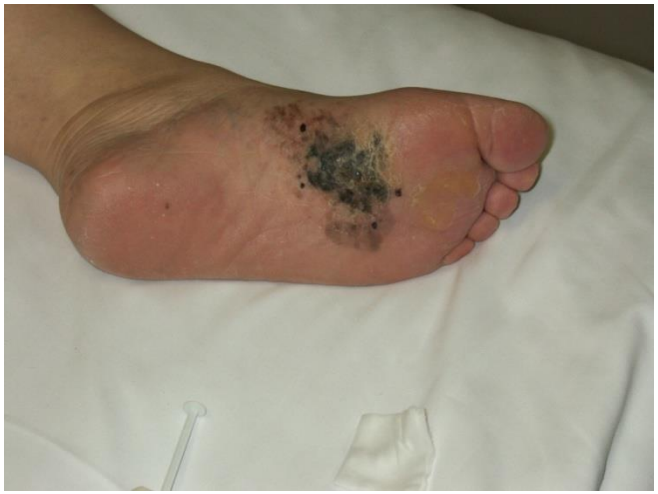
The numbers of deaths from the malignant melanoma in Japan
(1972 – 2011)



Melanoma drug therapy

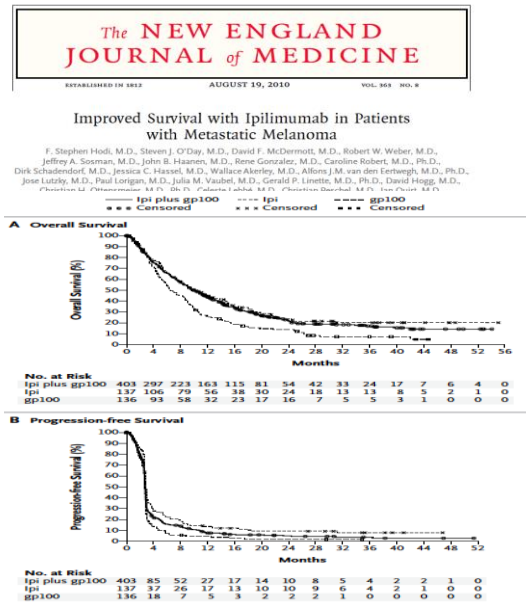


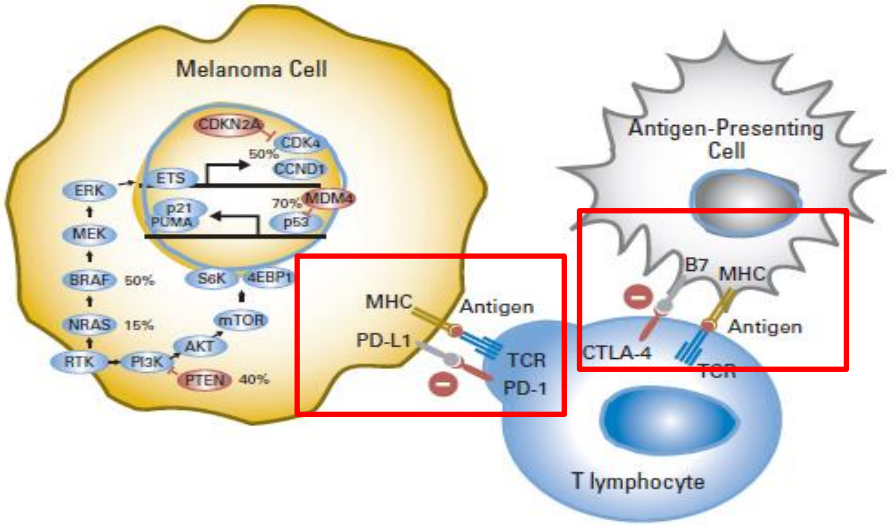
break through



2011 in westren countries

2014 in Japan

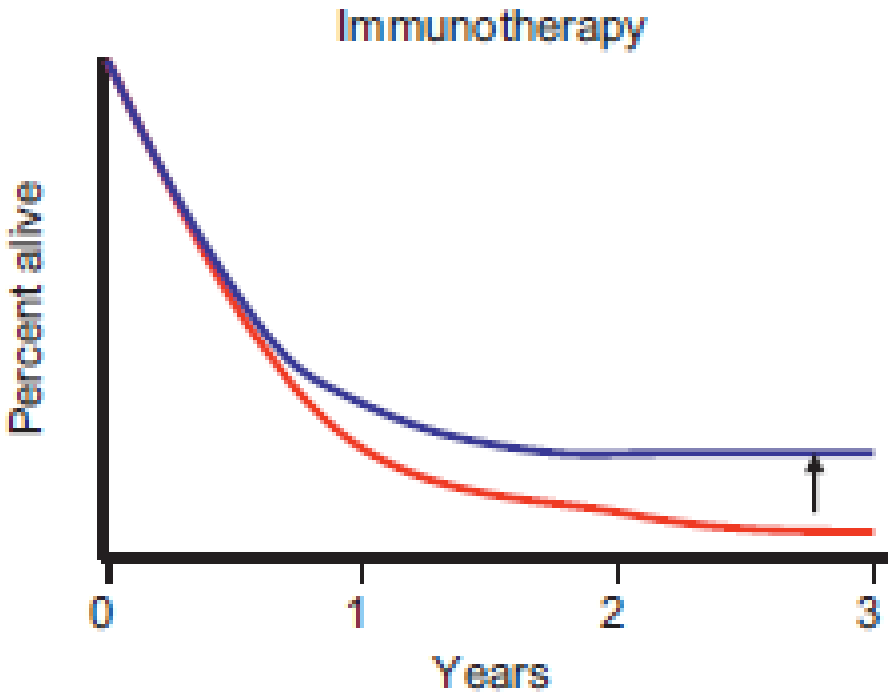


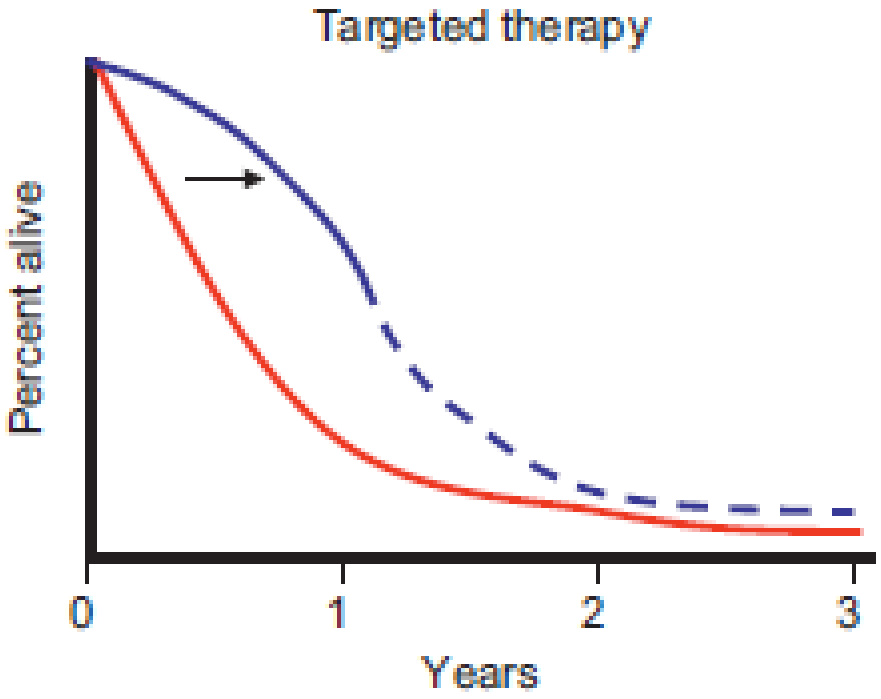


McArthur and Ribas, J Clin Oncol, 2013

Immune checkpoint blockade
Ipilimumab

Targeted drug therapy
Vemurafenib





Ribas A, et al. Clin Cancer Res:18(2), 2012.

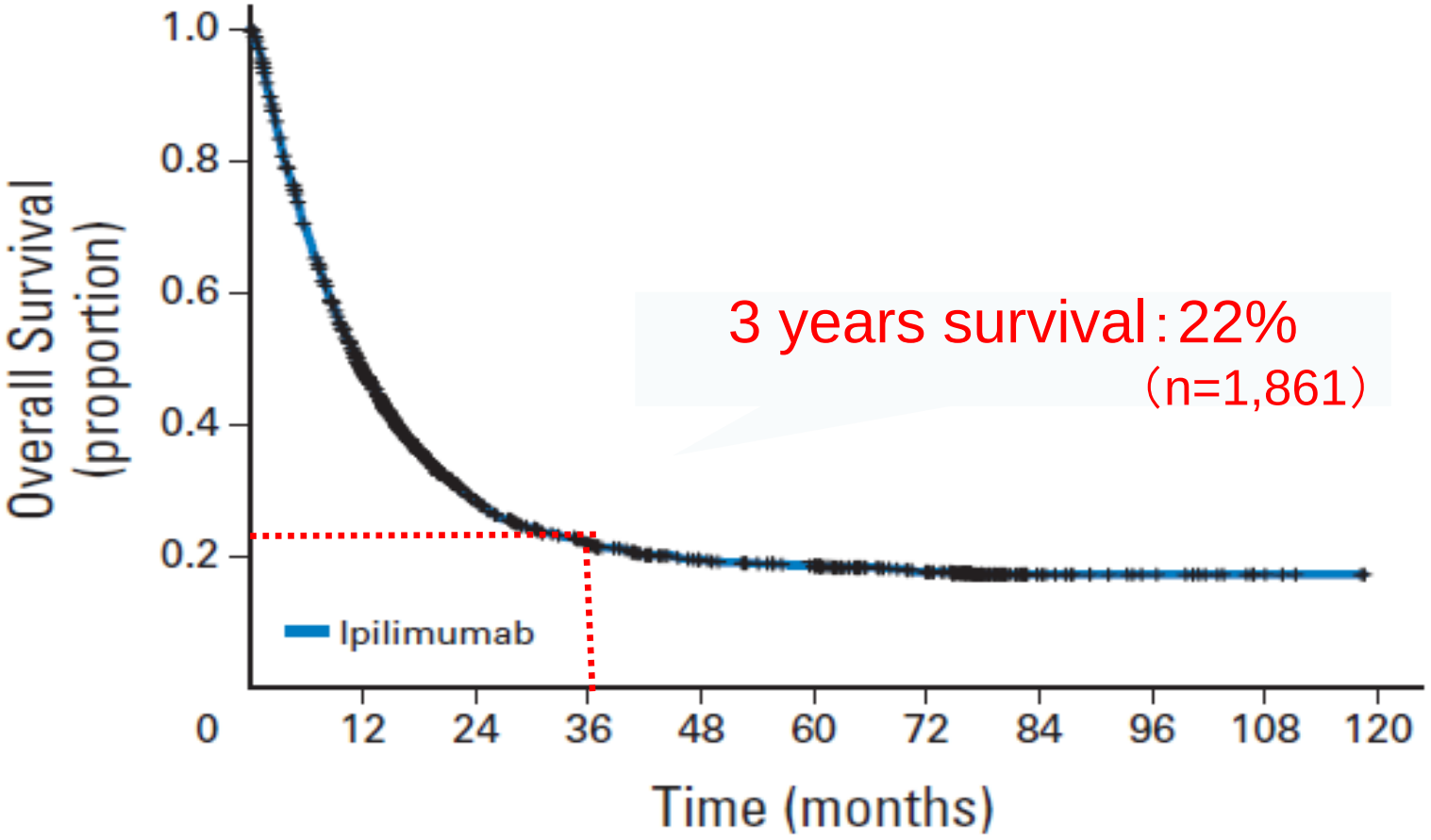
VOLUME 33 · NUMBER 17 · JUNE 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

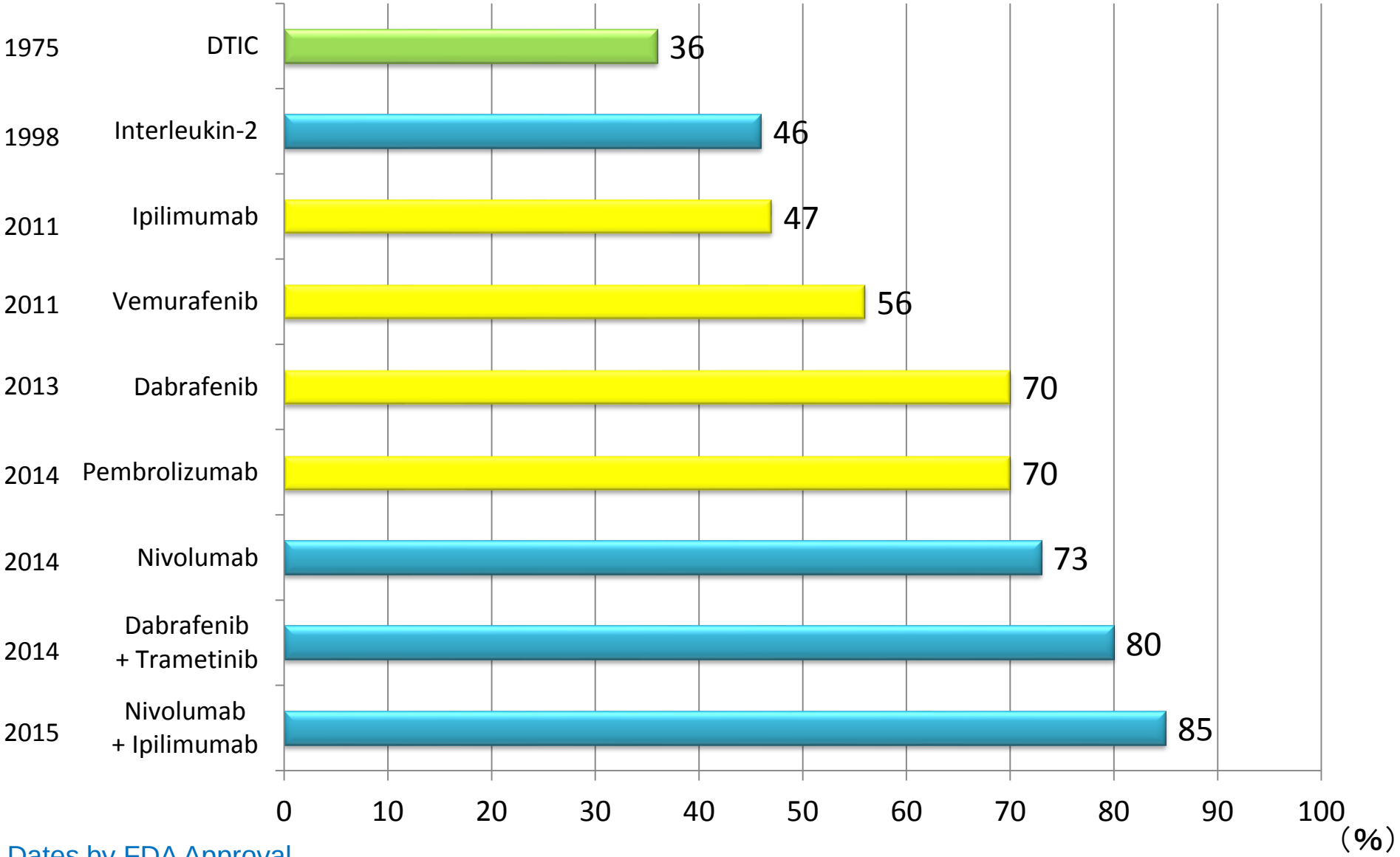
Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid,



3 years survival：22%
（n=1,861）

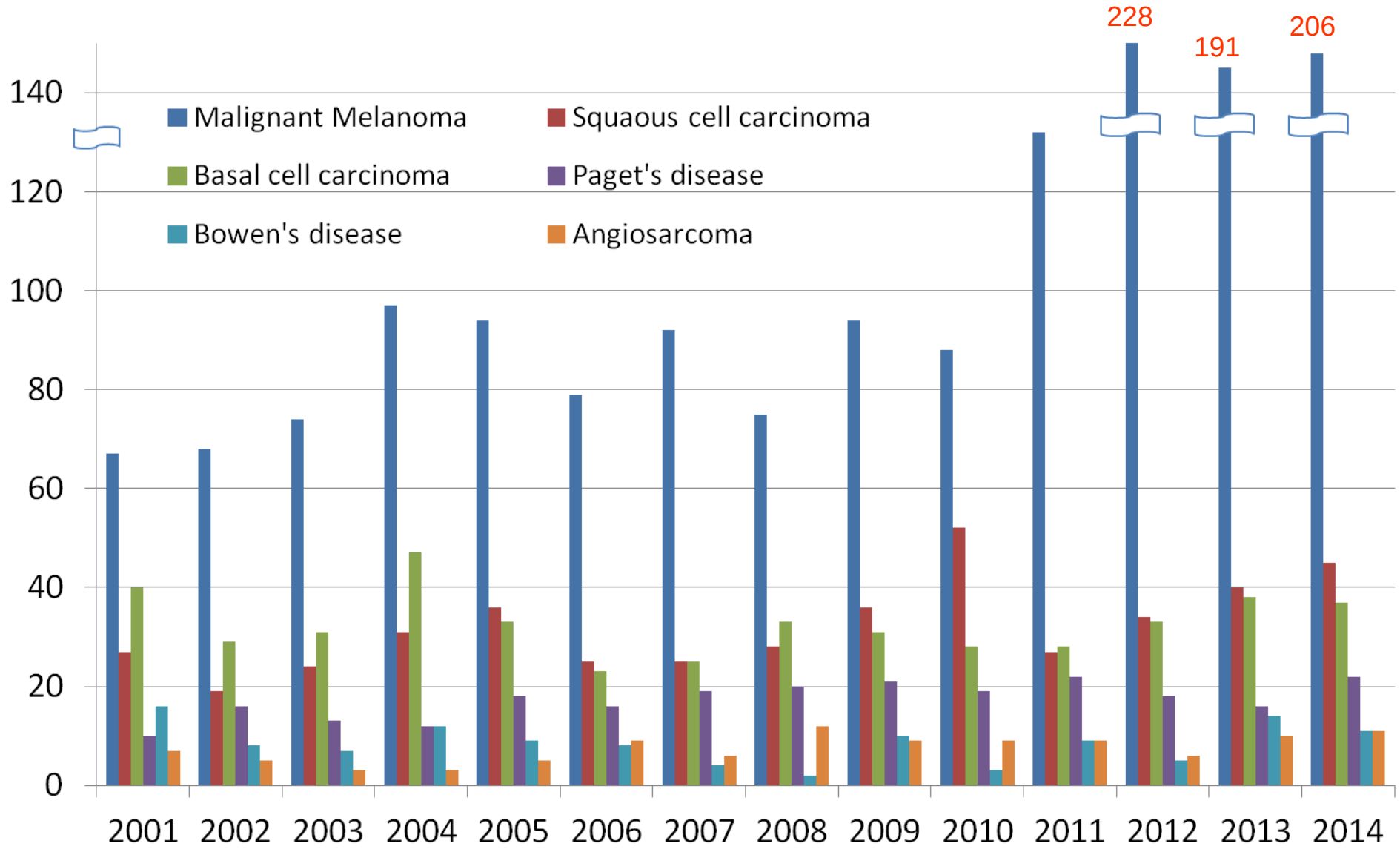
12 month survival for patients with advanced melanoma

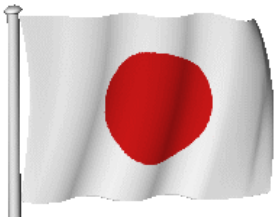


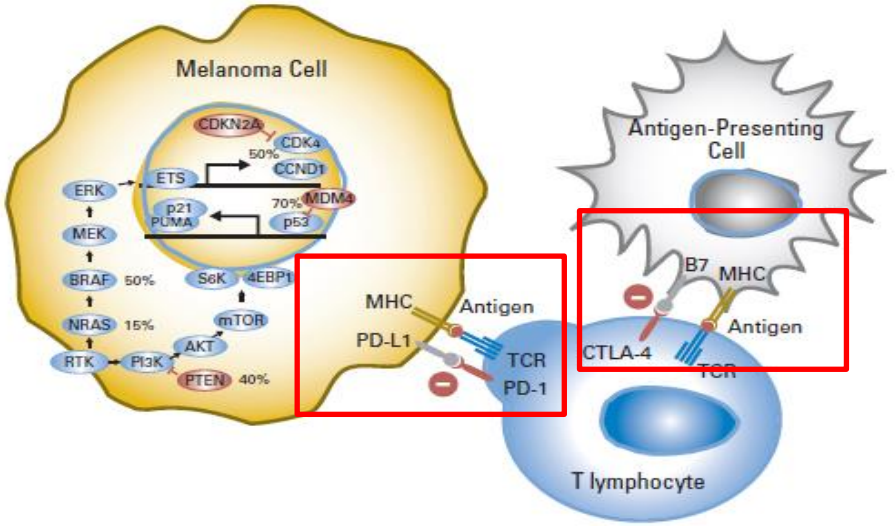
Dates by FDA Approval

McArtur et al, Lancet Oncol, 2014; Athins et al, J Cline Oncol, 1999; Hodi et al, NEJM, 2011; Grob et al, SMR, 2014; Fiathery et al, ASCO, 2014; Ribas et al, ASCO, 2014; Long et al, SMR, 2014; Ribas et al, Lancet Oncol, 2014

Numbers of New Patients

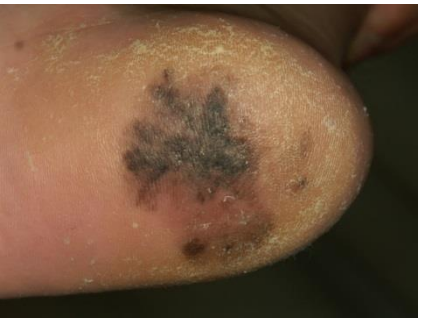




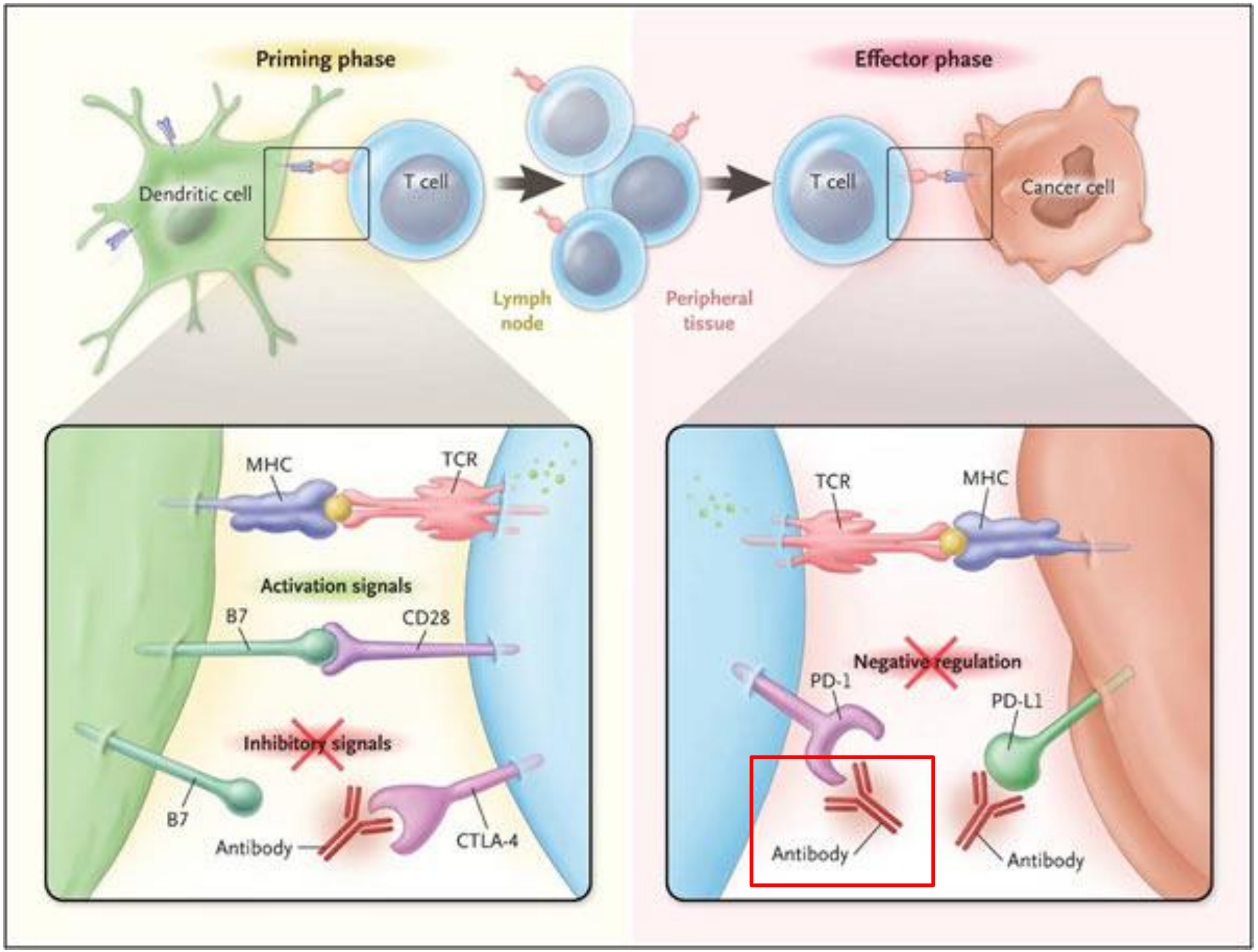


2014 in Japan
break through
Immune checkpoint blockade
Nivolumab (second line)
Targeted drug therapy
Vemurafenib

McArthur and Ribas, J Clin Oncol, 2013



2015 in Japan
Ipilimumab(first line)


Priming phase
Effector phase
Dendritic cell
T cell
Lymph node
Peripheral tissue
T cell
Cancer cell
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
Antibody
CTLA-4
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

The EMBO Journal vol.11 no.11 pp.3887 – 3895, 1992

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death

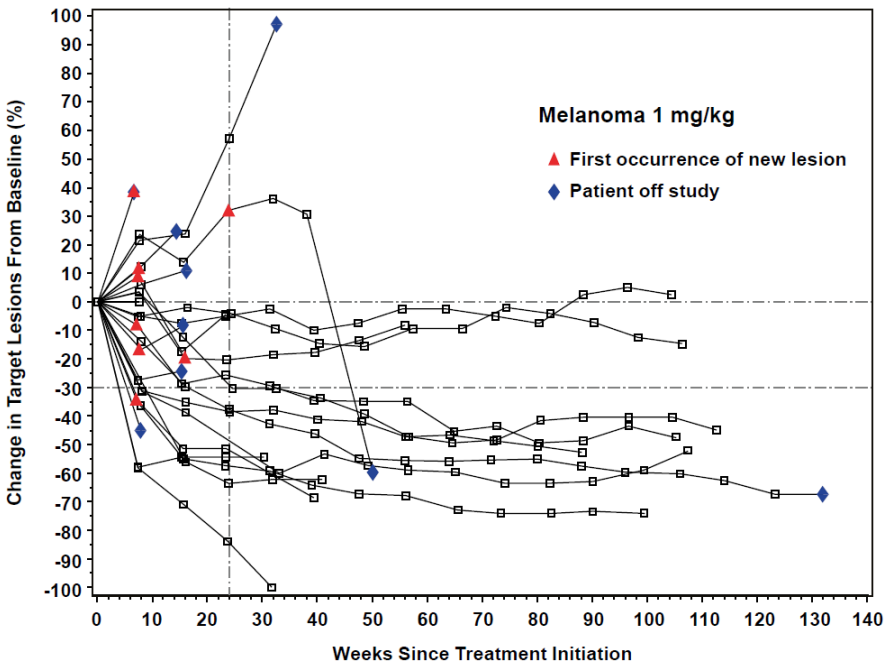
Yasumasa Ishida, Yasutoshi Agata, Keiichi Shibahara and Tasuku Honjo[1]

Department of Medical Chemistry, Kyoto University Faculty of Medicine, Yoshida, Sakyo-ku, Kyoto 606, Japan

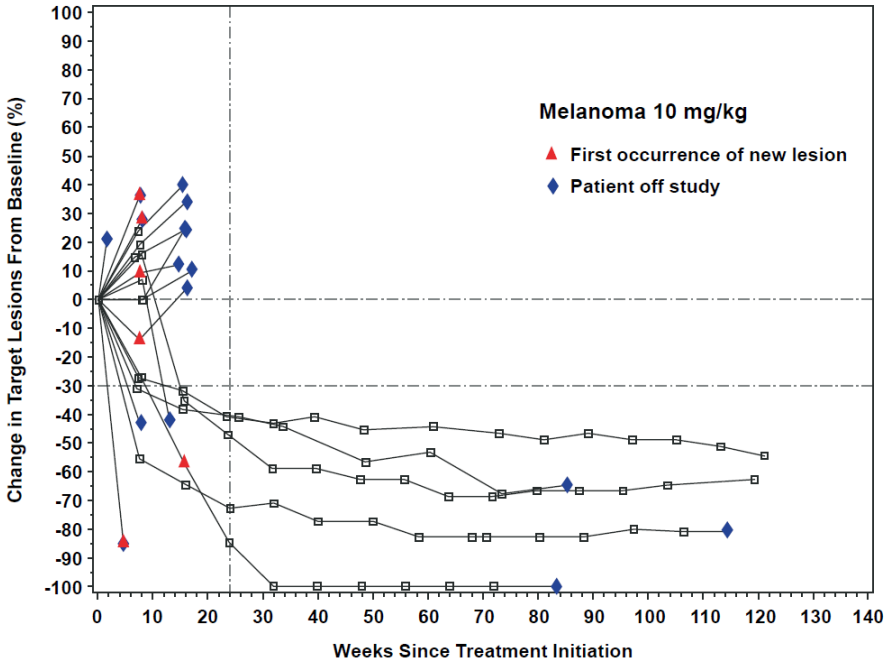
[1]Corresponding author

Changes in Target Lesions Over Time in Melanoma Patients

1 mg/kg



10 mg/kg

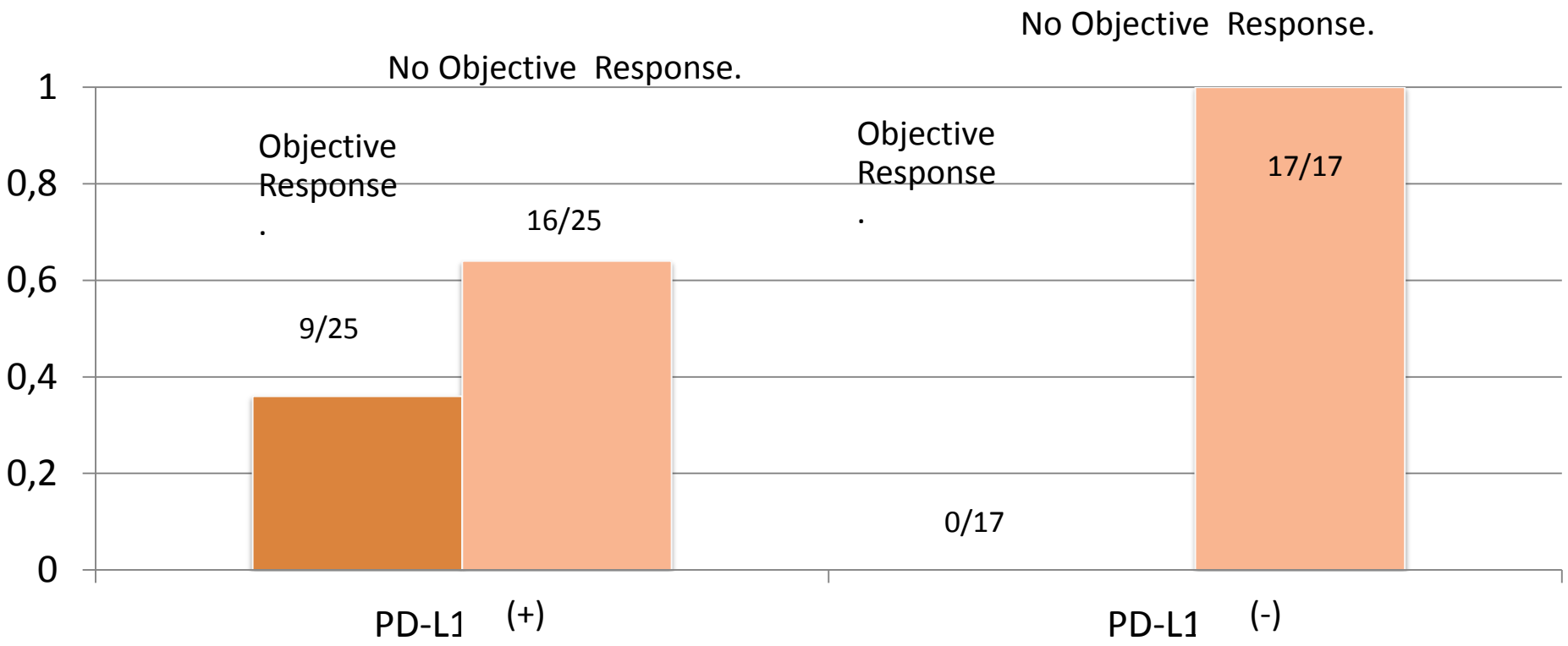


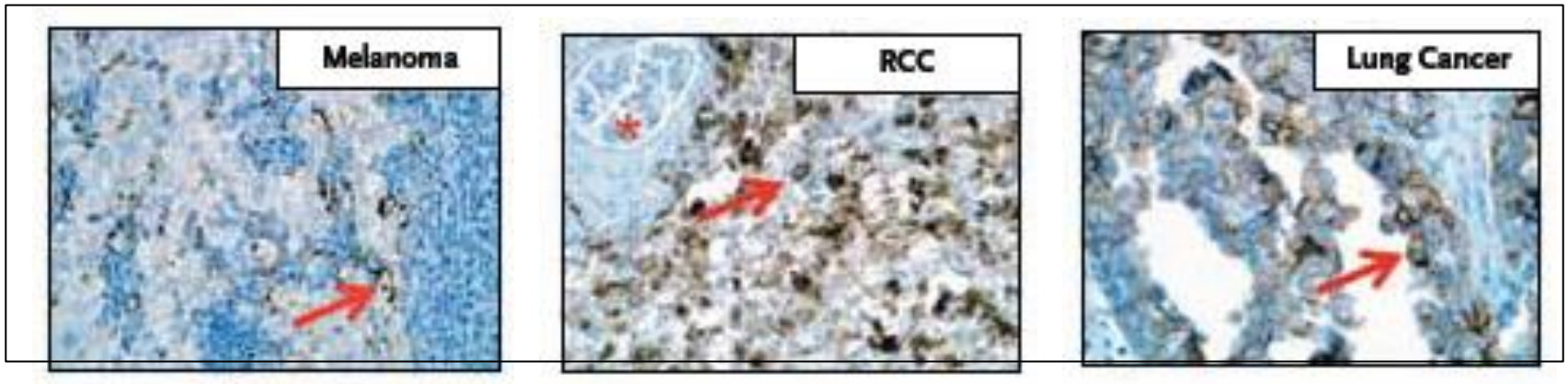
- Of 26 patients with OR
  - 18 were treated ≥1 year (before Feb 24, 2012) and 13 had responses of ≥1 year
  - 8 were treated <1 year and 6 had responses ranging from 1.9-5.6 months

Topalian SL et al. NEJM, 2012

PD-L1 expression and relationship with response

Topalian SL et al.
NEJM 2012.



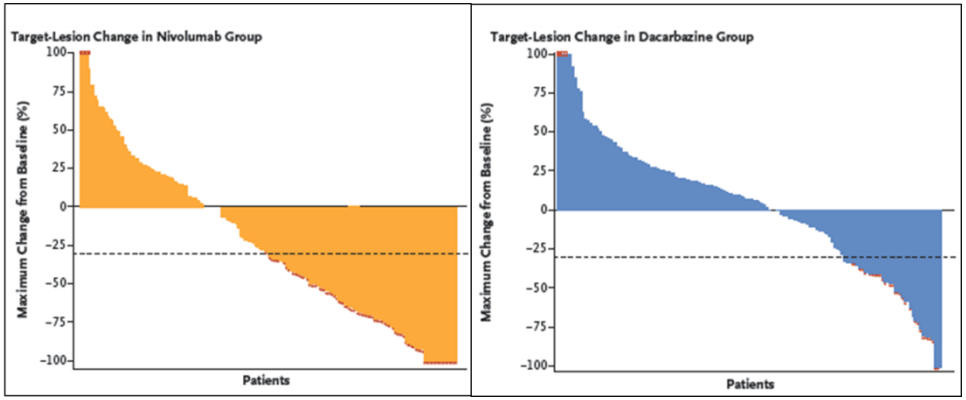


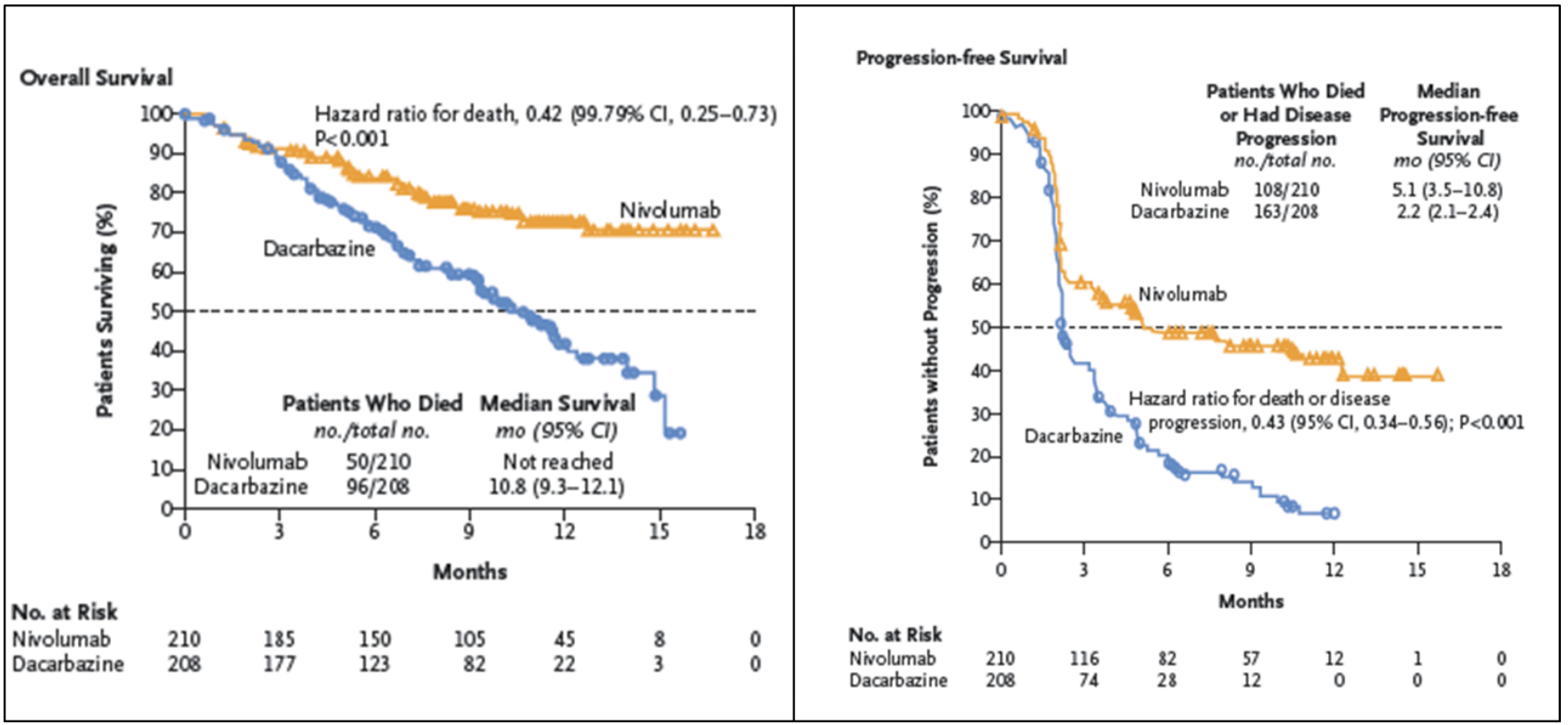
ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

N ENGL J MED.372;4 nejm.org January 22, 2015





EADO European Association of Dermato Oncology
11TH EADO CONGRESS & 8TH WORLD MEETING OF INTERDISCIPLINARY MELANOMA/SKIN CANCER CENTERS

Phase 2 study of Nivolumab (Anti-PD-1; ONO-4538/BMS-936558) in Japanese Patients with Advanced Melanoma: Final Report

Yoshio Kiyohara[1], Naoya Yamazaki[2], Hisashi Uhara[3], Hideaki Tahara[4]

[1]Dermatology Division, Shizuoka Cancer Center Hospital, Shizuoka, Japan
[2]National Cancer Central Hospital, Dermatology Division, Dermatologic Oncology, Tokyo, Japan
[3]Department of Dermatology, Shinshu University School of Medicine, Nagano, Japan
[4]Department of Surgery and Bioengineering, Advanced Clinical Research Center Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Study Design

- **Study Design**
  - Multi-centre, Open-label, Single arm
  - Nivolumab **2 mg/kg, Q3W**, IV
- **Endpoints**
  - **Primary** : Overall Response Rate (ORR)
  - **Secondary** : Overall Survival (OS), Progression-Free Survival (PFS), Immune related-ORR (ir-ORR), ir-PFS, ir-DCR, Adverse events, Pharmacokinetic parameters, Potential biomarkers
- **Eligibility Criteria**

  Key Inclusion Criteria
  - Recurrent or unresectable Stage III/ IV melanoma
  - DTIC failure
  - Age ≥ 20 yrs
  - ECOG PS : 0 – 1

  5 mucosal melanoma were enrolled.
  (1 vulval melanoma, 1 nasal melanoma, 3 oral melanoma)

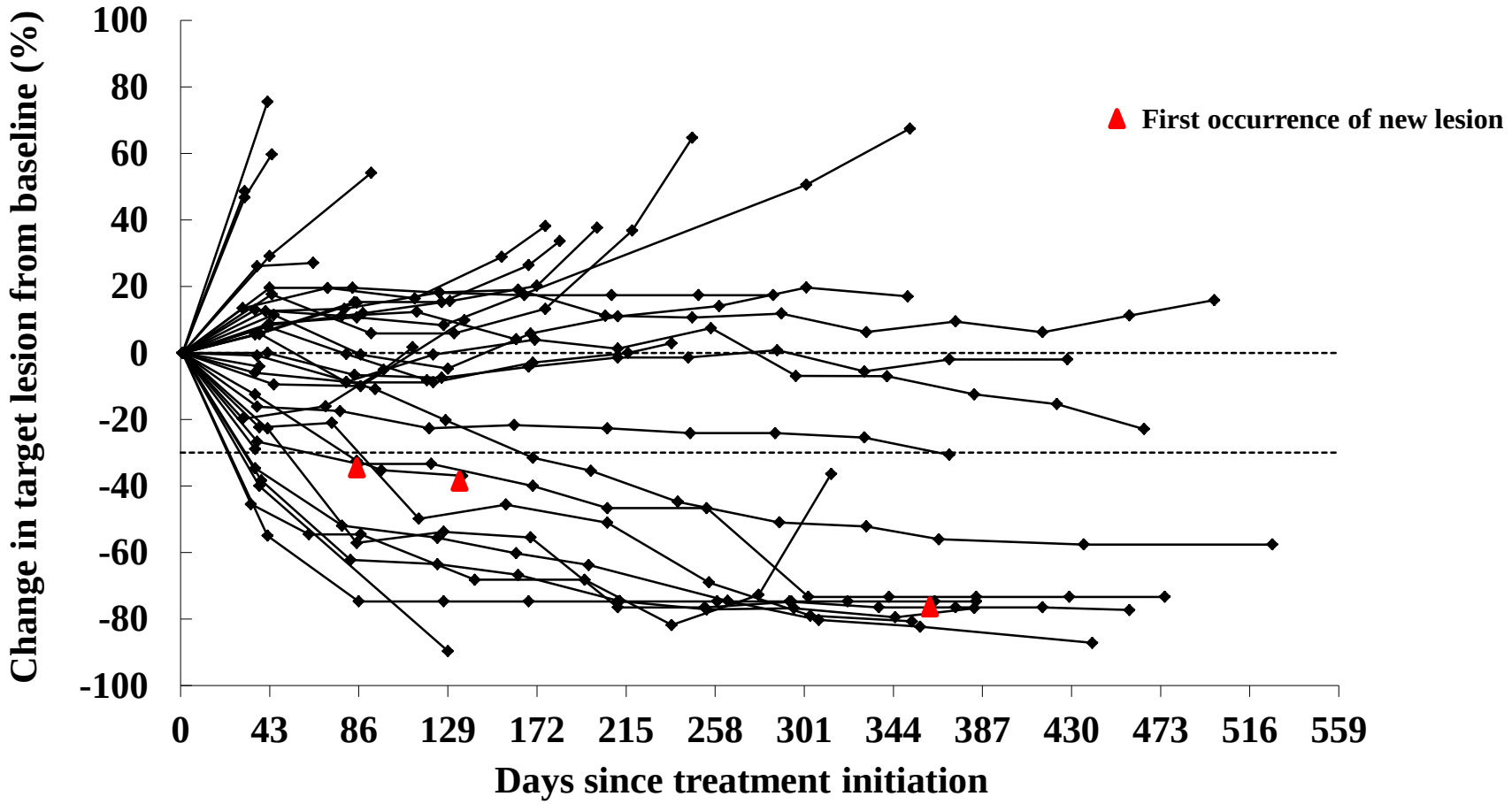
  Key Exclusion Criteria
  - Melanomas with primary region in esophagus and rectum
  - Patients with tumor in the brain or meninges (primary/metastasis)
- **Number of Pts :** N=35 (enrolled)

Summary of Clinical Activity (N=35)

	Investigator	Central review
ORR, %, (90%CI)	25.7 (15.6, 39.3)	28.6 (17.9, 42.3)
ir-ORR, %, (90%CI)	34.3 (22.6, 48.2)	-
PFS, Days, (90%CI)	184.0 (112.0, 314.0)	169.0 (72.0, 384.0)
ir-PFS, Days, (90%CI)	279.0 (126.0, 507.0)	-
OS, Days, (90%CI)	547.0 (276.0, -)	
OS at 1 year, (90%CI)	54.3 (39.6 , 66.9)	
OS at 2 year, (90%CI)	42.9 (29.0 , 56.0)	
DCR at 6 months, %, (90%CI)	48.6 (35.3, 62.1)	45.7 (32.7, 59.4)
ir-DCR at 6 months, %, (90%CI)	48.6 (35.3, 62.1)	-

1 patient was excluded because no diagnostic imaging was performed after Nivolumab administration

Response Over Time (N=35)

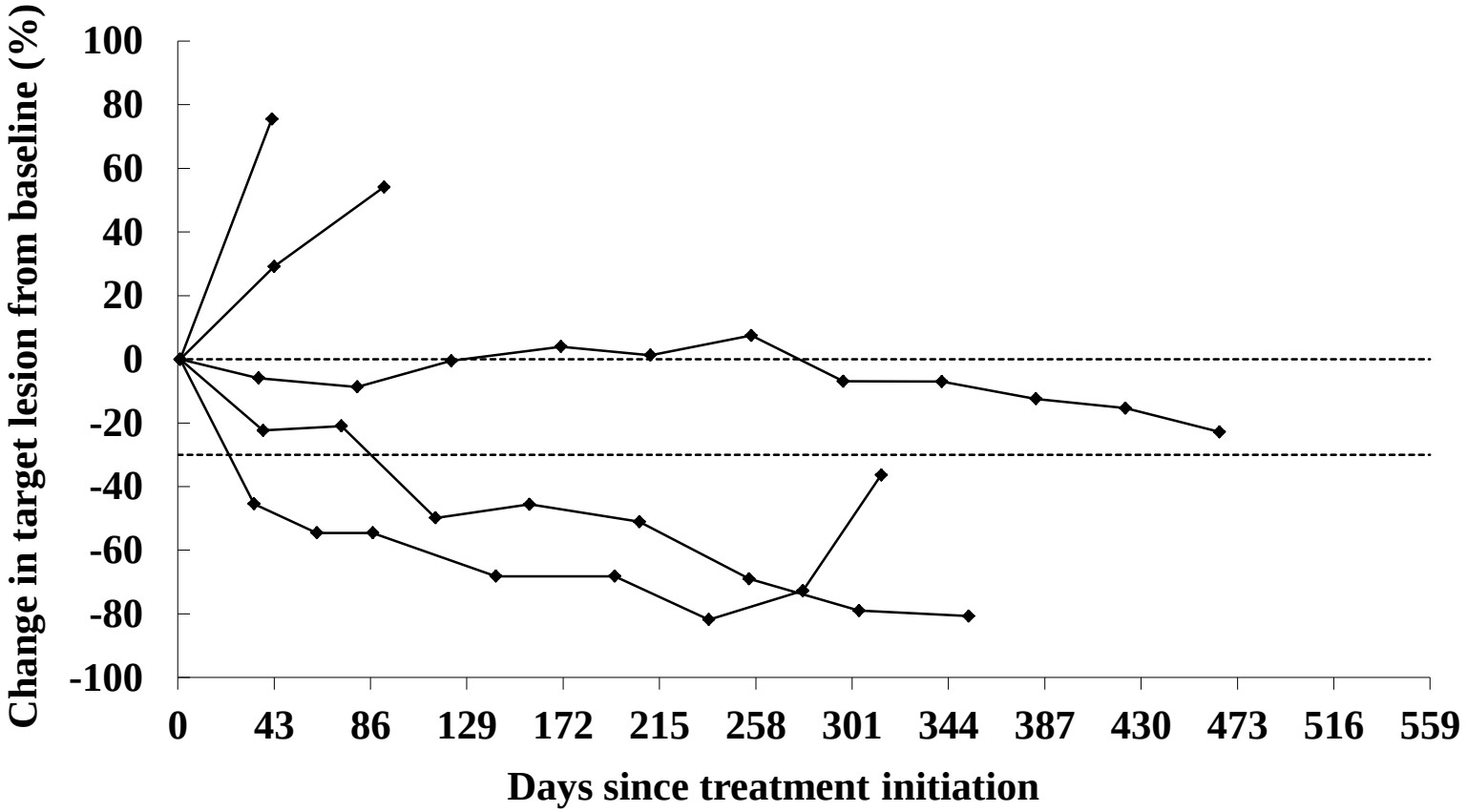


ESMO 2014 P1096

Long-term survival of Patients with Advanced Melanoma in Phase 2 study of Nivolumab

Response Over Time (N=5)

~ Primary mucosal malignant melanoma ~



ESMO 2014 P1096

Long-term survival of Patients with Advanced Melanoma in Phase 2 study of Nivolumab

Drug-Related Adverse Events Reported in ≥ 15 % of All Treated Patients (N=35)

Category	Any Grades (%)	Grade 3-4 (%)
Any DR-AEs	31 (85.7)	11 (31.4)
Pruritus	11 (31.4)	–
FT3 decreased	8 (22.9)	–
TSH increased	7 (20.0)	–
WBC decreased	7 (20.0)	–
CRP increased	6 (17.1)	1 (2.9)
FT4 decreased	6 (17.1)	–
Leukoderma	6 (17.1)	–

- Drug-Related AEs leading to discontinuation were reported in only 4 patients (hepatic AEs, pulmonary AE etc.).

Drug-related Serious Adverse Events

Category	Grade	Gender/Age
Liver disorder	3	Female / 31
Liver disorder	3	Female / 64
Interstitial lung disease	2	Female / 69
Hypothyroidism Pneumonia bacterial	2 3	Female / 56
Psoriasis	3	Male / 78

- G3/4 pneumonitis or drug-related deaths were not reported.
- All events were resolved.

Drug-Related Select Adverse Events* Reported in ≥ 10% of All Treated Patients (N=35)

Category	Any Grades (%)	Grade 3-4 (%)
Pruritus	11 (31.4)	—
FT3 decreased	8 (22.9)	—
TSH increased	7 (20.0)	—
FT4 decreased	6 (17.1)	—
AST increased	5 (14.3)	2 (5.7)
Hypothyroidism	5 (14.3)	—
ALT increased	4 (11.4)	1 (2.9)
Diarrhea	4 (11.4)	1 (2.9)

*: defined as AEs with potential immunological etiologies

- The incidence of pulmonary AEs was less than 10%.

Treatment experience at the National Cancer Center Hospital

Patients receiving nivolumab, and available for follow-up and treatment assessment: 67patients

(From July 2014 to end of June 2015)

Patient demographic characteristics (in 67 patients)

Factor		Opdivo treatment (67 patients)	
Gender	Male	33	
	Female	34	
Age	Median	65	
	Minimum - Maximum	17-93	
PS (ECOG)	0	27	(40.3%)
	1	34	(50.7%)
	2	5	(7.5%)
	3	1	(1.5%)
Primary sites	Skin	31	(46.3%)
	Non-skin	31	(46.3%)
	Uvea	7	(10.4%)
	Nasal cavity	11	(16.4%)
	Esophagus	4	(6.0%)
	Palate	3	(4.5%)
	Conjunctiva	3	(4.5%)
	Urethra/ bladder	2	(3.0%)
	Rectum	1	(1.5%)
	Primary unknown	5	(7.5%)

Patient demographic characteristics (in 67 patients)

Factor		Opdivo treatment (67 patients)	
Site of metastasis (at treatment initiation)	Lymph nodes	39	(58.2%)
	Lungs	34	(50.7%)
	Liver	24	(35.8%)
	Skin/subcutaneous	22	(32.8%)
	Bone	20	(30.0%)
	Brain	11	(16.4%)
	Intraperitoneal/retroperitoneal	10	(14.9%)
	Adrenal glands	8	(11.9%)
	Intramuscular	5	(7.5%)
	Kidneys	3	(4.5%)
	Pancreas	3	(4.5%)
	Others	14	(20.9%)
Number of metastatic organs (at treatment initiation)	Minimum - Maximum	0-10	(0: Nasal cavity primary tumor: 1 patient)
	1 organ	20	(30.0%)
	2 organs	13	(19.4%)
	3 organs	7	(10.4%)
	4 organs	15	(22.4%)
	≥5 organs	11	(16.4%)

Efficacy	Nivolumab（67cases）	
CR	2	(3.0%)
PR	13	(19.4%)
SD	18	(26.9%)
PD	34	(50.7%)

ORR：22.4%（15/67）

RECIST1.1

Responders

Response rate by primary site

Skin primary: 19.4% (6/31)

Mucosal primary: 33.3% (8/24)

uveal primary: 0% (0/7) (SD: 2 patients)

Primary unknown: 20% (1/5)

Mucosal primary cases

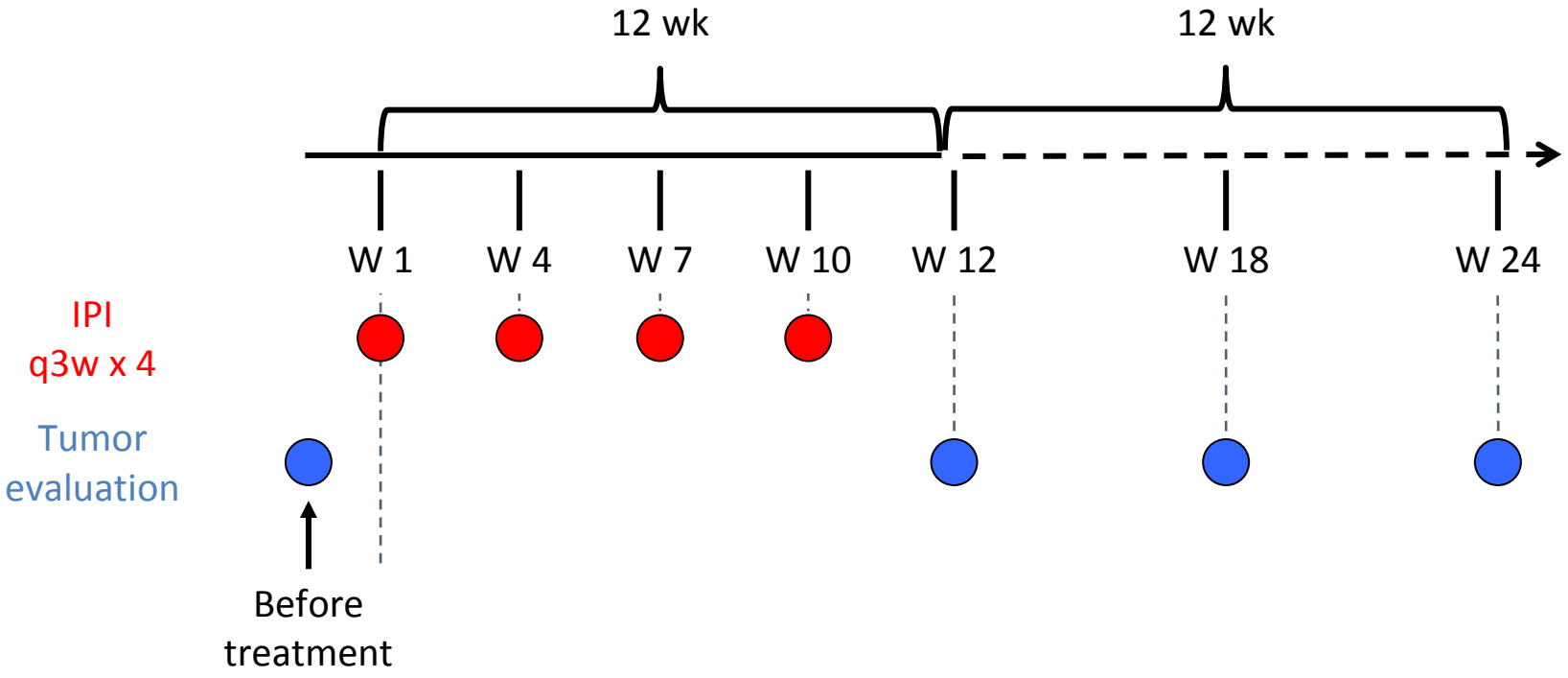
Site	Response rate
Nasal cavity	18.9% (2/11)
Esophagus	50% (2/4)
Palate	33.3% (1/3)
Conjunctiva	66.7% (2/3)
Urethra/ bladder	50% (1/2)
Rectum	0% (0/1)

Fourteen of 15 responders are under continued treatment while maintaining CR or PR.

Phase 2 Study of Ipilimumab in Japanese Patients With Advanced Melanoma

Study Design: CA184-396

Single-arm, open-label phase II study of IPI monotherapy 3 mg/kg



Safety Summary

AEs, n (%)	IPI (N=20)		
	Any Grade	Grade 3 or 4	Grade 5
Any AE	20 (100)	9 (45)	0
Drug-related serious AEs	3 (15)	2 (10)	0
Treatment-related AEs	12 (60)	3 (15)	0
Treatment-related AEs, n (%)[a,b]	**IPI (N=20)**		
	Any Grade (≥2 pts)	**Grade 3**	**Grade 4 or 5**
Rash	7 (35)	0 (0)	0
Pruritus	2 (10)	0 (0)	0
Pyrexia	3 (15)	0 (0)	0
ALT increased	3 (15)	1 (5)	0
AST increased	3 (15)	1 (5)	0
Decreased appetite	2 (10)	0 (0)	0
Diarrhea	2 (10)	0 (0)	0
Diabetes mellitus	-	1 (5)	0

[a]AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
[b]According to the most recent version of MedDRA.

- No patients discontinued due to a treatment-related AE
- No treatment-related deaths occurred

AEs = adverse events, ALT = alanine aminotransferase, AST = aspartate aminotransferase, MedDRA = Medical Dictionary for Regulatory Activities, pts = patients.

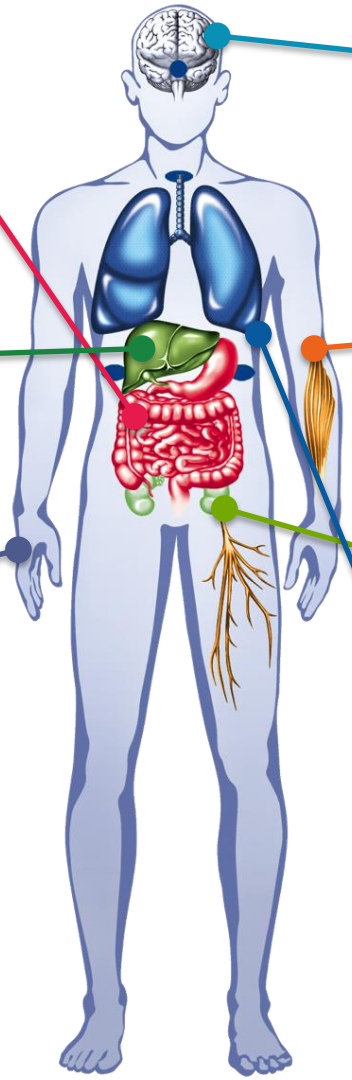
Sammary of clinical Activity

Best overall response, n (%)[a]	IPI (N=20)
Complete response	0 (0)
Partial response	2 (10)
Stable disease	2 (10)
Progressive disease	13 (65)
Not evaluable	3 (15)
Best overall response rate,[b] [95% CI]	2 (10) [1.2, 31.7]
Disease control rate,[c] [95% CI]	4 (20) [5.7, 43.7]

[a]By modified World Health Organization criteria.
[b]Number of pts with complete response or partial response / number of treated pts.
[c]Number of pts with complete response, partial response or stable disease / number of treated pts.

CI = confidence interval, pts = patients.

Immune-related adverse reactions



Diarrhea, colitis, gastrointestinal perforation

Diarrhea with or without fever
Increased bowel movements
Abdominal pain
Bloody stools, etc.

Hepatic impairment

Asymptomatic liver function test abnormalities (with generalized malaise, loss of appetite, jaundice, etc. in some cases)

Skin disorders

Rash, itching, etc.

Hypophysitis, hypopituitarism, hypothyroidism, adrenal insufficiency

Headache, malaise, visual field defects, behavioral changes, electrolyte abnormality, hypotension, etc.

Peripheral neuropathy

Weakness, sensory abnormality, perceptual disturbance, sensory and motor neuropathy, myasthenia gravis-like symptoms, etc.

Renal impairment

Nephritis, etc.

Interstitial lung disease

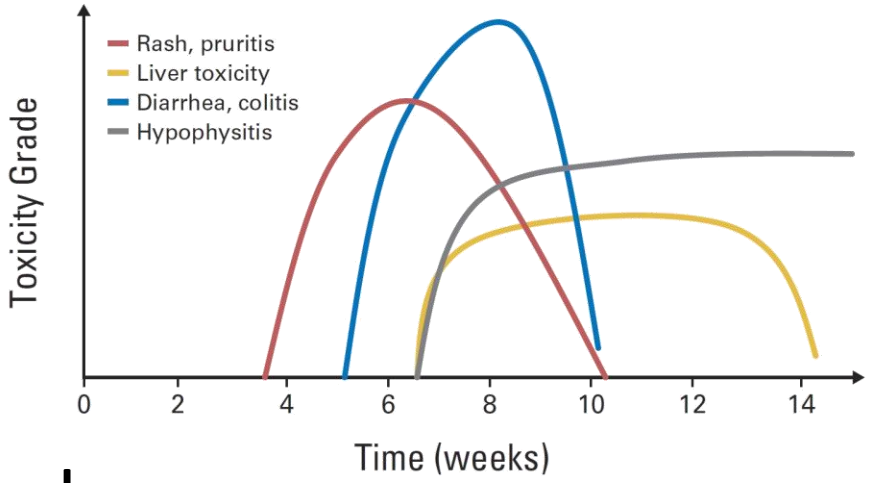
Infusion reaction

Excessive immune responses

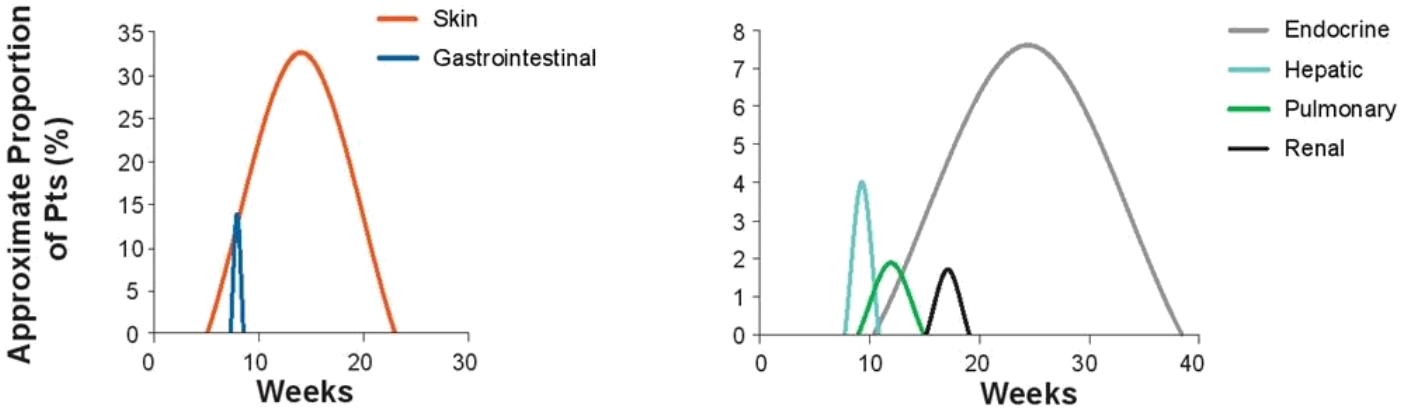
Eye disorders
(e.g., uveitis and iridocyclitis), etc.

Kinetics of appearance of immune-related adverse event

- Ipilimumab（Weber JS, et al., JCO 2012）



- Nivolumab（Weber JS, et al., ASCO 2015）



Summary of assessment and measures

Grade 1: Continuation of treatment

Monitor for any worsening of symptoms

Grade 2 (Except for skin disorders)

: Temporary interruption of treatment, resume the treatment after improvement to Grade 1.

If no improvement within 1 week or so, initiate PSL at the dose of 0.5 mg/kg.

Grade 3 (Except for skin disorders) / Grade 4

: Discontinuation of treatment, no rechallenge is allowed.

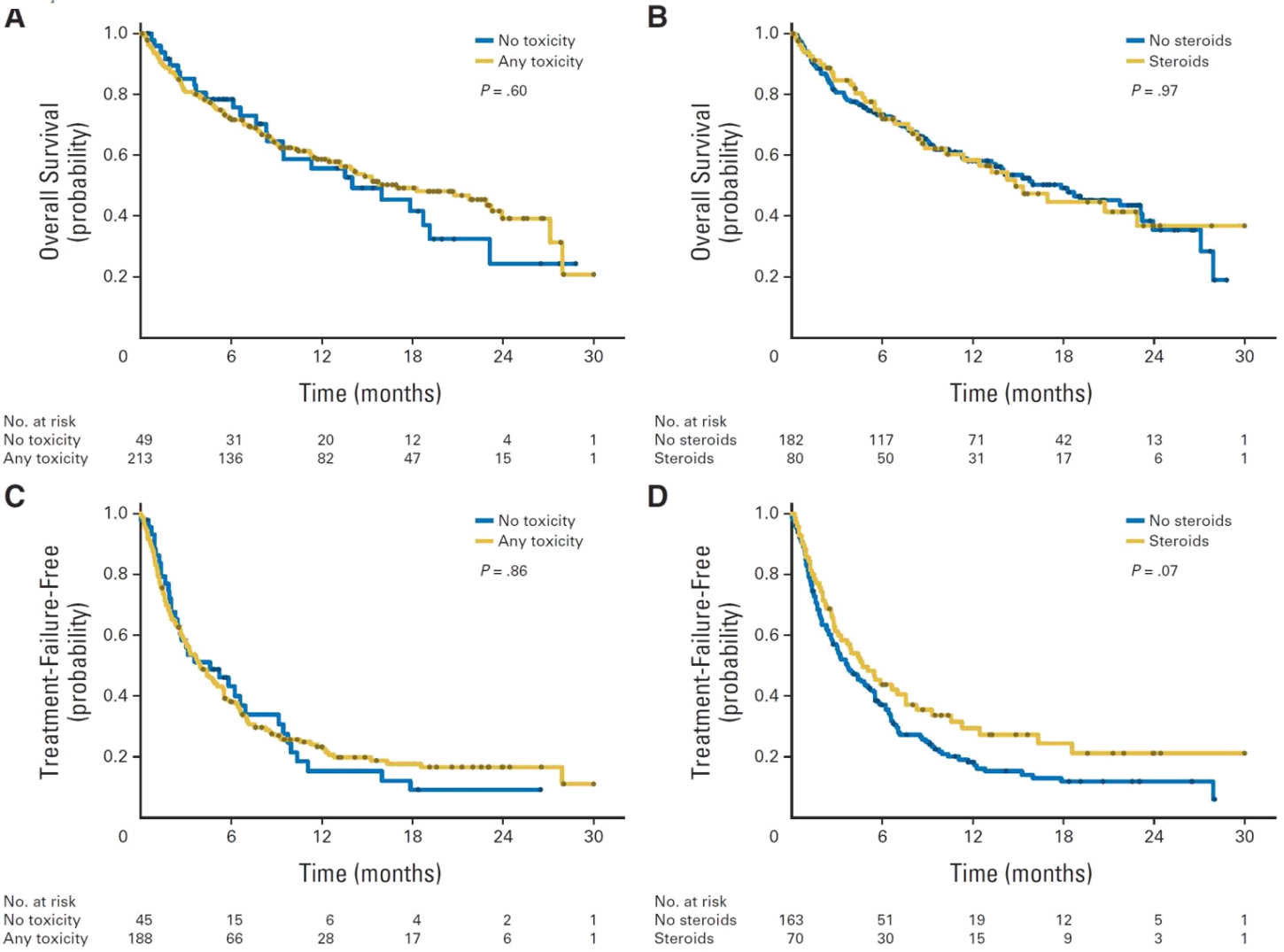
Initiate PSL at the dose of 1.0-2.0 mg/kg.

After improvement to Grade 1, taper the dose of PSL.

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center

Troy Z. Horvat, Nelly G. Adel, Thu-Oanh Dang, Parisa Momtaz, Michael A. Postow, Margaret K. Callahan, Richard D. Carvajal, Mark A. Dickson, Sandra P. D'Angelo, Kaitlin M. Woo, Katherine S. Panageas, Jedd D. Wolchok, and Paul B. Chapman



KEYNOTE-006: Phase III Study of Pembrolizumab (MK-3475) versus Ipilimumab in Patients With Ipilimumab-Naive Advanced Melanoma

Antoni Ribas,[1] Jacob Schachter,[2] Georgina V. Long,[3] Ana Arance,[4] Jean Jacques Grob,[5] Laurent Mortier,[6] Adil Daud,[7] Matteo S. Carlino,[8] Catriona McNeil,[9] Michal Lotem,[10] James Larkin,[11] Paul Lorigan,[12] Bart Neyns,[13] Christian U. Blank,[14] Omid Hamid,[15] Michele Kosh,[16] Honghong Zhou,[16] Nageatte Ibrahim,[16] Scot Ebbinghaus,[16] Caroline Robert[17]

[1]University of California, Los Angeles, Los Angeles, CA; [2]Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; [3]Melanoma Institute Australia, The University of Sydney, and Mater Hospital, Sydney, Australia; [4]Department of Medical Oncology, Hospital Clinic and Translational Genomics and Targeted Therapeutics in Solid Tumors (IDIBAPS), Barcelona, Spain; [5]Hôpital de la Timone, Marseille, France; [6]Université Lille, CHRU LILLE, Lille, France; [7]University of California, San Francisco, San Francisco, CA; [8]Westmead and Blacktown Hospitals, The University of Sydney, and Melanoma Institute Australia, Sydney, Australia; [9]Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, Australia; [10]Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [11]The Royal Marsden Hospital, London, UK; [12]University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [15]The Angeles Clinic and Research Institute, Los Angeles, CA; [16]Merck & Co., Inc., Kenilworth, NJ; [17]Gustave Roussy Département de Médecine Oncologique, Service de Dermatologie, F-94805, Villejuif France and Université Paris-Sud, Faculté de Médecine, F-94270 Le Kremlin–Bicetre Paris-Sud, France

Ribas_AACR 2015_19Apr15

The NEW ENGLAND JOURNAL of MEDICINE

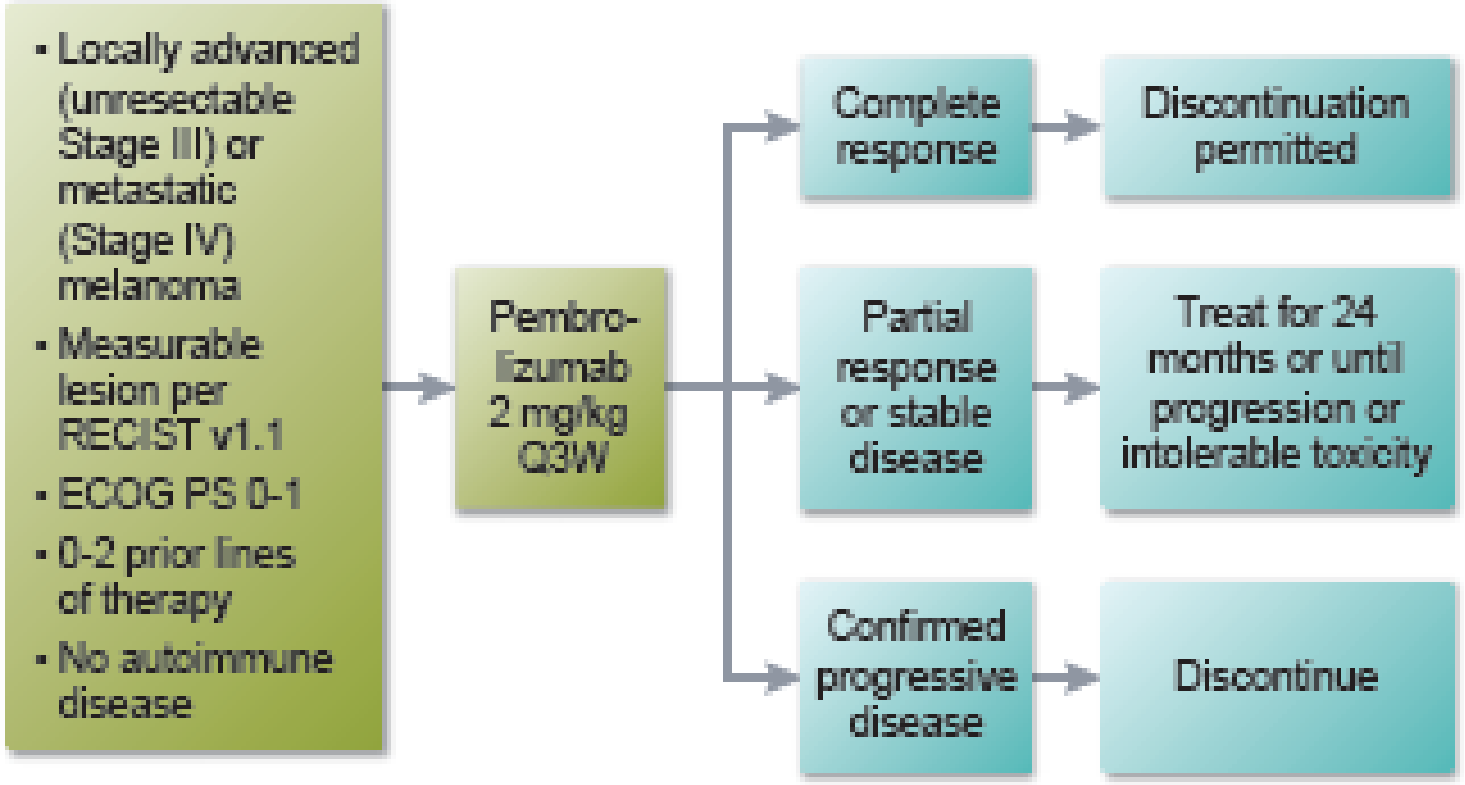
ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

Safety and Efficacy of Pembrolizumab (MK-3475) for Japanese Patients (pts) With Advanced Melanoma: Preliminary Results From KEYNOTE-041 Phase 1b Study

Study Design



Treatment: 2 mg/kg IV every 3 weeks (Q3W)

Response assessment: Performed at week 12 and every 6 weeks for the first 12 months and every 12 weeks thereafter per RECIST v1.1

Tumor response by histology (RECIST v1.1, investigator review)

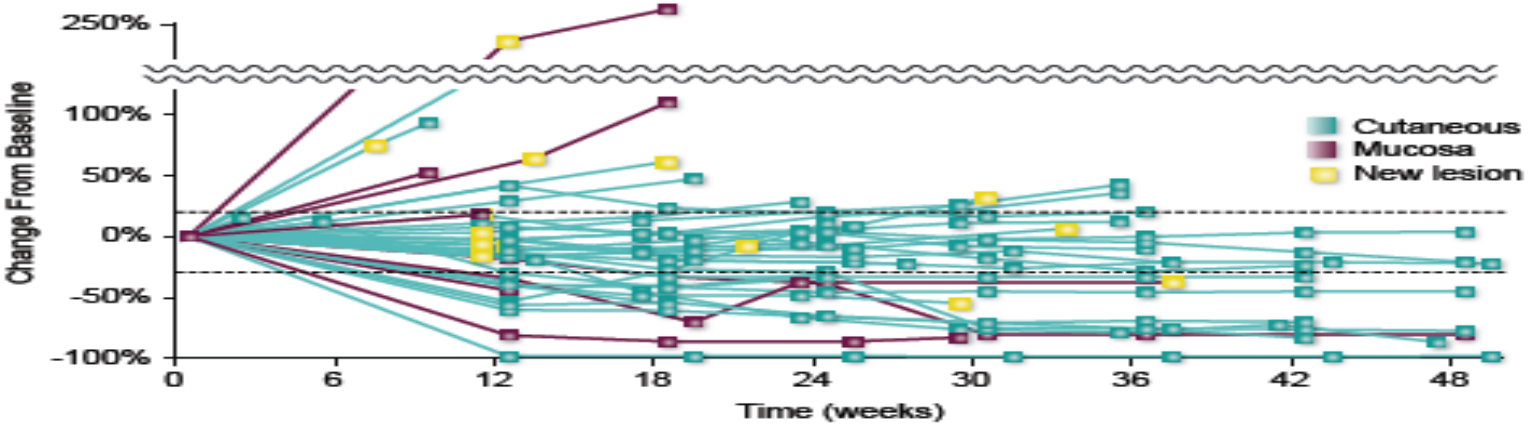
	Total N = 42	Cutaneous n = 34	Mucosal n = 8
ORR† (95% CI)	38.1 (23.6-54.4)	35.3‡ (19.8-53.5)	50.0 (15.7-84.3)
DCR† (95% CI)	66.7 (50.5-80.4)	67.6 (49.5-82.6)	62.5 (24.5-91.5)
Best overall response†, n (%)			
Complete response	2 (4.8)	2 (5.9)	0 (0.0)
Partial response	14 (33.3)	10 (29.4)	4 (50.0)
Stable disease	12 (28.6)	11 (32.4)	1 (12.5)
Progressive disease	14 (33.3)	11 (32.4)	3 (37.5)

†Confirmed and unconfirmed responses were included.

‡ORR for subtypes was 30.0% (3/10 pts) in NM, 42.9% (3/7 pts) in SSM, 0% (0/1 pts) in LMM, 33.3% (4/12 pts) in ALM, and 50.0% (1/2 pts) in NC, respectively.

Analysis cutoff date: August 5, 2015.

Change from baseline in tumor size (RECIST v1.1, investigator review)



Analysis cutoff date: August 5, 2015.

Adverse events of interest based on immune etiology

Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	5 (11.9)	0
Hyperthyroidism	2 (4.8)	0
Colitis	2 (4.8)	1 (2.4)
Hypophysitis	2 (4.8)	1 (2.4)
Pneumonitis	1 (2.4)	0
Uveitis	1 (2.4)	0

Analysis cutoff date: August 5, 2015.

- Other immune-mediated events observed in ≥2 patients: rash maculopapular (n=5); vitiligo (n=3); pruritus, AST increased, and skin hypopigmentation (n=2 each)

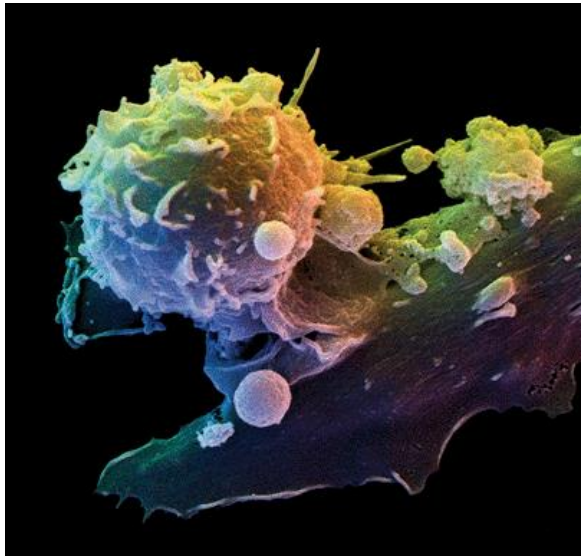
Areas to watch in 2015

Combined immunotherapy

Solar systems encounters

Arctic sea ice

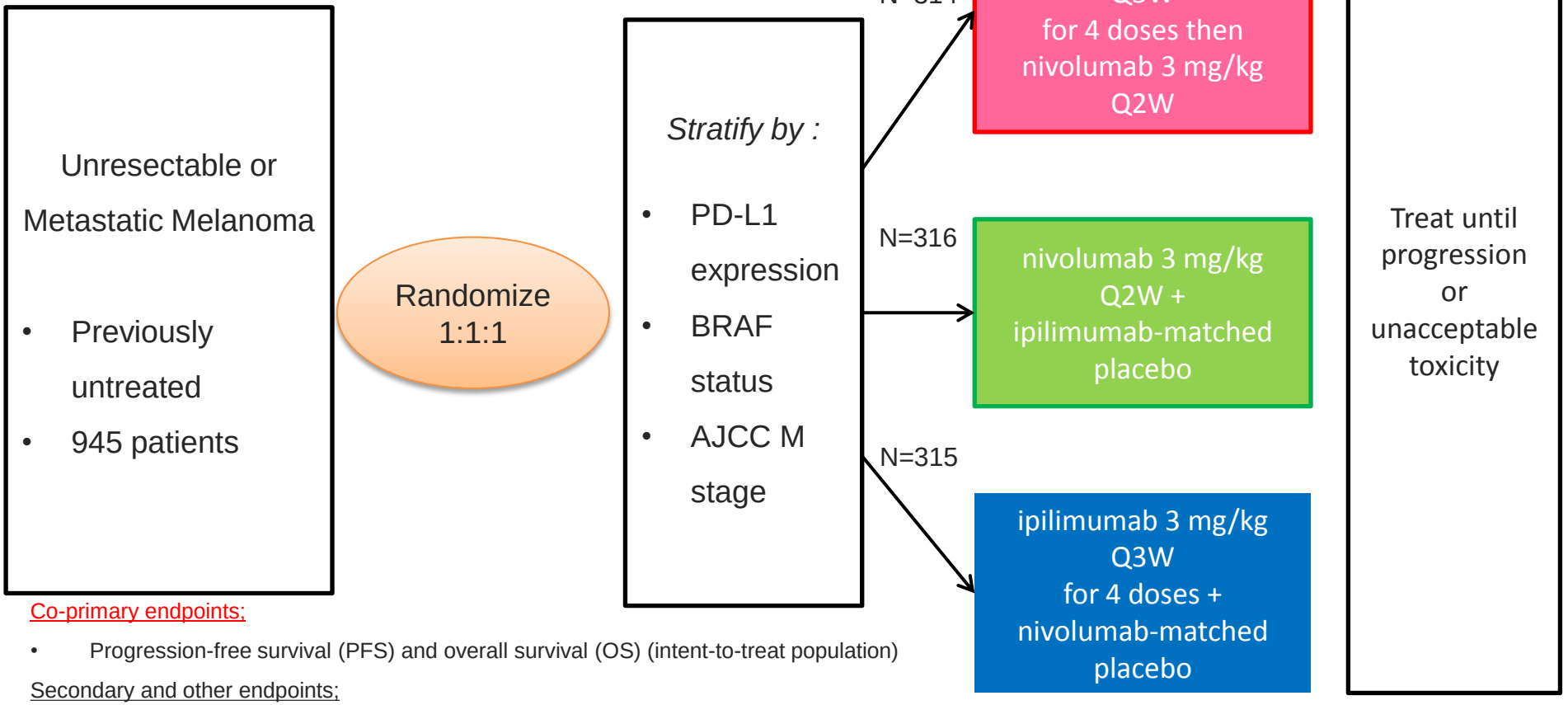
LHC restart



Checkmate067

CA209-067 : Study Design

Randomized, double-blind, phase III study to compare nivolumab + ipilimumab or nivolumab alone to ipilimumab alone



Co-primary endpoints:

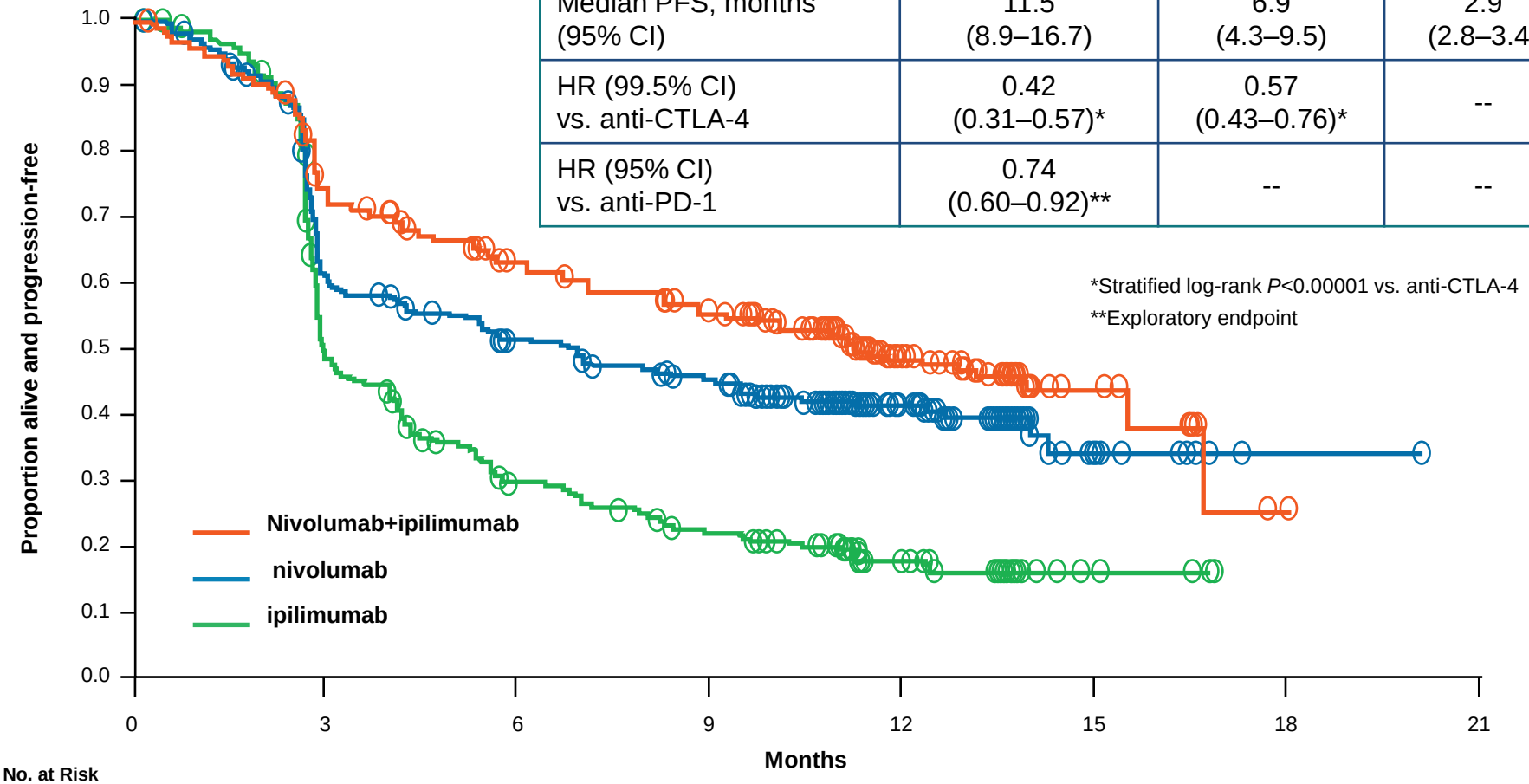
- Progression-free survival (PFS) and overall survival (OS) (intent-to-treat population)

Secondary and other endpoints:

- ORR by RECIST v1.1
- Predefined tumor PD-L1 expression level as a predictive biomarker of efficacy
- Safety profile

PFS (Intent-to-Treat)

	nivolumab+ ipilimumab (N=314)	nivolumab (N=316)	ipilimumab (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. anti-CTLA-4	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. anti-PD-1	0.74 (0.60–0.92)**	--	--



*Stratified log-rank *P*<0.00001 vs. anti-CTLA-4

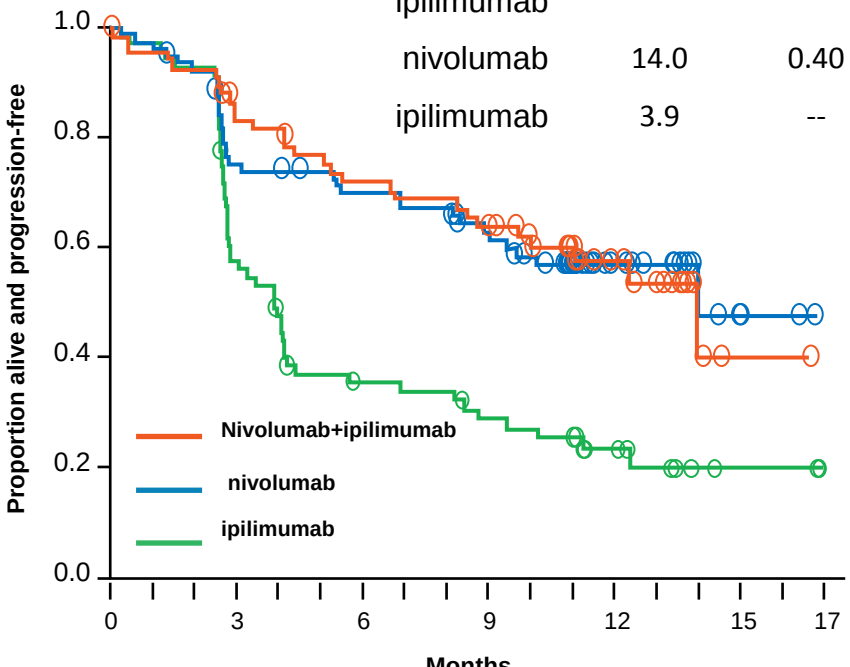
**Exploratory endpoint

No. at Risk								
anti-PD-1 + anti-CTLA-4	314	219	173	151	65	11	1	0
anti-PD-1	316	177	147	124	50	9	1	0
anti-CTLA-4	315	137	77	54	24	4	0	0

PFS by PD-L1 Expression Level (5%)

PD-L1 ≥5%*

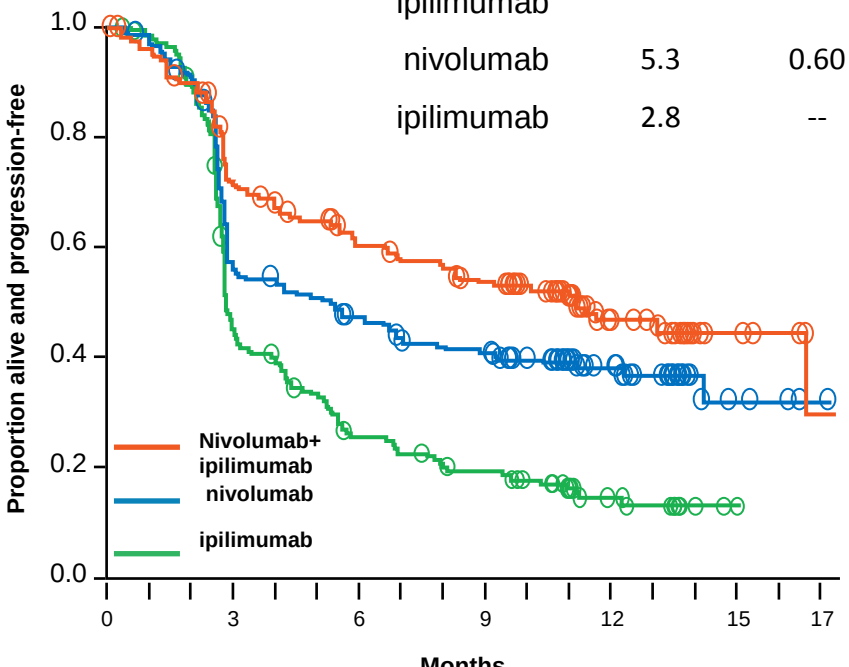
	mPFS	HR
nivolumab+ ipilimumab	14.0	0.40
nivolumab	14.0	0.40
ipilimumab	3.9	--



No. at Risk							
anti-PD-1 + anti-CTLA-4	68	53	44	39	16	1	0
anti-PD-1	80	57	51	43	16	4	0
anti-CTLA-4	75	40	22	17	9	2	0

PD-L1 <5%*

	mPFS	HR
nivolumab+ ipilimumab	11.2	0.42
nivolumab	5.3	0.60
ipilimumab	2.8	--



No. at Risk							
anti-PD-1 + anti-CTLA-4	210	142	112	96	42	9	2
anti-PD-1	208	108	88	74	31	5	2
anti-CTLA-4	202	82	44	31	12	1	–

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Response to Treatment

	nivolumab + ipilimumab (N=314)	nivolumab (N=316)	ipilimumab (N=315)
ORR, % (95% CI)	**57.6** (52.0-63.2)	**43.7** (38.1-49.3)	**19.0** (14.9-23.8)
Two-sided P value vs IPI	<0.001	<0.001	-
Best overall response - %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1, NR)	NR (11.7, NR)	NR (6.9, NR)

Treatment-Related Select AEs Reported in ≥10% of Patients

Patients Reporting Event , %	nivolumab + ipilimumab (N=313)		nivolumab (N=313)		ipilimumab (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	16.6	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2.	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	17.6	8.3	3.6	1.3	3.9	1.6
Increase in aspartate aminotransferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0		14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for anti-PD-1 + anti-CTLA-4, 50-100% for anti-PD-1, and 83-100% for anti-CTLA-4
- As observed in prior studies, most endocrine events did not resolve

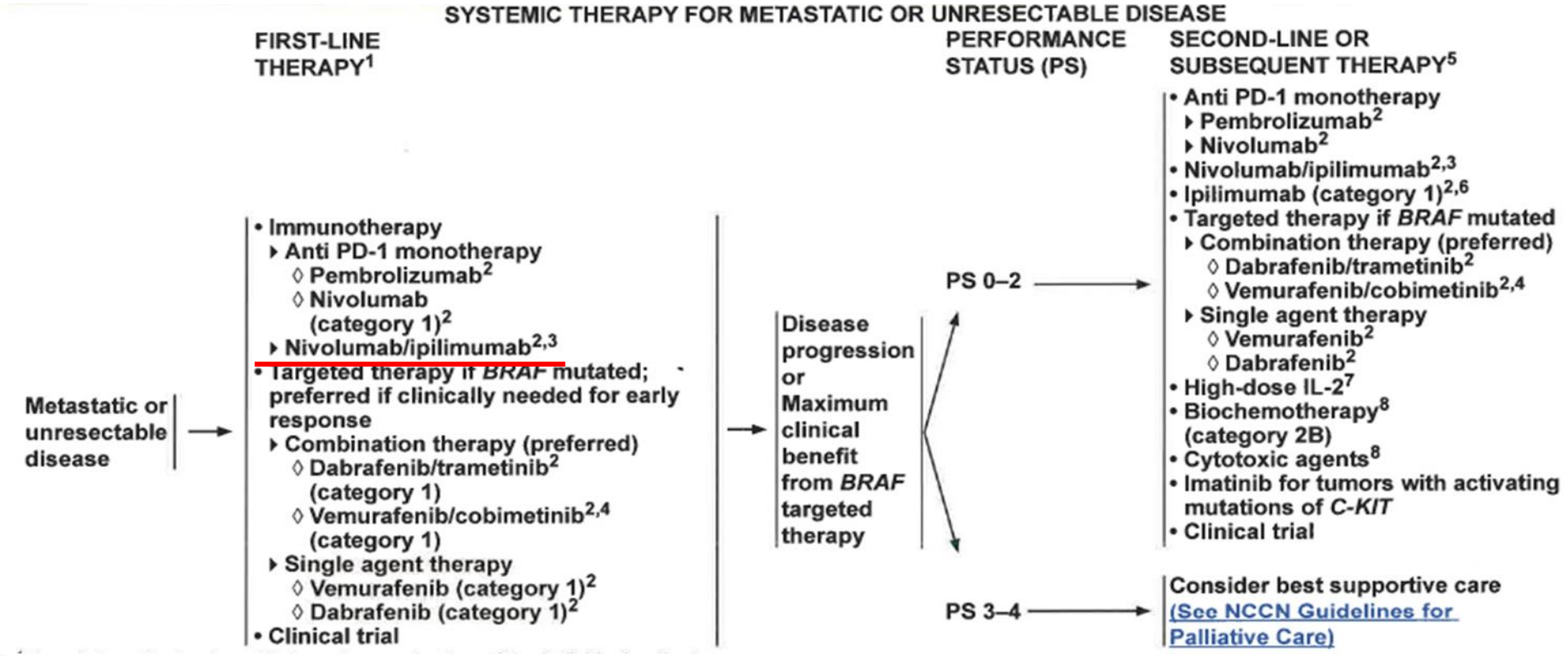
NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients



NCCN Guidelines Version 2. 2016 Melanoma

Bench to Bedside

Many therapeutic options

Single-agent therapy?, concomitant use of drugs?, combined therapies?

Safely

Effectively

Complete use of the contents

Acknowledgements

Gratitude to the patients who participated in the clinical trials

We wish to express our appreciation for all the healthcare and other staff, including physicians and CRC, for their cooperation in the development of a nationwide treatment system.

All Activities for Cancer Patients

National Cancer Center Hospital
Tokyo, Japan

Thank you for your attention

Naoya Yamazaki