Kombination von Checkpointinhibitoren beim malignen Melanom

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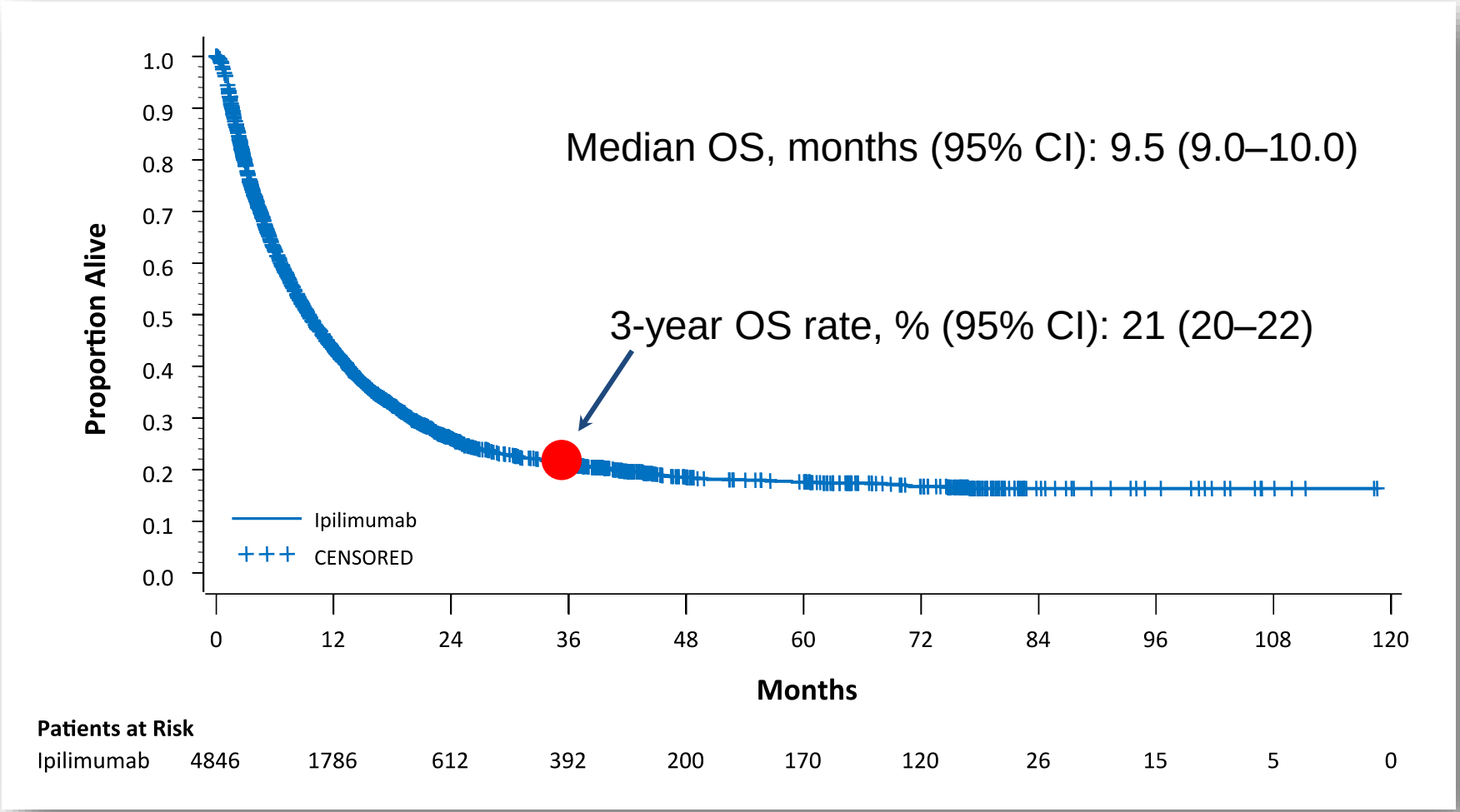
NCT

Ipilimumab beim metastasierten Melanom



Schadendorf, et al. J Clin Oncol 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

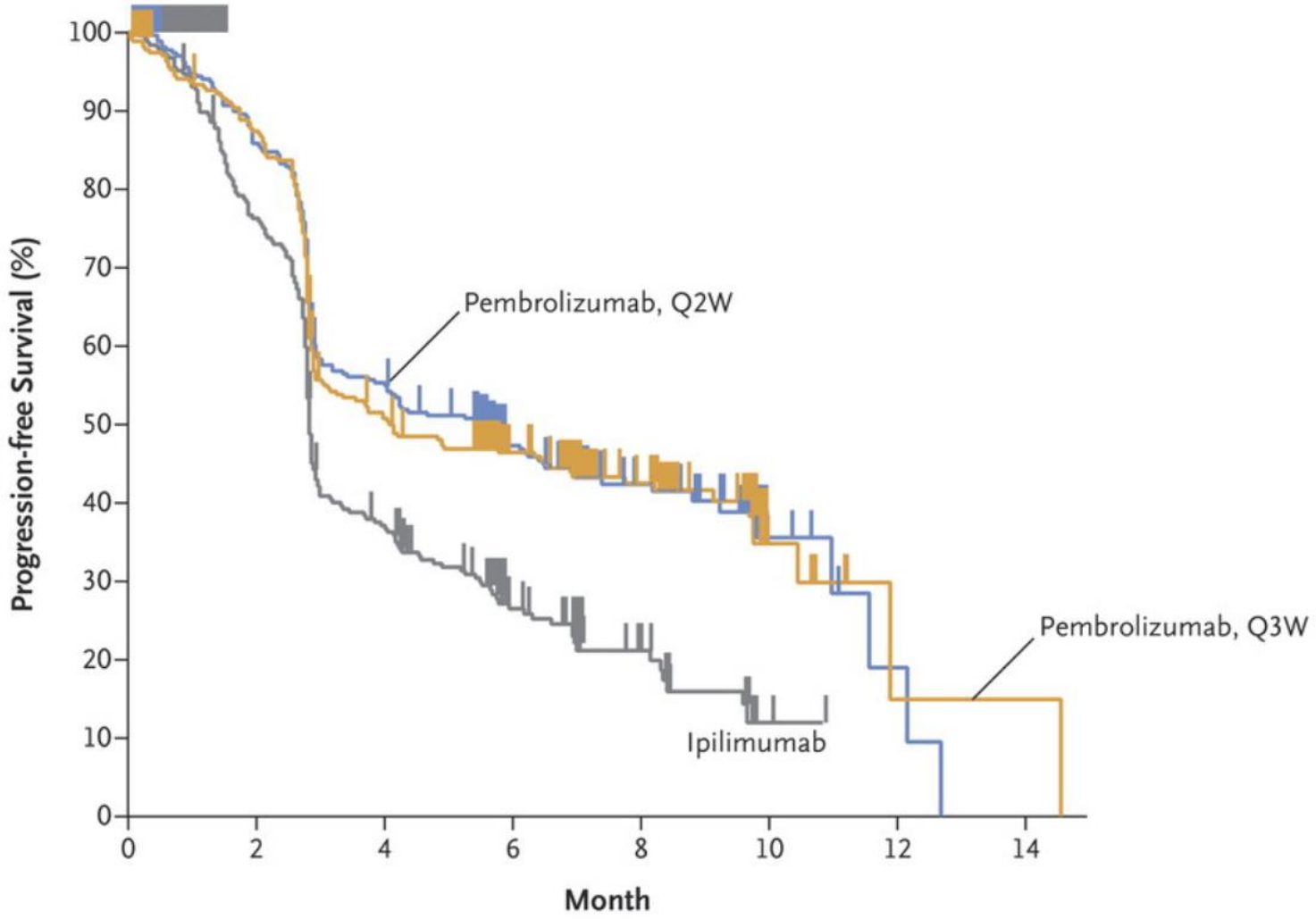
Pembrolizumab versus Ipilimumab in Advanced Melanoma

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*

N Engl J Med 2015; 372:2521-2532 | June 25, 2015 | DOI: 10.1056/NEJMoa1503093

NCT

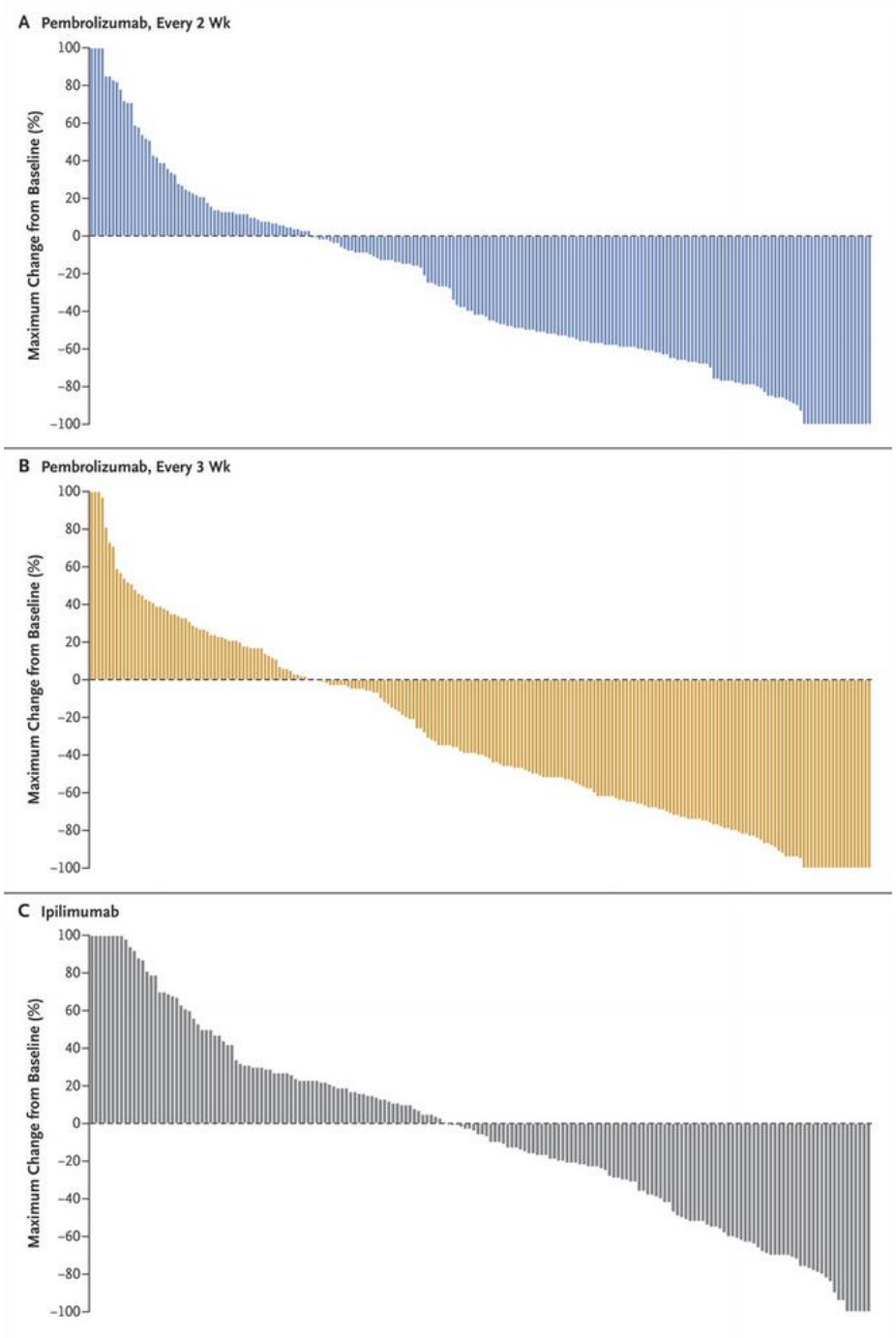
A Progression-free Survival



No. at Risk								
Pembrolizumab, Q2W	279	231	147	98	49	7	2	0
Pembrolizumab, Q3W	277	235	133	95	53	7	1	1
Ipilimumab	278	186	88	42	18	2	0	0

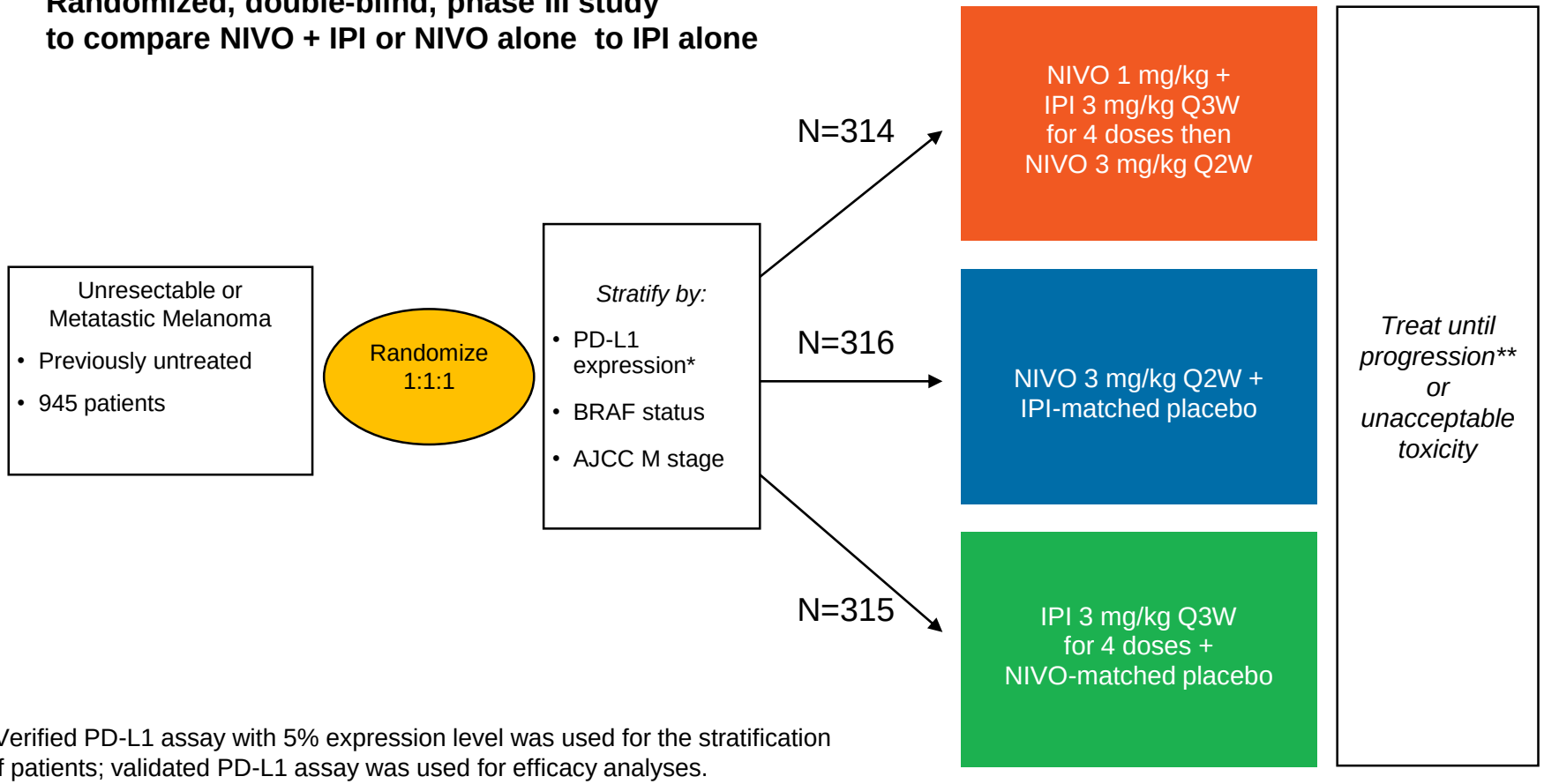
Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Every 2 Wk (N=279)	Pembrolizumab Every 3 Wk (N=277)	Ipilimumab (N=278)
Median age (range) — yr	61 (18–89)	63 (22–89)	62 (18–88)
Male sex — no. (%)	161 (57.7)	174 (62.8)	162 (58.3)
ECOG performance status — no. (%)			
0	196 (70.3)	189 (68.2)	188 (67.6)
1	83 (29.7)	88 (31.8)	90 (32.4)
Elevated baseline LDH level — no. (%)	81 (29.0)	98 (35.4)	91 (32.7)
Metastasis stage — no. (%)†			
M0	9 (3.2)	9 (3.2)	14 (5.0)
M1‡	6 (2.2)	4 (1.4)	5 (1.8)
M1a	21 (7.5)	34 (12.3)	30 (10.8)
M1b	64 (22.9)	41 (14.8)	52 (18.7)
M1c	179 (64.2)	189 (68.2)	177 (63.7)
PD-L1–positive tumor — no. (%)	225 (80.6)	221 (79.8)	225 (80.9)
BRAF V600 mutation — no. (%)	98 (35.1)	97 (35.0)	107 (38.5)
Brain metastasis — no. (%)	23 (8.2)	27 (9.7)	28 (10.1)
Line of previous systemic therapy — no. (%)§			
0	183 (65.6)	185 (66.8)	181 (65.1)
1	96 (34.4)	91 (32.9)	97 (34.9)
Type of previous systemic therapy — no. (%)¶			
Chemotherapy	36 (12.9)	41 (14.8)	29 (10.4)
Immunotherapy	8 (2.9)	7 (2.5)	12 (4.3)
BRAF or MEK inhibitor or both	50 (17.9)	45 (16.2)	56 (20.1)


A Pembrolizumab, Every 2 Wk
Maximum Change from Baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
B Pembrolizumab, Every 3 Wk
Maximum Change from Baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
C Ipilimumab
Maximum Change from Baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

James Larkin, M.D., Ph.D., Vanna Chiarion-Sileni, M.D., Rene Gonzalez, M.D., Jean Jacques Grob, M.D., C. Lance Cowey, M.D., Christopher D. Lao, M.D., M.P.H., Dirk Schadendorf, M.D., Reinhard Dummer, M.D., Michael Smylie, M.D., Piotr Rutkowski, M.D., Ph.D., Pier F. Ferrucci, M.D., Andrew Hill, M.D., John Wagstaff, M.D., Matteo S. Carlino, M.D., John B. Haanen, M.D., Michele Maio, M.D., Ph.D., Ivan Marquez-Rodas, M.D., Ph.D., Grant A. McArthur, M.D., Paolo A. Ascierto, M.D., Georgina V. Long, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Kenneth Grossmann, M.D., Mario Sznol, M.D., Brigitte Dreno, M.D., Lars Bastholt, M.D., Arvin Yang, M.D., Ph.D., Linda M. Rollin, Ph.D., Christine Horak, Ph.D., F. Stephen Hodi, M.D., and Jedd D. Wolchok, M.D., Ph.D.

N Engl J Med 2015; 373:23-34 | July 2, 2015 | DOI: 10.1056/NEJMoa1504030

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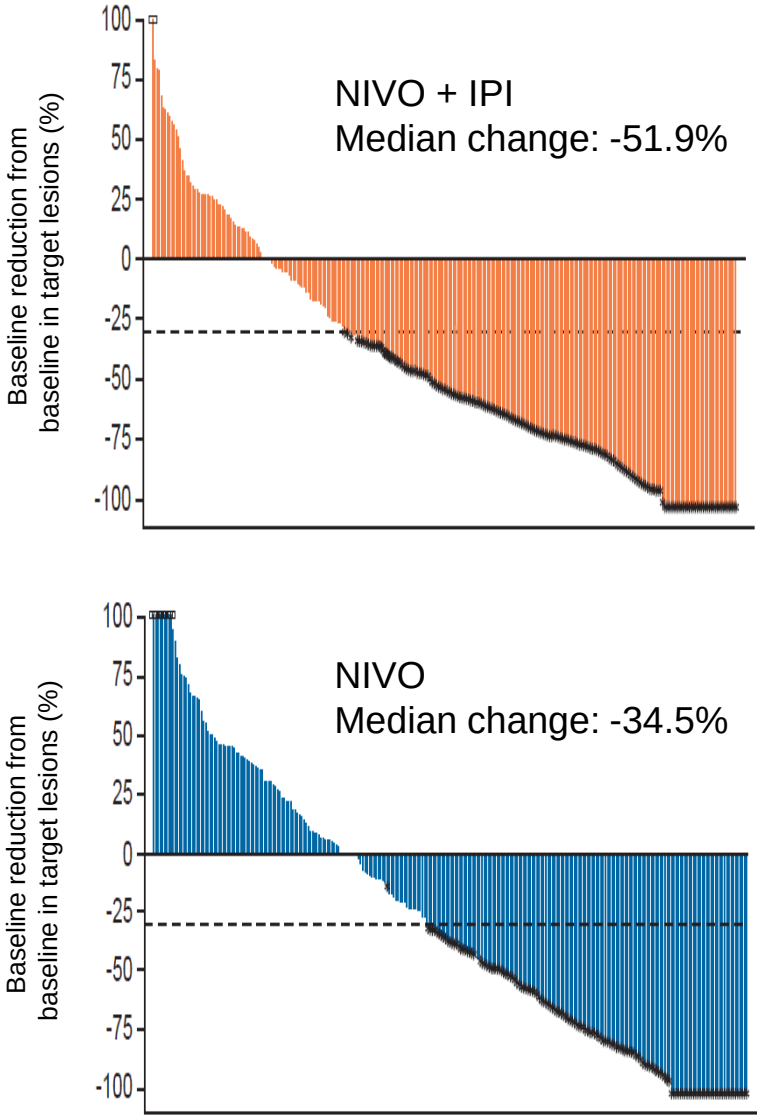
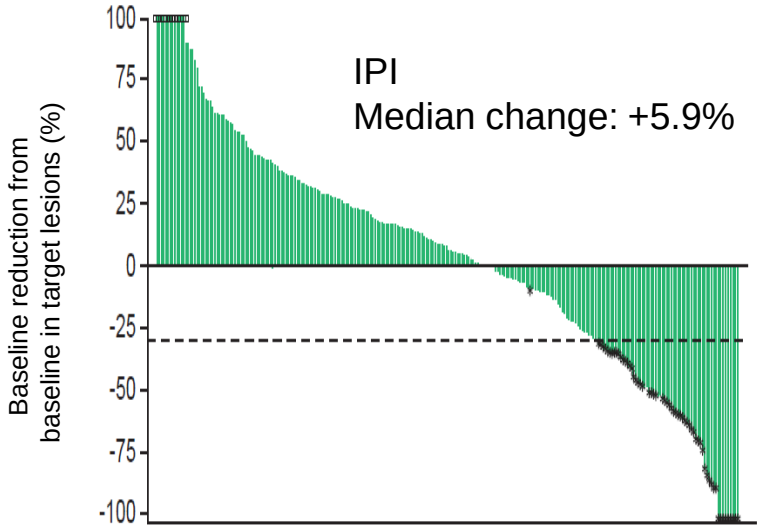
Tumor Burden Change From Baseline





Confirmed responder

30% reduction in tumor burden by RECIST v1.1

Response to Treatment

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (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)

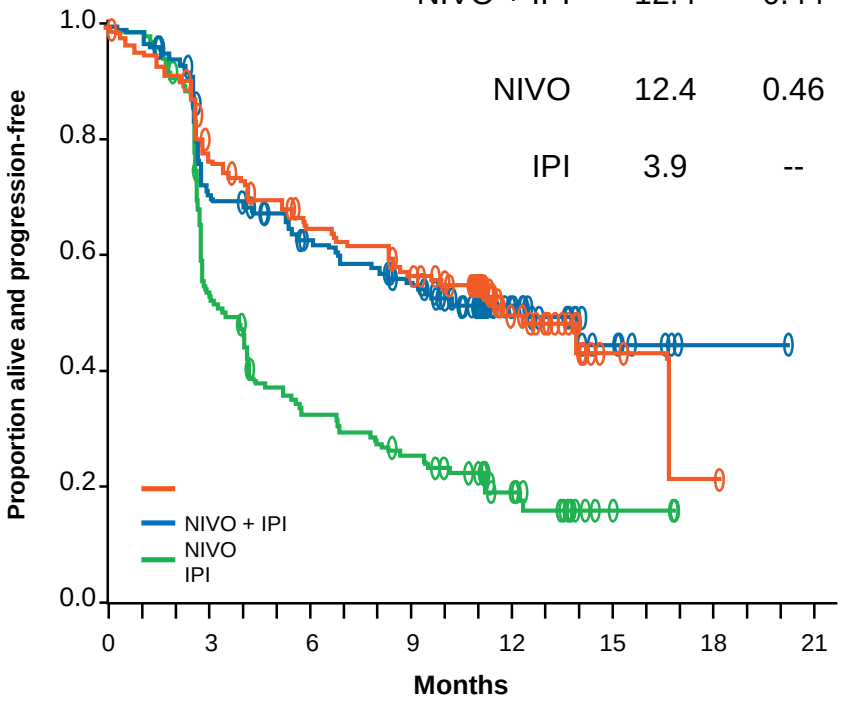
*By RECIST v1.1.

NR, not reached.

PFS by PD-L1 Expression Level (1%)

PD-L1 ≥1%*

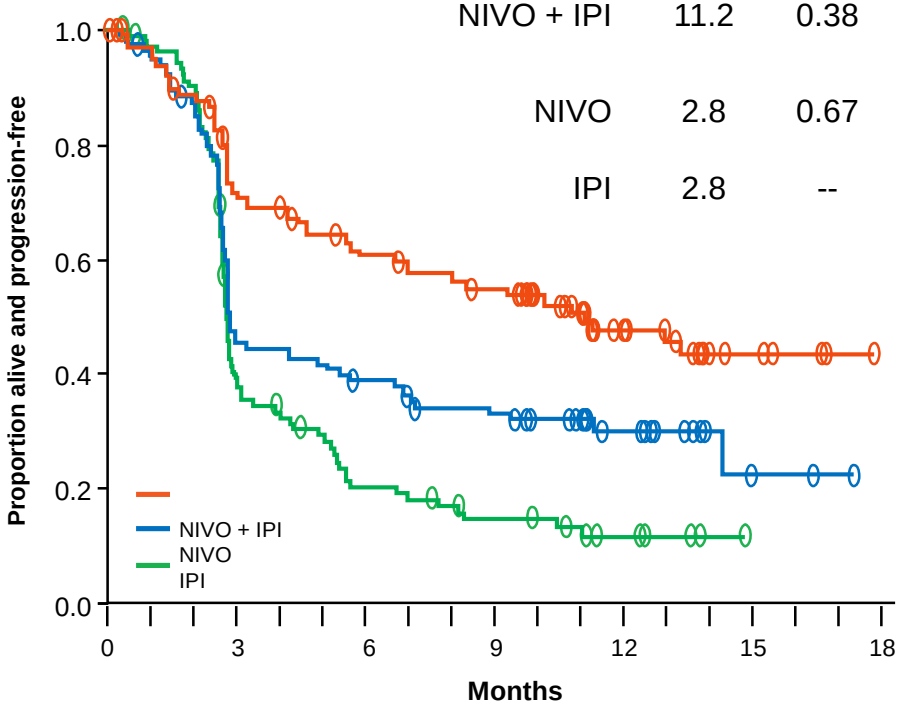
	mPFS	HR
NIVO + IPI	12.4	0.44
NIVO	12.4	0.46
IPI	3.9	--



No. at Risk								
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*

	mPFS	HR
NIVO + IPI	11.2	0.38
NIVO	2.8	0.67
IPI	2.8	--



No. at Risk							
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

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

Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

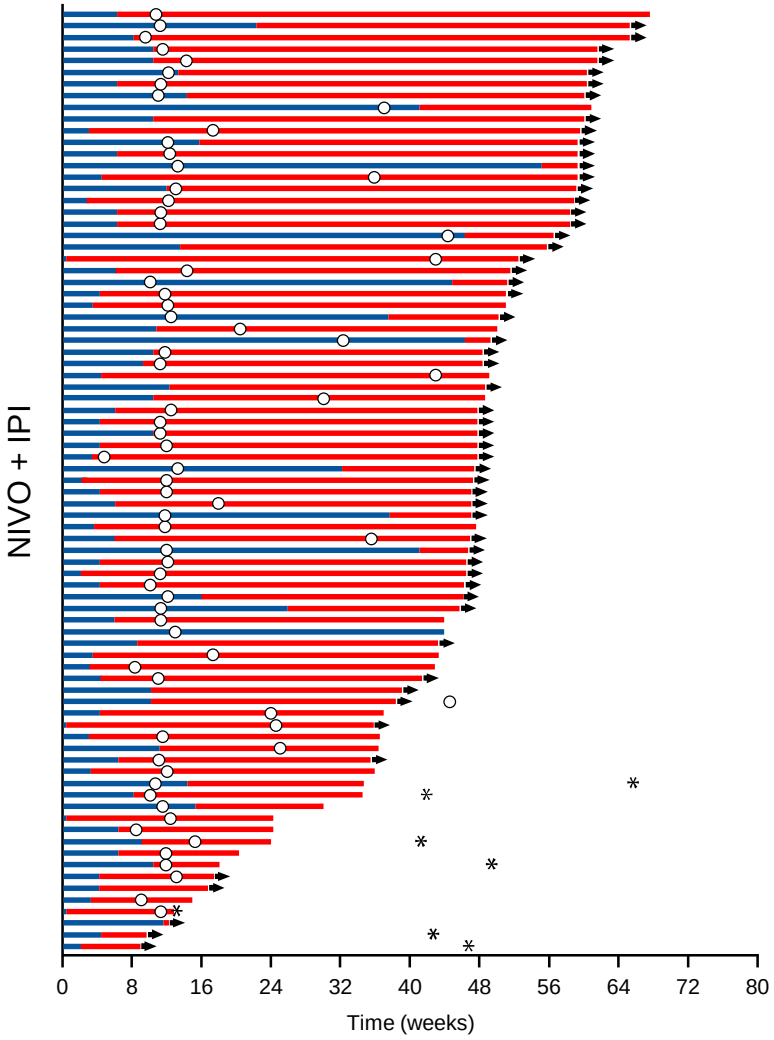
Most Common Treatment-related Select AEs

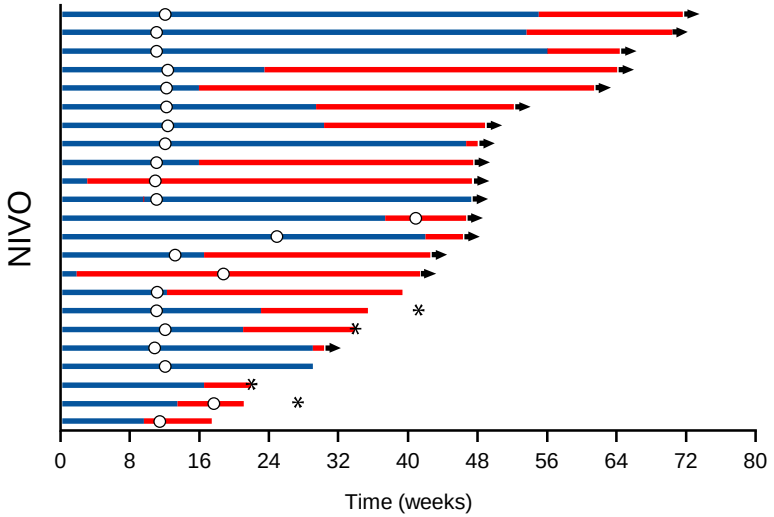
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

Database lock Nov 2015

Time to and Durability of Response in Patients Who Discontinued Due to Toxicity



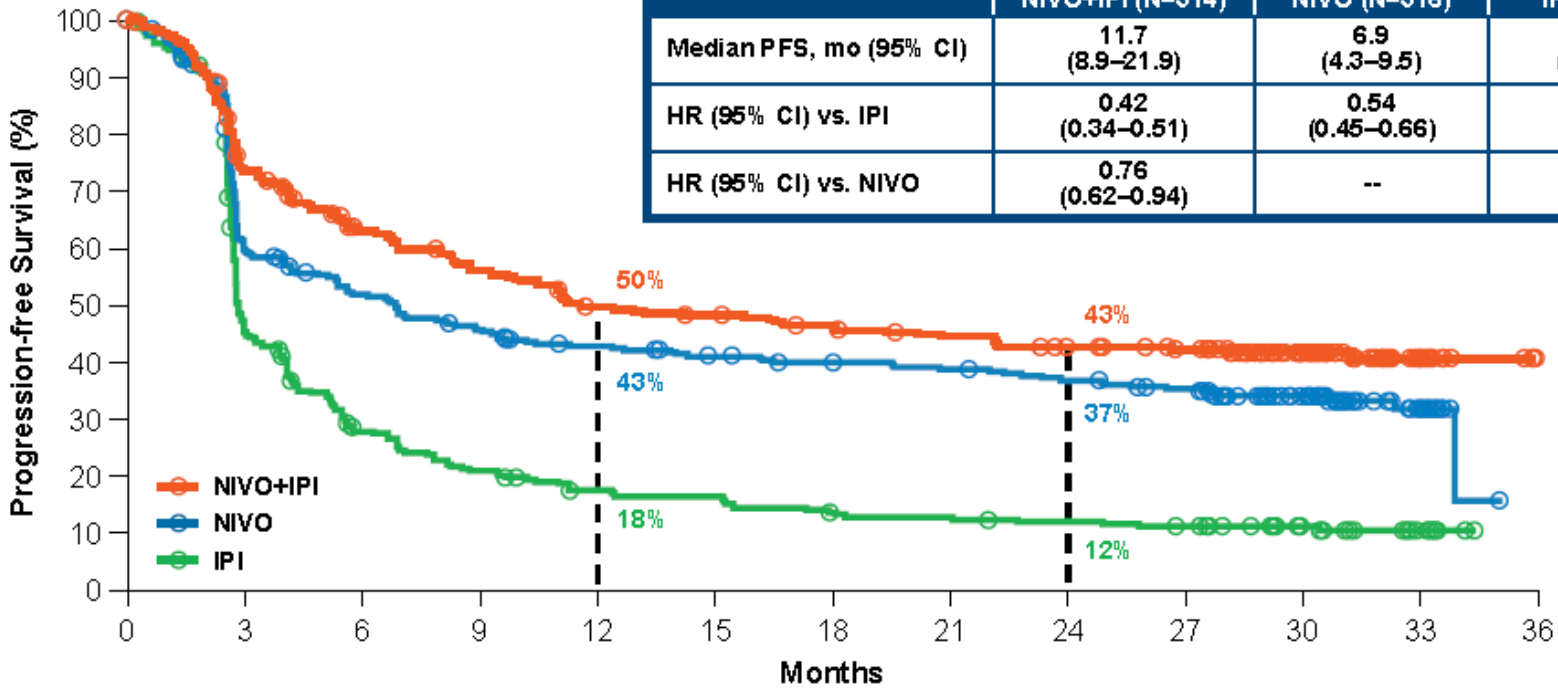


On treatment
Off treatment
First response
Ongoing response
Death

Larkin at ECCO 2015

Updated Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Patients at risk:

NIVO+IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

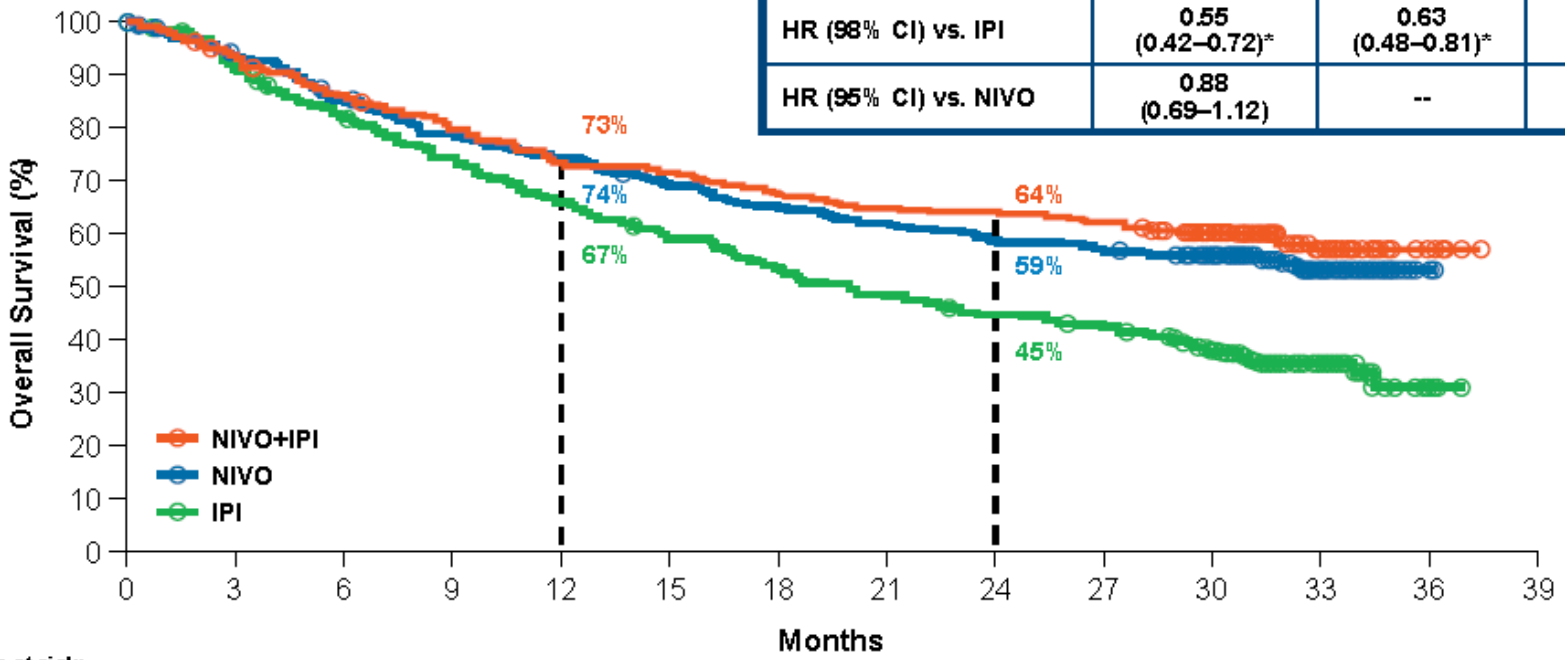
Database lock: Sept 13, 2016, minimum f/u of 28 months

Larkin et al, AACR 2017

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*$P<0.0001$



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

Larkin et al, AACR 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Vanna Chiarion-Sileni, M.D., Rene Gonzalez, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Jacques Grob, M.D., C. Lance Cowey, M.D., Christopher D. Lao, M.D., M.P.H., John Wagstaff, M.D., Dirk Schadendorf, M.D., Pier F. Ferrucci, M.D., Michael Smylie, M.D., Reinhard Dummer, M.D., Andrew Hill, M.D., David Hogg, M.D., John Haanen, M.D., Matteo S. Carlino, M.D., Oliver Bechter, M.D., Ph.D., Michele Maio, M.D., Ph.D., Ivan Marquez-Rodas, M.D., Ph.D., Massimo Guidoboni, M.D., Grant McArthur, M.D., Celeste Lebbé, M.D., Ph.D., Paolo A. Ascierto, M.D., Georgina V. Long, M.B., B.S., Ph.D., Jonathan Cebon, M.B., B.S., Ph.D., Jeffrey Sosman, M.D., Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Dana Walker, M.D., M.S.C.E., Linda Rollin, Ph.D., Rafia Bhore, Ph.D., F. Stephen Hodi, M.D., and James Larkin, F.R.C.P., Ph.D.

September 11, 2017 | DOI: 10.1056/NEJMoa1709684

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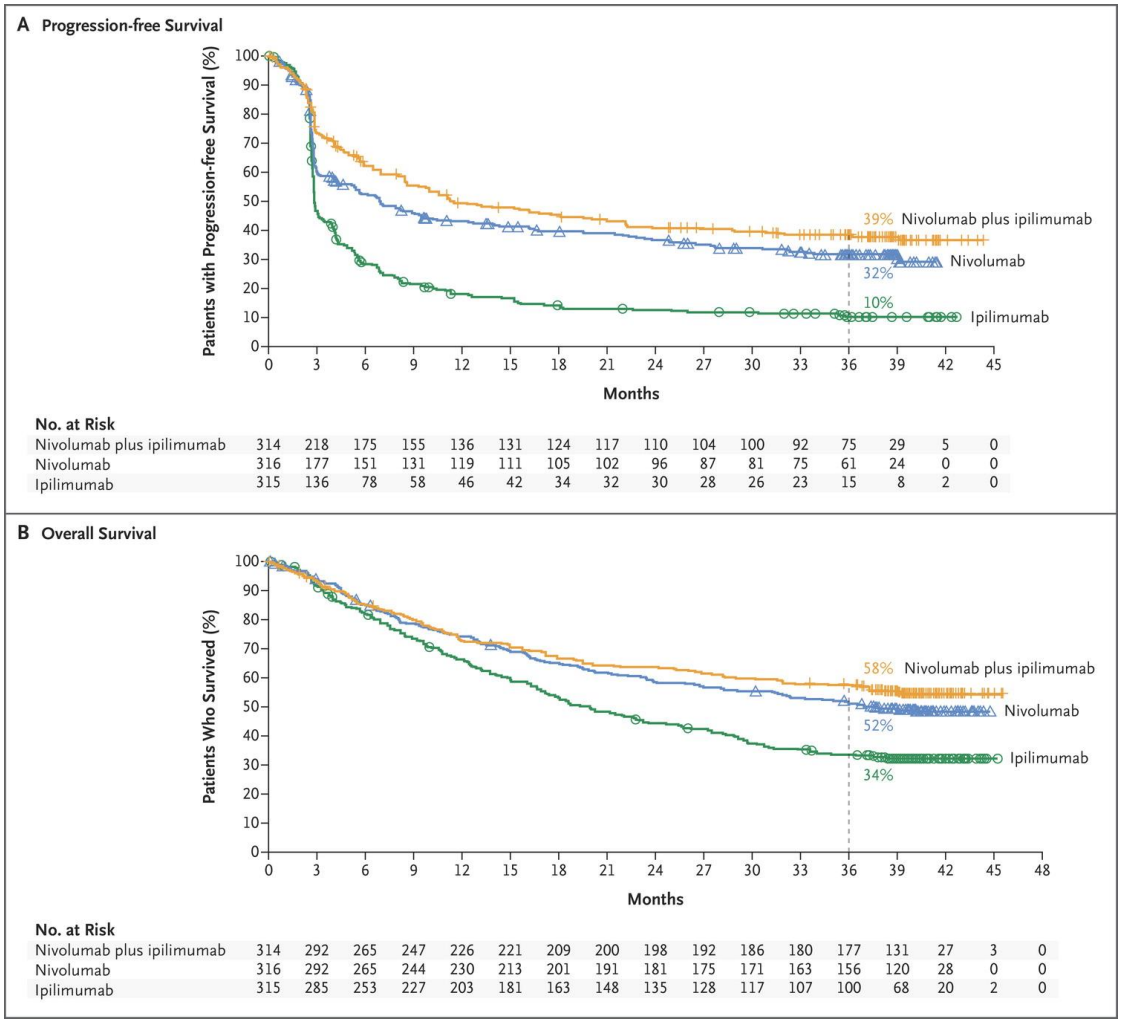
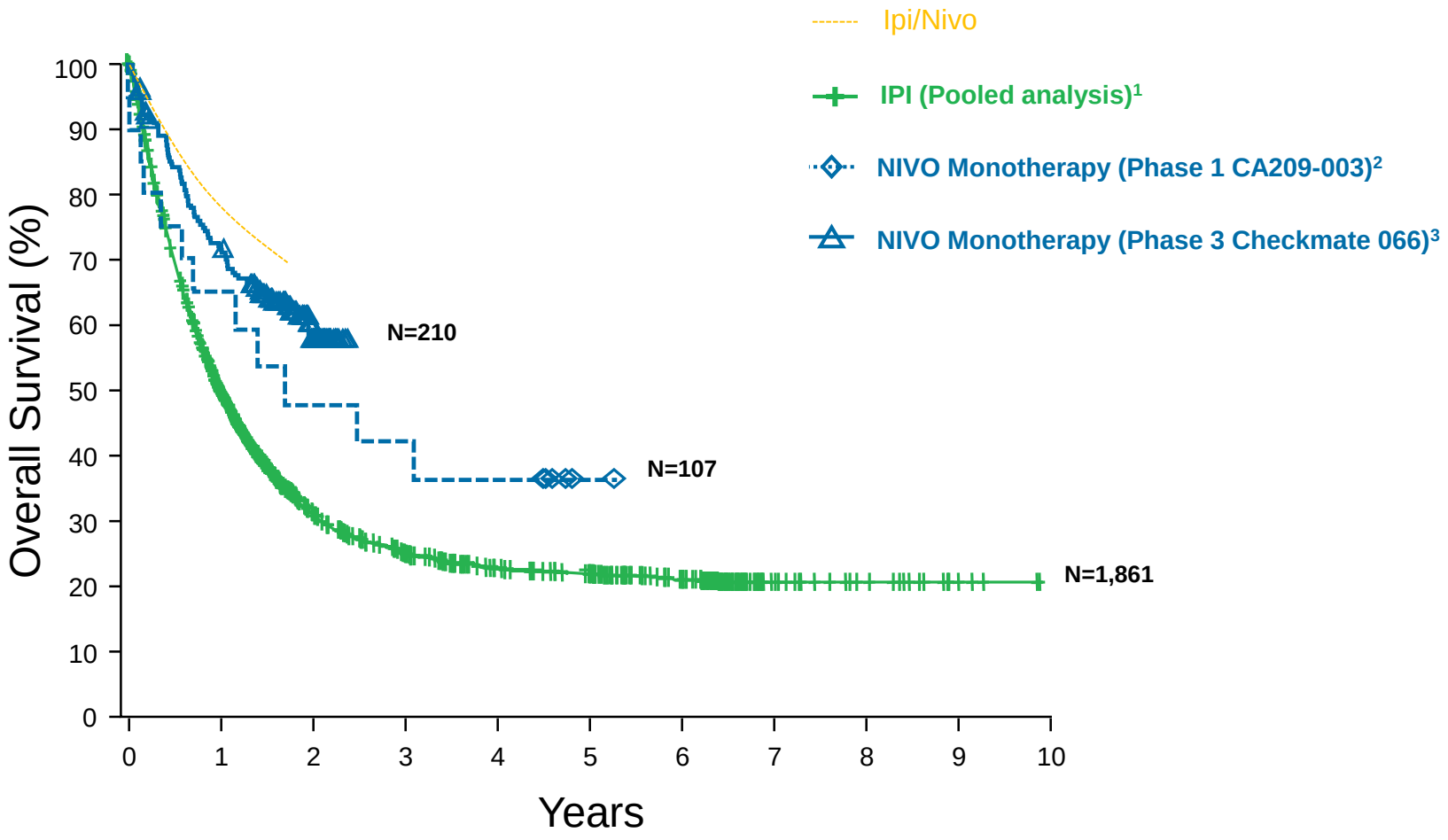


Wolchok JD et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709684

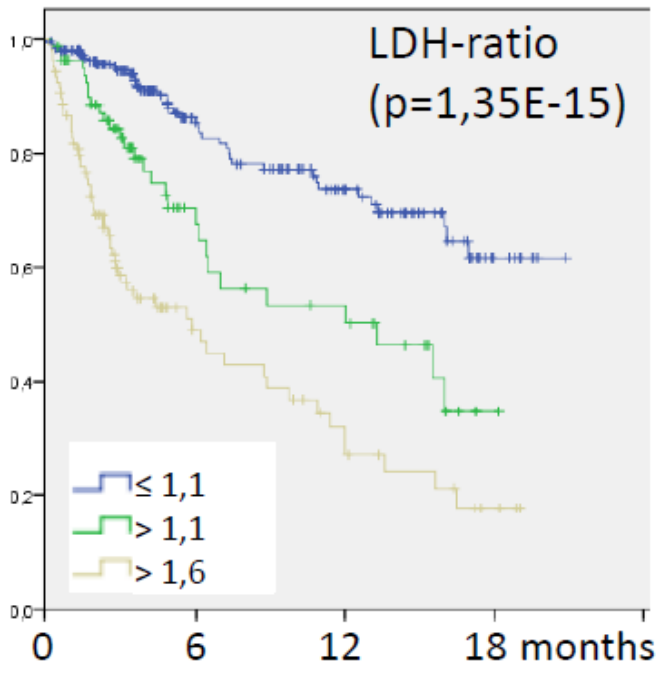
Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma

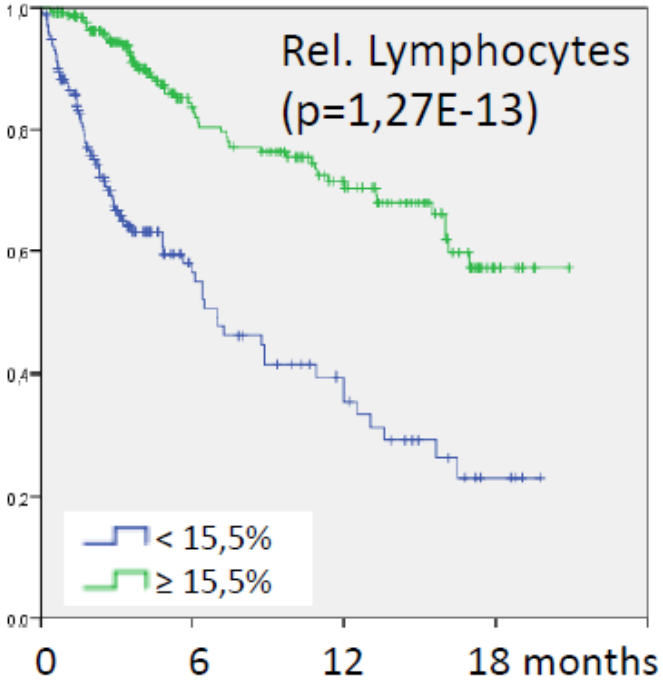


1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

Biomarker für Benefit unter PD1 Mono

Kaplan Meier curves for strongest factors in univariate analysis





Weide et al, CCR 2016

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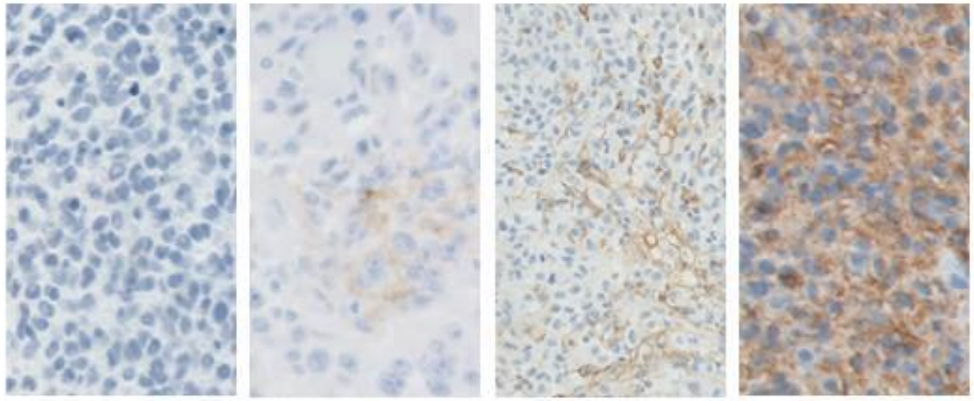
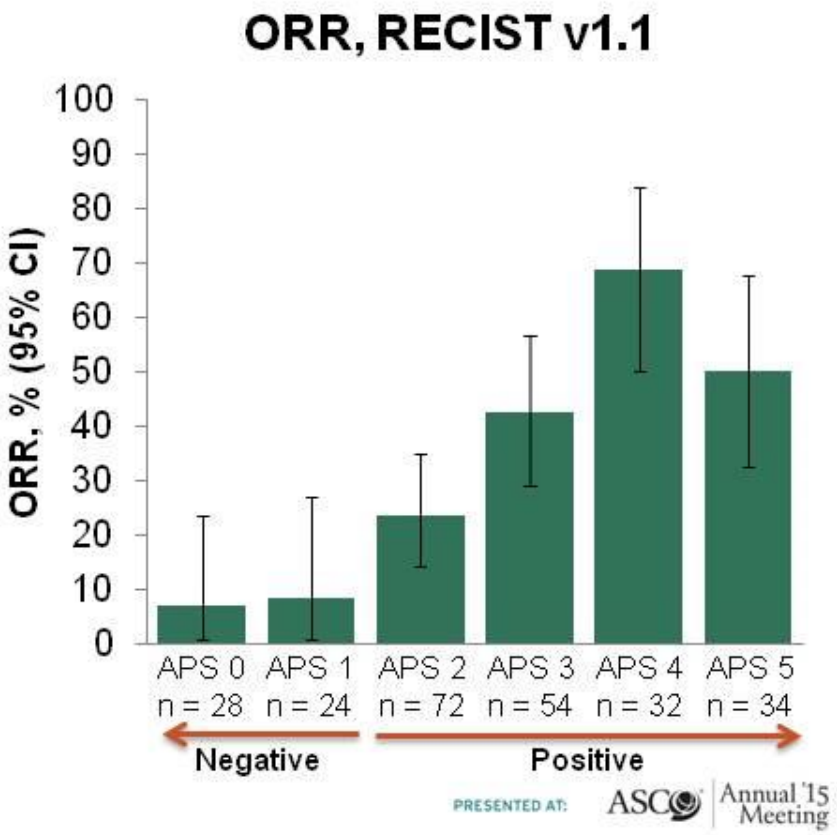
PD-L1 Expression and Relationship With Response

- Among first 411 patients enrolled, 67% evaluable for PD-L1 status
- Correlation between PD-L1 expression and ORR ($P < 0.0001$)



PD-L1 Negative 0% Staining APS = 0 | PD-L1 Positive 1-10% Staining APS = 2 | PD-L1 Positive 10-33% Staining APS = 3 | PD-L1 Positive 66-100% Staining APS = 5

APS, Allred proportion score.
Analysis cut-off date: October 18, 2014.



Keynote 001

Presented By Adil Daud at 2015 ASCO Annual Meeting

NCT

CANCER IMMUNOTHERAPY HIGHLIGHT ACHIEVEMENTS

Immune checkpoint inhibition:

- demonstrated that response to ipilimumab depends on mutation number in metastatic melanoma

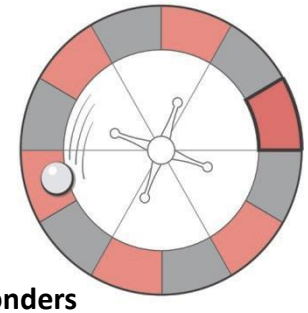
Van Allen et al., and Schadendorf; **Science** 2015

- demonstrated that clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

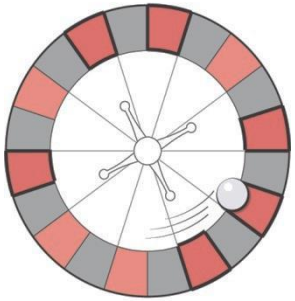
McGranahan ... Schadendorf et al.; **Science** 2016

Neoantigen roulette.

Nonresponders
Cancer patients with fewer mutations have a lower chance of responding to therapy



Responders
Cancer patients with more mutations have a higher chance of responding to therapy



From: Gubin and Schreiber; **Science** 2015

NCT

NLG2103: Phase II Studie: Pembrolizumab + Indoximod

- 60 auswertbare Patienten mit fortgeschrittenem Melanom (auch Aderhautmelanom), die die Kombination aus Pembro + IDO Inhibitor erhielten
  - ORR: 52% (31/60)
  - DCR: 73% (44/60)

- Non ocular melanoma:
  - ORR: 59% (30/51)
  - DCR: 80% (41/51)

- Geringe Rate an Grad ¾ Toxizität (vergleichbar zu PD1 Mono)

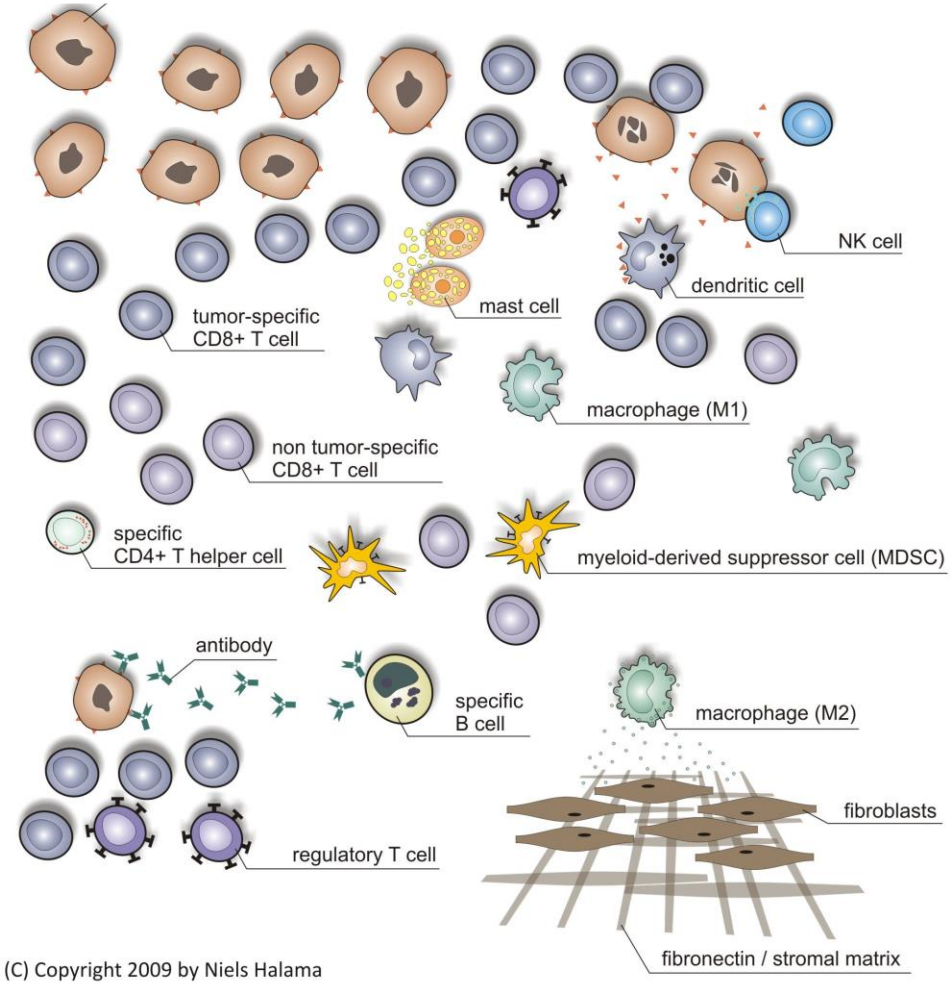
AACR 2017

Kombinationstherapien

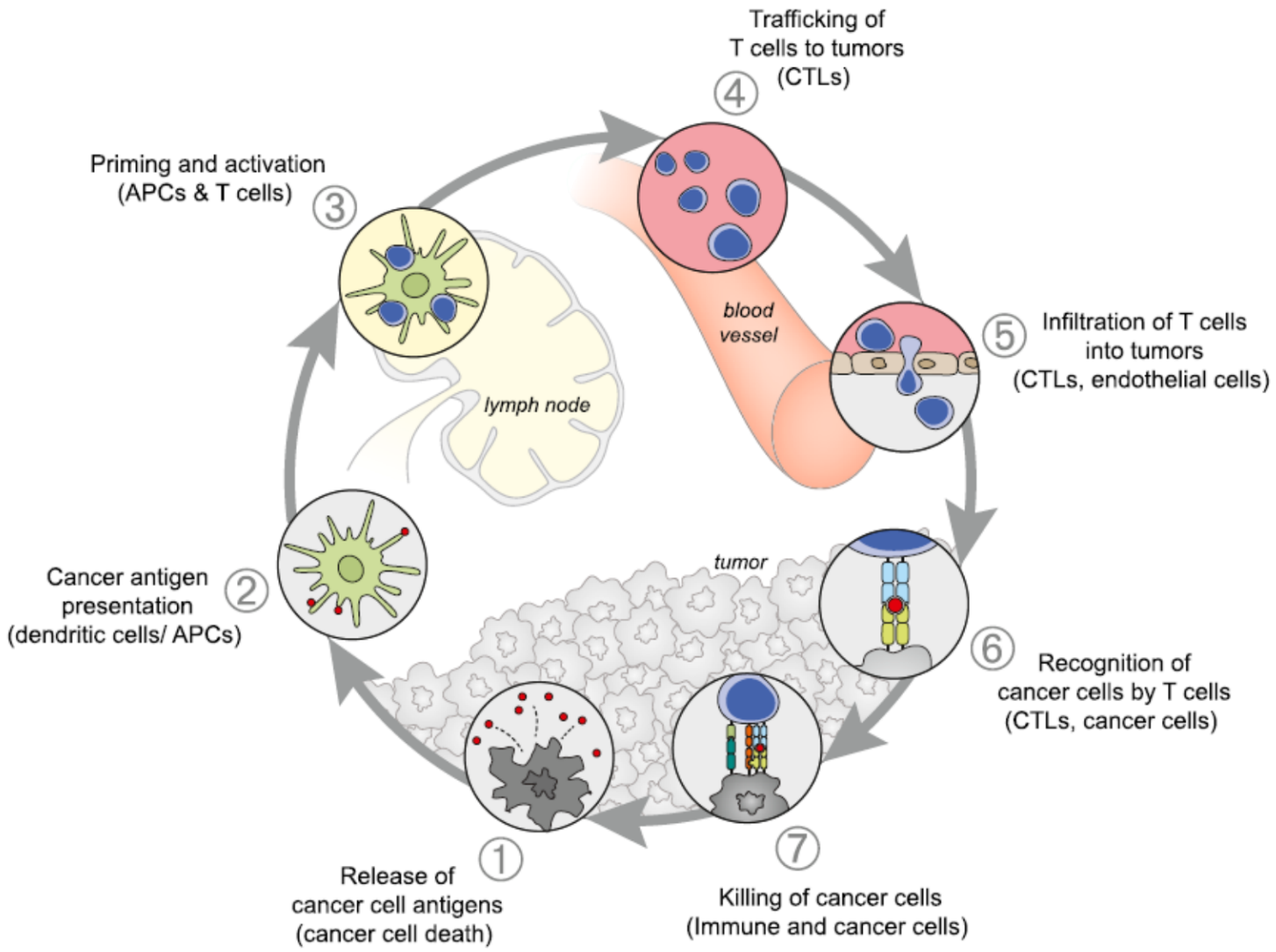
- Checkpointinhibitor(en) + oncolytisches Virus
- Checkpointinhibitoren + TKIs
- T Zelltransfer + Checkpointinhibitoren
- Sequentielle Therapien

Informationstiefe...

Tumormilieu

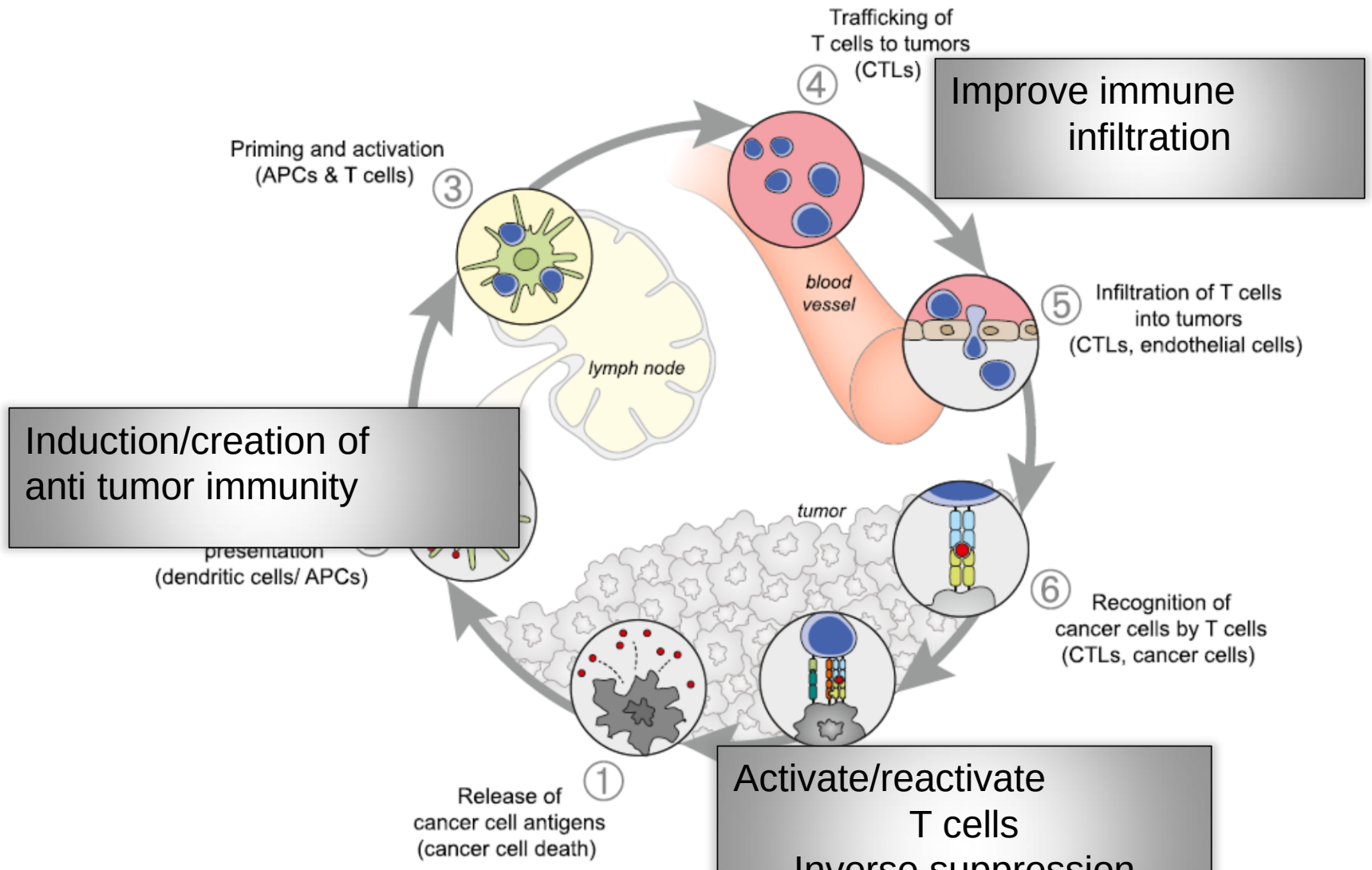


Komplexität von Tumor-Host Interaktionen



APC = antigen presenting cell
Chen DS & Mellman I. Immunity 2013

Komplexität von Tumor-Host Interaktionen



Improve immune infiltration

Induction/creation of anti tumor immunity

Activate/reactivate
T cells
Inverse suppression

APC = antigen presenting cell

Chen DS & Mellman I. Immunity 2013

NCT

Precision oncology

- Molekulare Diagnostik von individuellen Erkrankungen hinsichtlich Genetik, Epigenetik und Immunologie
- Integration aller molekularer und immunologischer Daten in ein Modell der individuellen Erkrankung
- Basierend auf diesen Daten Design einer `optimalen´ Kombinationstherapie:
  - Targeted Drugs (TKI etc)
  - Immunmodulation
  - Individualisierte Vakzine
  - Zell-basierte Therapien (adoptiver Transfer mit (un)modifizierten Zellen)
  - Intelligente Kombinationen
- Behandlung umfasst das Monitoring der Therapieeffekte im Tumor (sequentielle Biopsien)
- Alle Daten werden zur Optimierung der Modelingalgorithmen genutzt...