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Biomarker für Immunonkologika beim Melanom

Claus Garbe

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Universitäts-Hautklinik, Tuebingen**

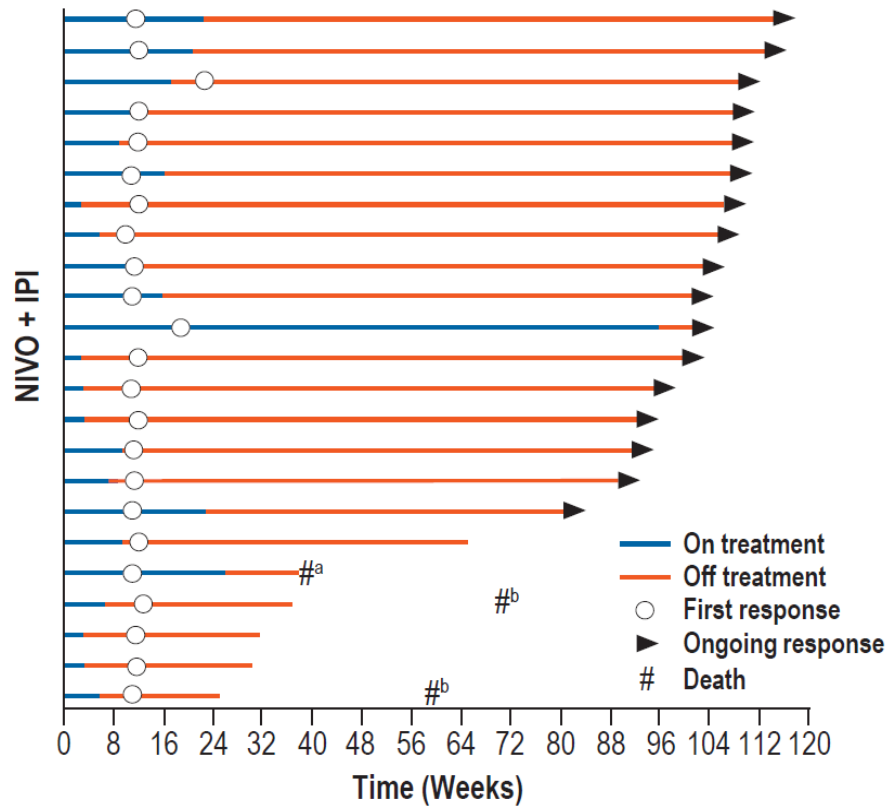
Disclosures

Honoraries and Grants

- Amgen
- BMS
- GSK
- LEO
- MerckSerono
- MSD
- Novartis
- Philogen
- Roche

Frühes Ansprechen - The First Shot Theory

Figure 3. Time to response and durability of response at 2 years of follow-up in patients who discontinued NIVO+IPI due to AEs

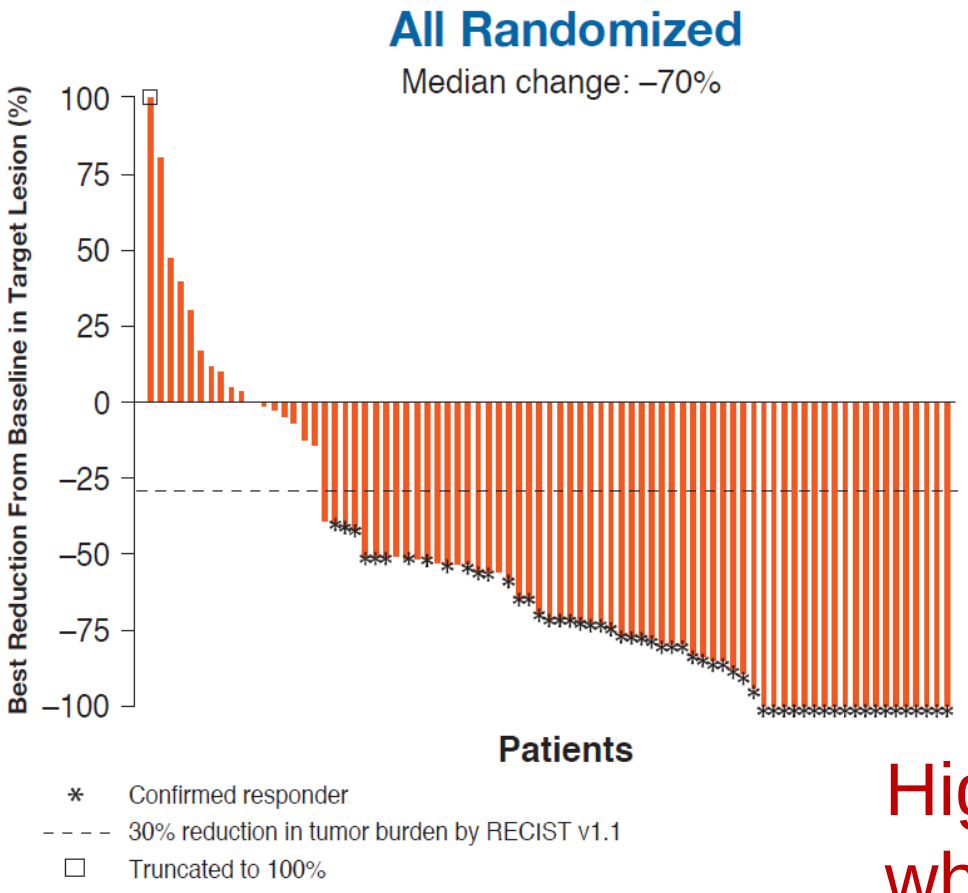


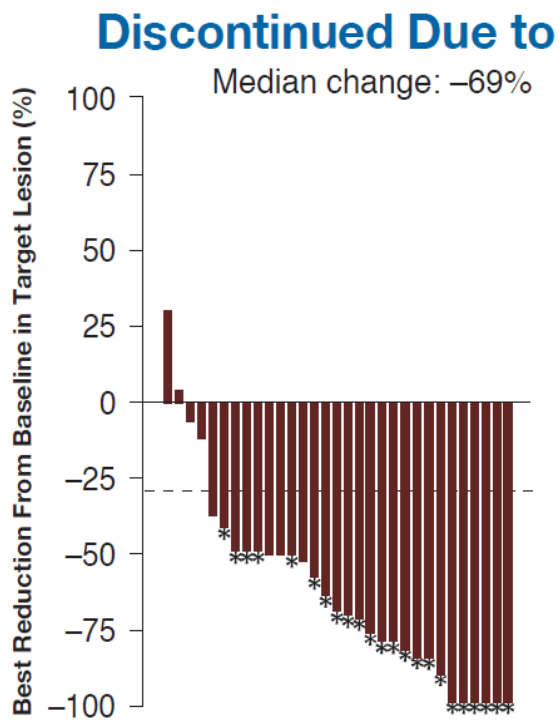
	NIVO+IPI	
	All randomized (N = 95)	Discontinued due to AEs (n = 35)
Median time to response, months (range)	2.8 (2.3-17.1)	2.6 (2.3-5.3)
Median duration of response, months (range)	NR	NR
Ongoing response among responders, n (%)	45/65 (80)	17/23 (74)

Durable responses in patients who discontinued treatment

Steve Hodi et al.: Overall Survival in Patients With Advanced Melanoma (MEL) Who Discontinued Treatment With Nivolumab (NIVO) Plus Ipilimumab (IPI) Due to Toxicity in a Phase II Trial (CheckMate 069), ASCO 2016

Figure 2. Tumor burden reduction (NIVO+IPI patients)

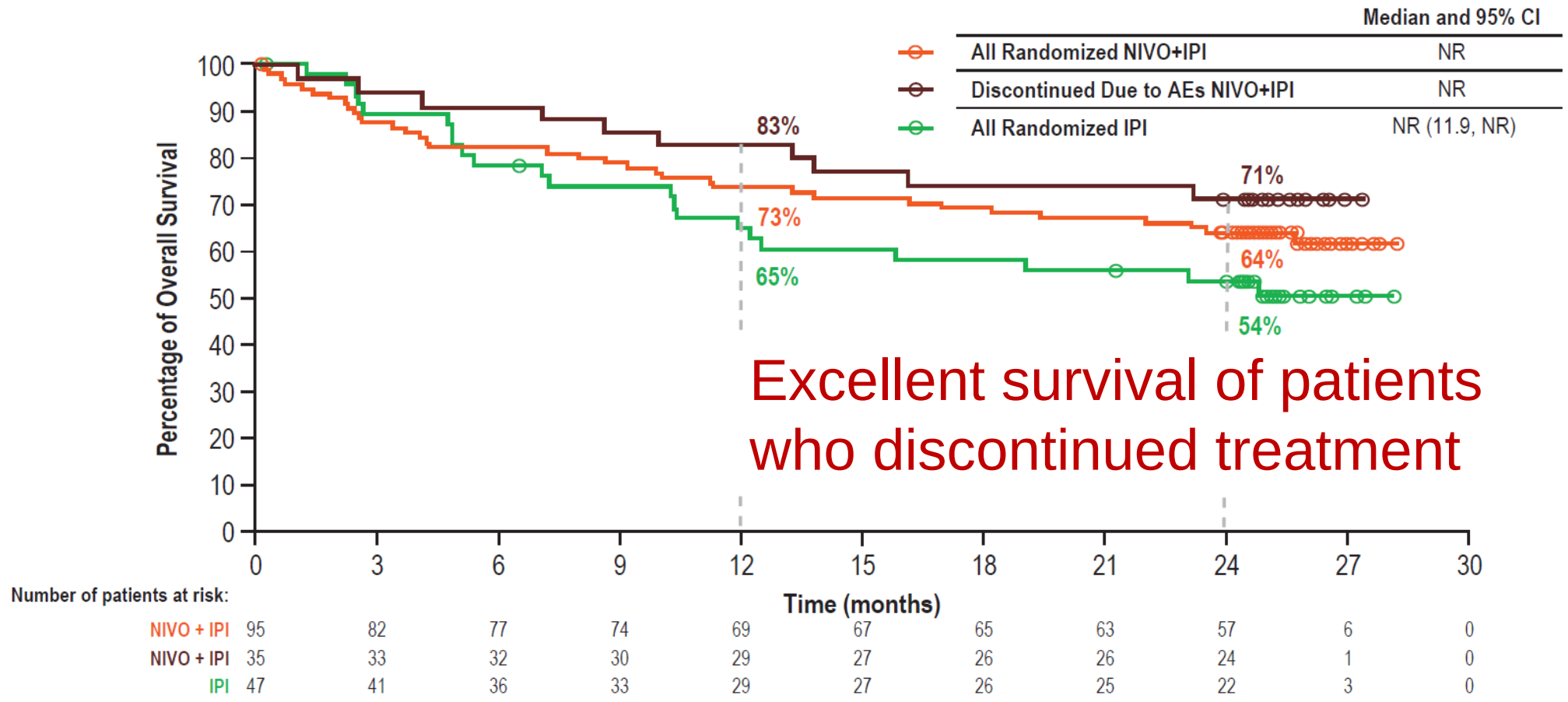




High response rate in patients who discontinued treatment

Steve Hodi et al.: Overall Survival in Patients With Advanced Melanoma (MEL) Who Discontinued Treatment With Nivolumab (NIVO) Plus Ipilimumab (IPI) Due to Toxicity in a Phase II Trial (CheckMate 069), ASCO 2016

Figure 4A. Overall survival at 2 years of follow-up



Excellent survival of patients who discontinued treatment

Steve Hodi et al.: Overall Survival in Patients With Advanced Melanoma (MEL) Who Discontinued Treatment With Nivolumab (NIVO) Plus Ipilimumab (IPI) Due to Toxicity in a Phase II Trial (CheckMate 069), ASCO 2016

First shot theory

- Response after a period of ~3 months is an excellent marker of efficacy of checkpoint inhibition.
- The first shot counts!

PD-L1 expression

Canditate: PD-L1 expression in tumor

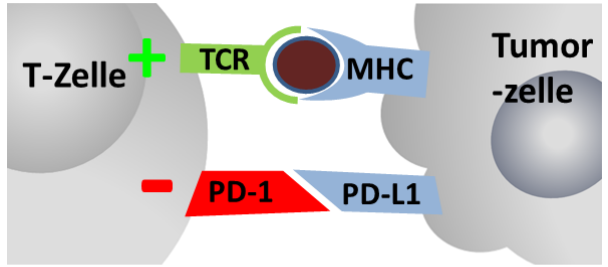


Table 1 Selected immune-checkpoint companion diagnostics in clinical development for NSCLC

Diagnostic company	PD-L1 IHC assay	Cutoff for PD-L1 positivity	Companion immunotherapy	Combination status
Dako (Agilent)	22C3 PharmDx	50% of tumor cells	Keytruda (pembrolizumab)	Approved
Dako (Agilent)	28-8 PharmDx	1%, 5% or 10% of tumor cells	Opdivo (nivolumab)(BMS)	Approved (as com-plementary assay)
Ventana (Roche)	SP142	Highest threshold: 5% of tumor cells, 50% of immune cells	Atezolizumab (RG7155) (Genentech/Roche)	In development
Ventana (Roche)	SP263	25% of tumor cells	Durvalumab (MEDI4736) (Medimmune/Amgen)	In development

Response by PD-L1 Expression Level (5%) in Checkmate067

		NIVO	NIVO + IPI	IPI
PD-L1-positive	**ORR, % (95% CI)**	**57.5** (45.9, 68.5)	**72.1** (59.9, 82.3)	**21.3** (12.7, 32.3)
PD-L1-negative	**ORR, % (95% CI)**	**41.3** (34.6, 48.4)	**54.8** (47.8, 61.6)	**17.8** (12.8, 23.8)

Wolchok et al., ASCO 2015

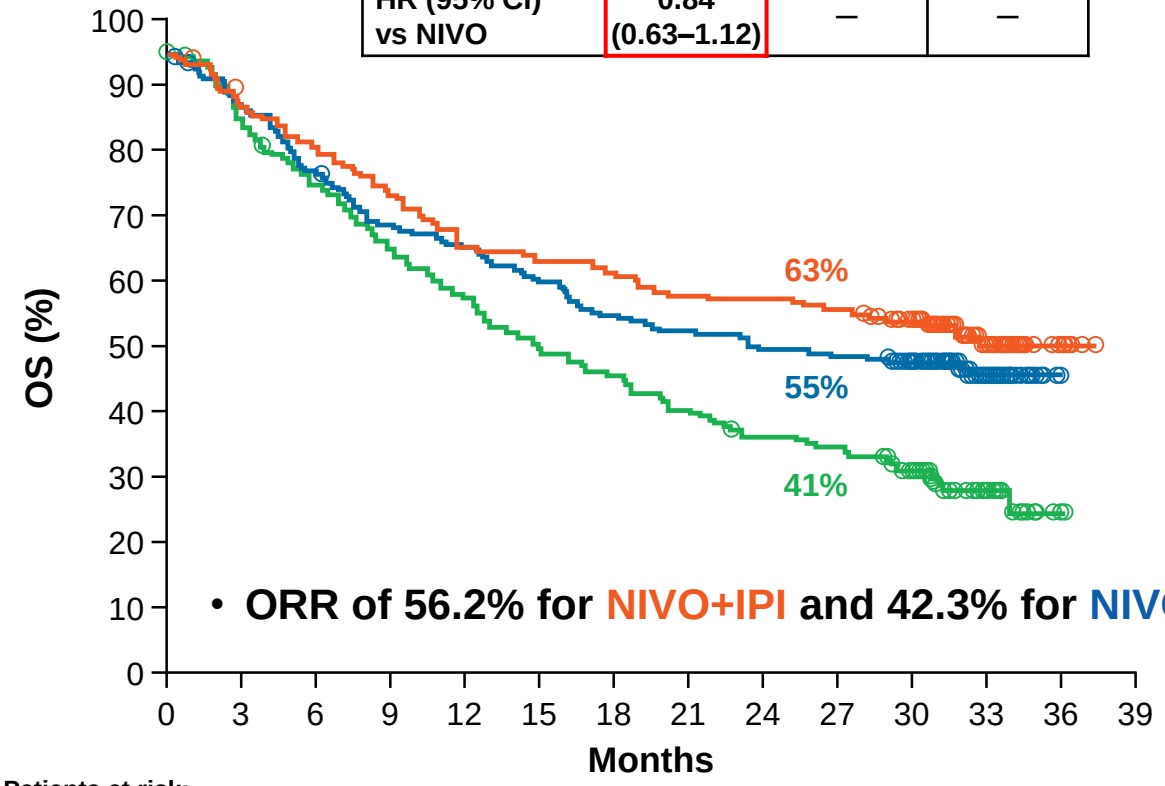
Objective response rate with Nivo + Ipi vs Nivo alone 15% higher in PD-L1+ and 13% higher in PD-L1-

PD-L1 expression is no valid selection criterion

OS by Tumor PD-L1 Expression, 5% Cutoff

PD-L1 Expression Level <5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (31.8–NR)	NR (23.1–NR)	18.5 (13.7–22.5)
HR (95% CI) vs NIVO	0.84 (0.63–1.12)	–	–



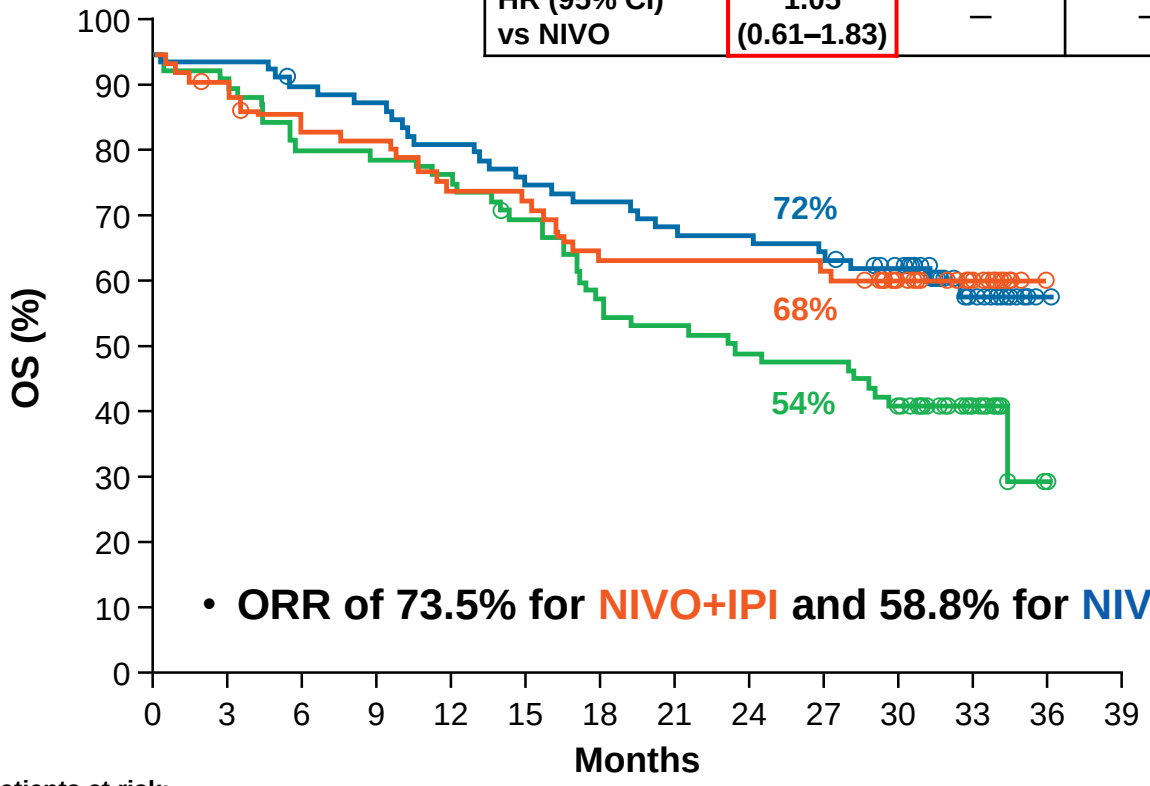
- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

Patients at risk:

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	116	34	7	0
NIVO	208	189	169	151	144	133	123	118	112	110	99	34	2	0
IPI	202	179	158	140	125	108	100	90	81	78	63	18	2	0

PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	28.9 (18.1–NR)
HR (95% CI) vs NIVO	1.05 (0.61–1.83)	–	–



- ORR of 73.5% for NIVO+IPI and 58.8% for NIVO

Patients at risk:

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	35	11	0	0
NIVO	80	79	75	73	68	63	61	58	57	54	49	18	1	0
IPI	75	72	67	65	61	55	46	43	40	39	33	13	1	0

PD-L1 expression

- Survival and response of PD-1 antibodies is increased in melanomas with PD-L1 expression
- However, PD-1 antibodies are still effective in melanomas without PD-L1 expression

Blood biomarkers

Personalized Medicine and Imaging

Clinical Cancer Research

Baseline Peripheral Blood Biomarkers Associated with Clinical Outcome of Advanced Melanoma Patients Treated with Ipilimumab

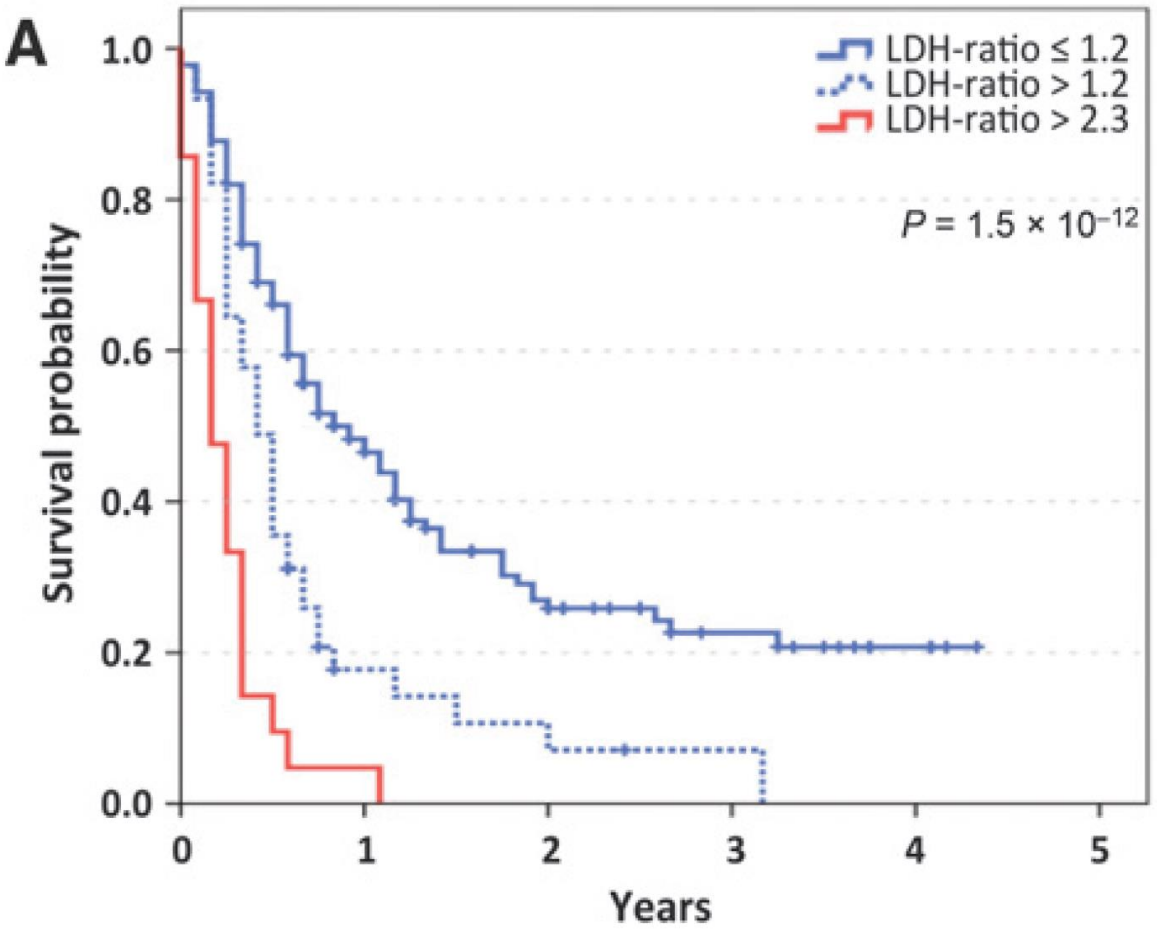
Alexander Martens[1,2], Kilian Wistuba-Hamprecht[1,2], Marnix Geukes Foppen[3], Jianda Yuan[4], Michael A. Postow[4,5], Phillip Wong[4], Emanuela Romano[6], Amir Khammari[7], Brigitte Dreno[7], Mariaelena Capone[8], Paolo A. Ascierto[8], Anna Maria Di Giacomo[9], Michele Maio[9], Bastian Schilling[10,11], Antje Sucker[10,11], Dirk Schadendorf[10,11], Jessica C. Hassel[11,12], Thomas K. Eigentler[1], Peter Martus[13], Jedd D. Wolchok[4,5], Christian Blank[3], Graham Pawelec[2], Claus Garbe[1], and Benjamin Weide[1,14]

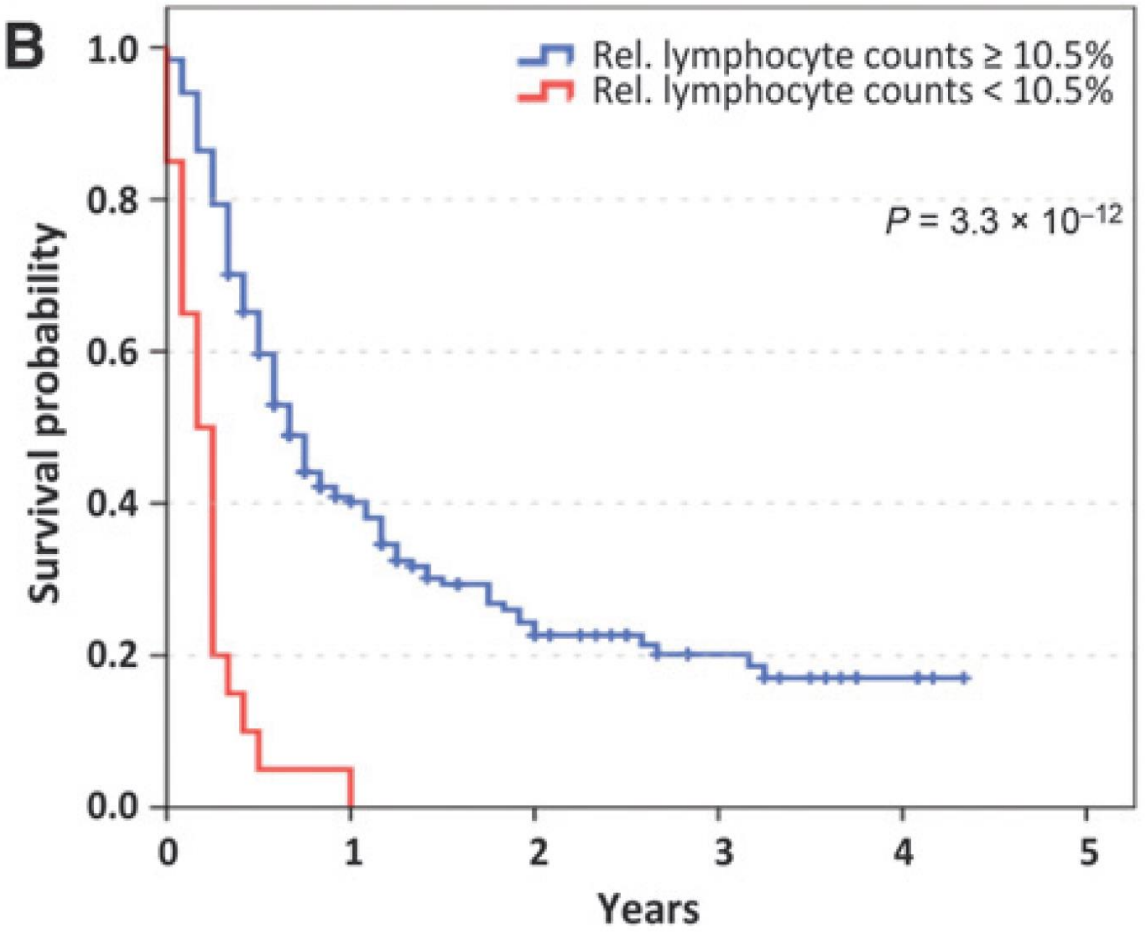
209 patients with baseline PBMC
myeloid-derived suppressor cells (MDSC) ,
regulatory T cells (Treg),
serum lactate dehydrogenase (LDH), routine blood counts, and clinical characteristics

Endpoints were overall survival (OS) and best overall response.

Martens et al., CCR 2016

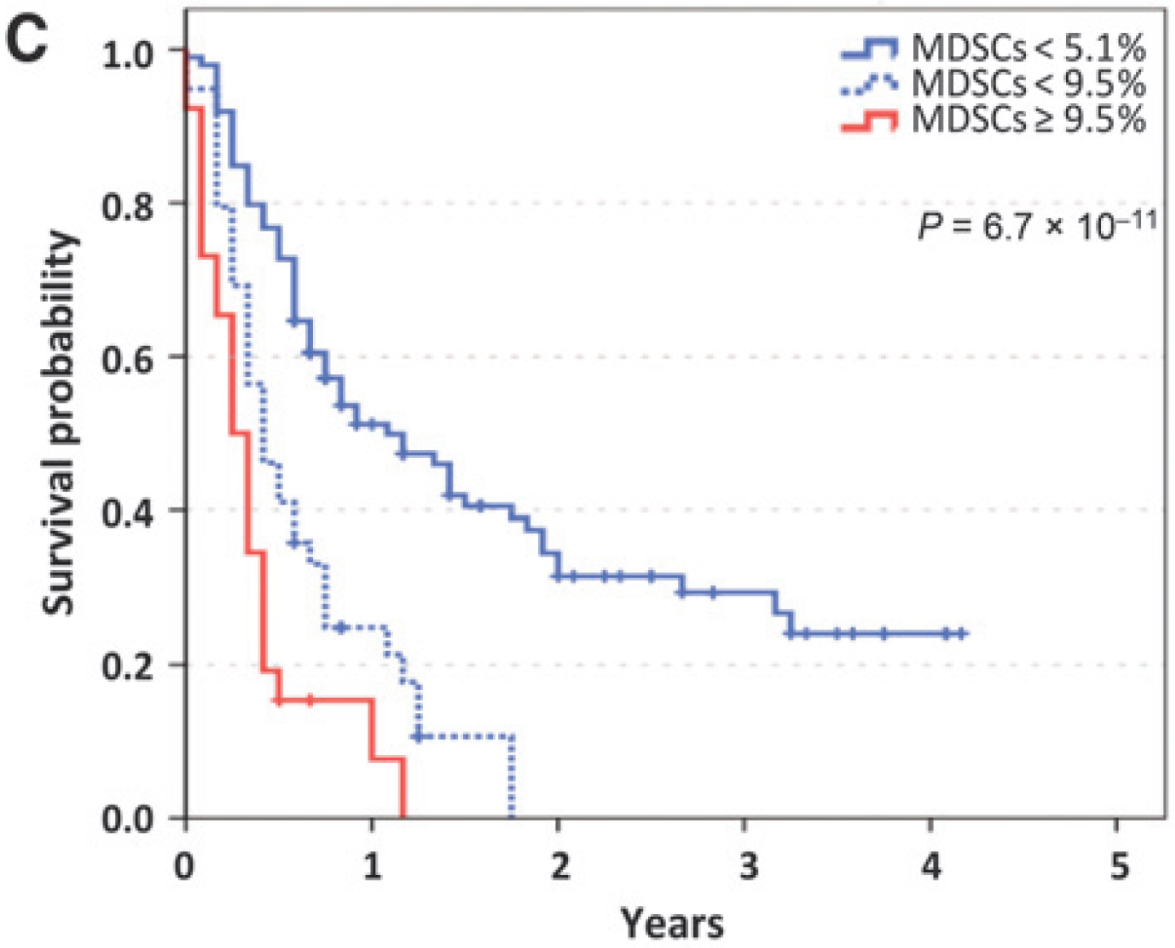
Peripheral blood biomarkers for ipilimumab

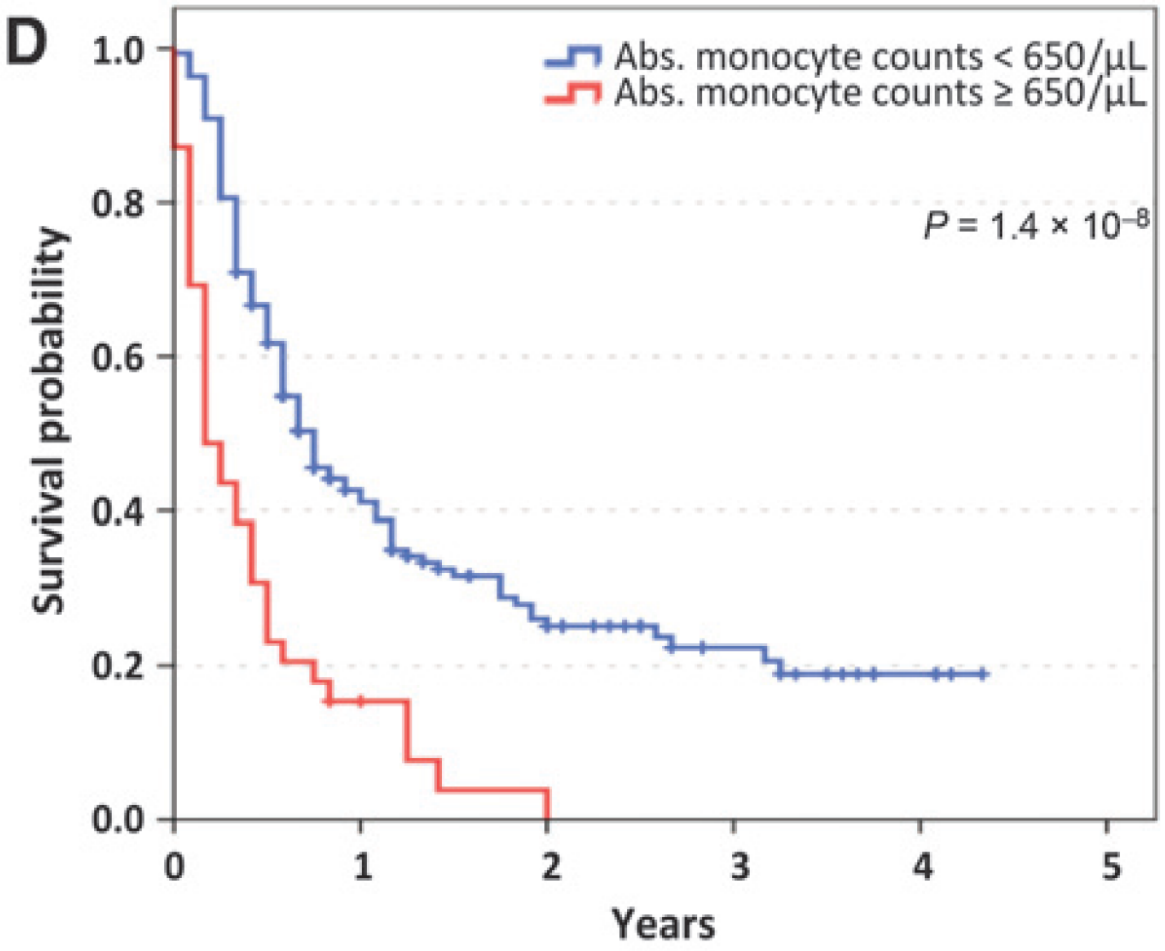




Martens et al., CCR 2016

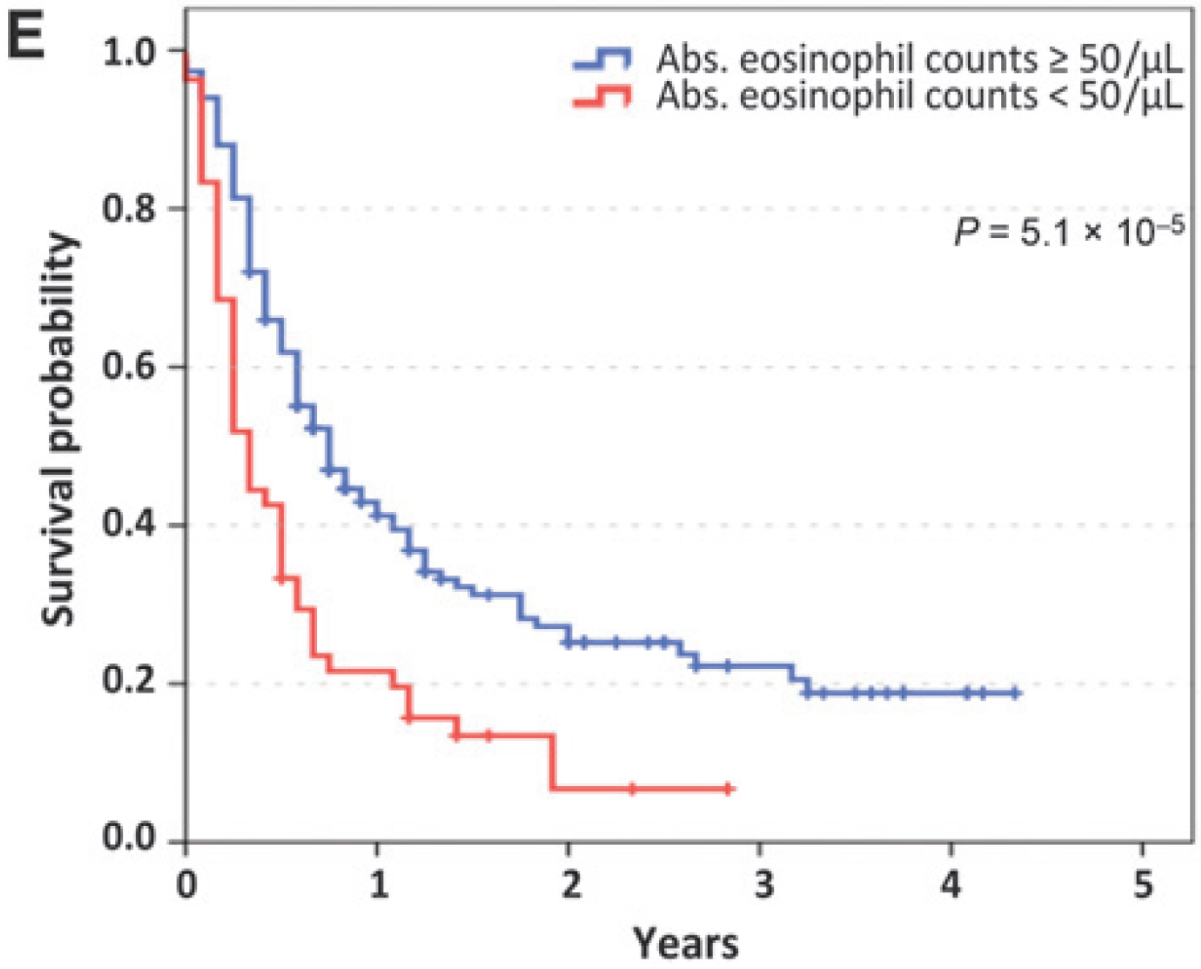
Peripheral blood biomarkers for ipilimumab

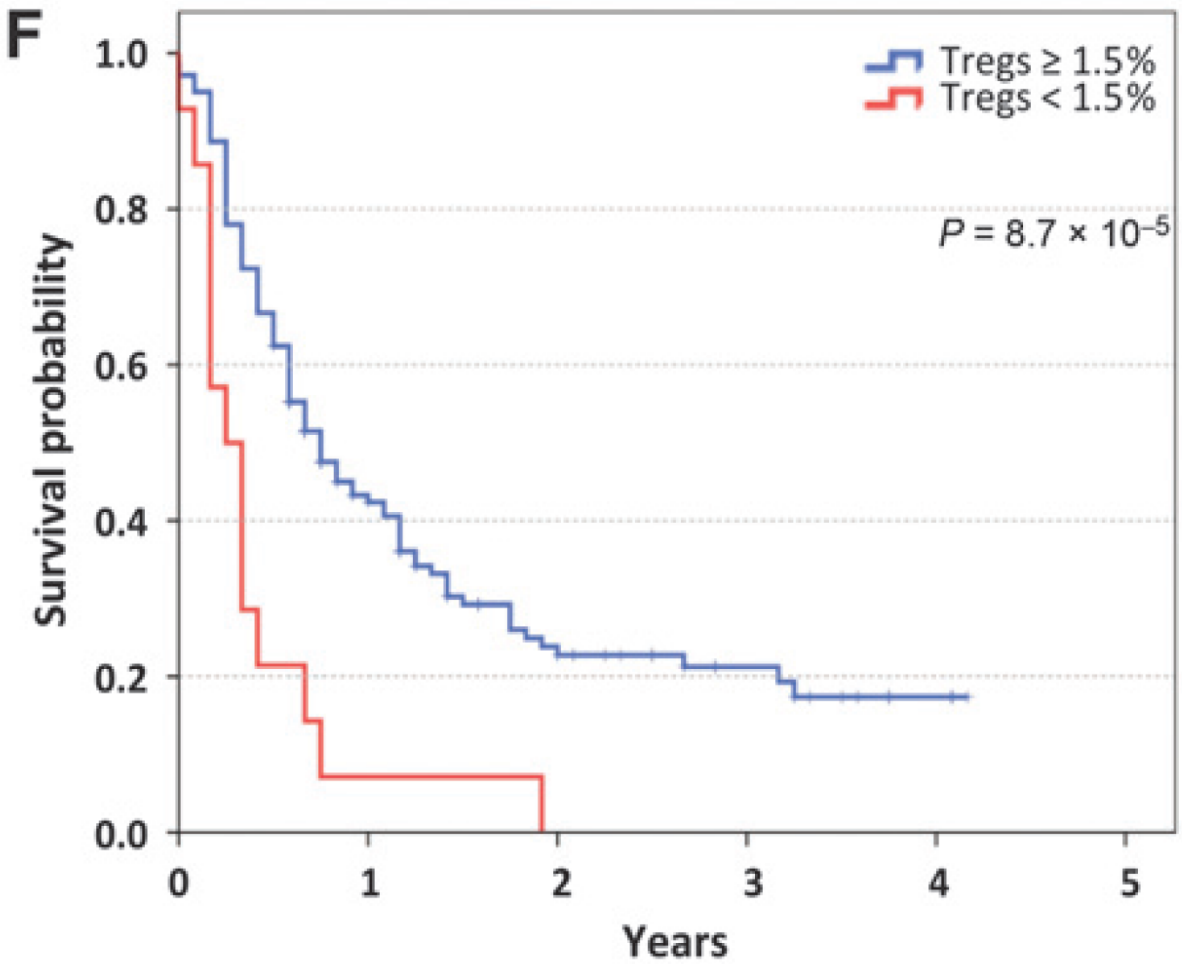




Martens et al., CCR 2016

Peripheral blood biomarkers for ipilimumab





Martens et al., CCR 2016

Peripheral blood biomarkers for ipilimumab

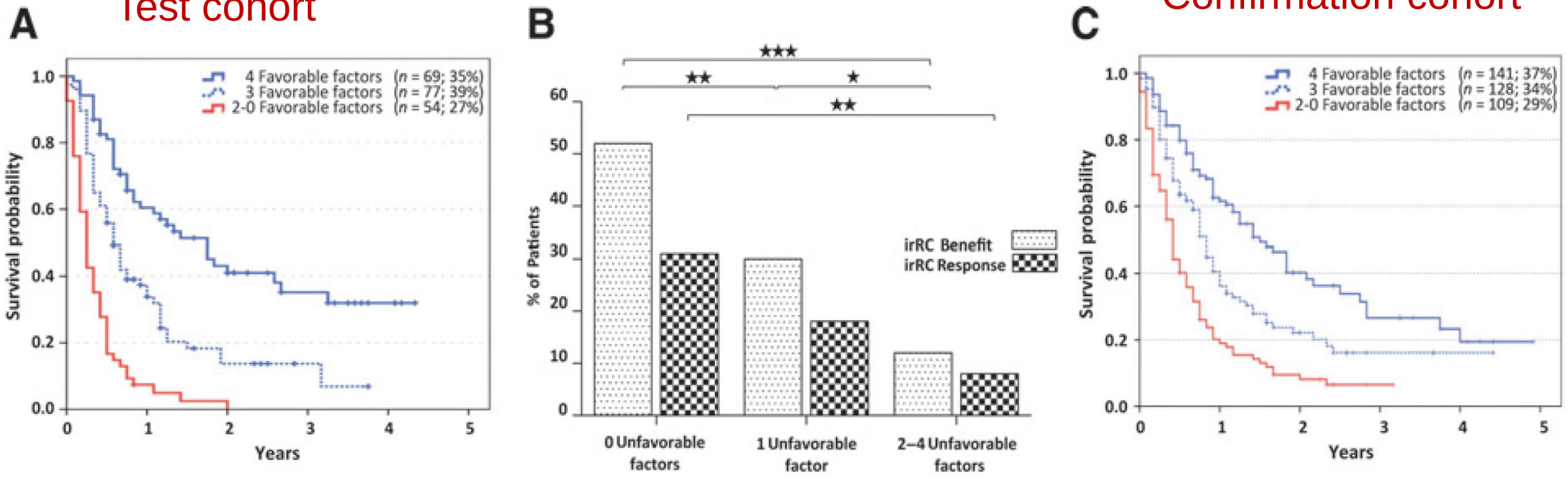
Multivariate model with Cox regression analysis for overall survival

- Lactate dehydrogenase
- Relative lymphocyte counts;
- Absolute eosinophil counts;
- Absolute monocyte counts;

Martens et al., CCR 2016

Peripheral blood biomarkers for ipilimumab

Test cohort



Confirmation cohort

Prognostic score consisting of:
Absolute eosinophil and monocyte counts,
the relative lymphocyte counts and LDH (categorized as elevated vs. normal)

Martens et al., CCR 2016

Personalized Medicine and Imaging

Clinical Cancer Research

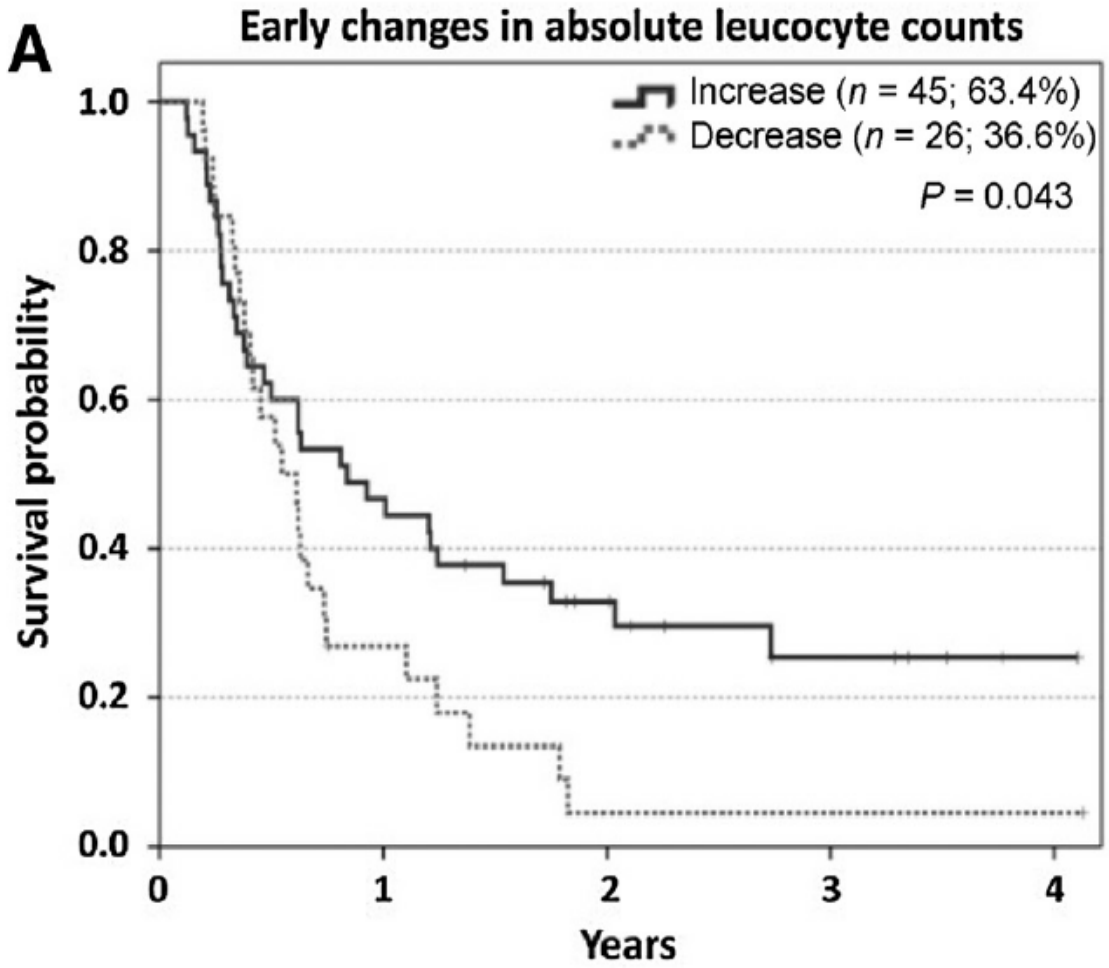
Increases in Absolute Lymphocytes and Circulating CD4$^+$ and CD8$^+$ T Cells Are Associated with Positive Clinical Outcome of Melanoma Patients Treated with Ipilimumab

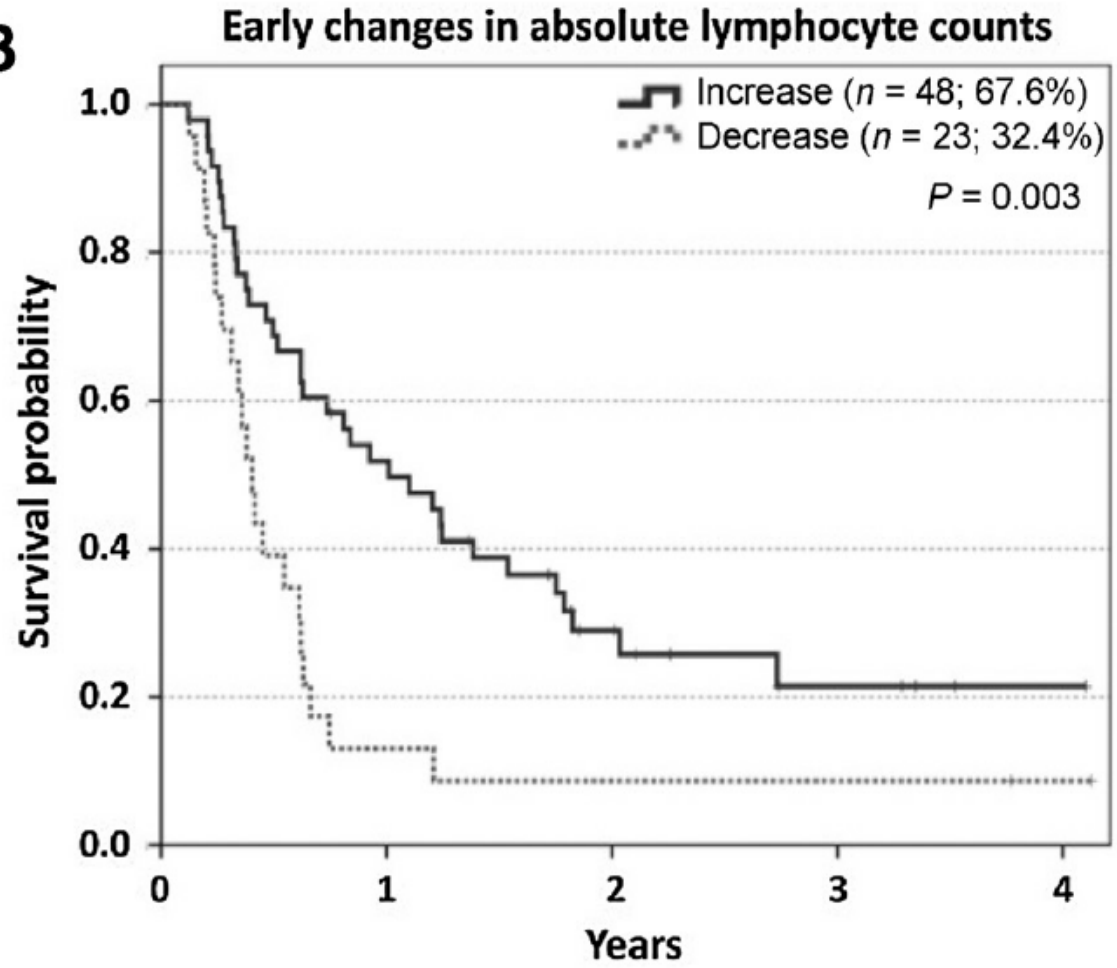
Alexander Martens[1,2], Kilian Wistuba-Hamprecht[1,2], Jianda Yuan[3], Michael A. Postow[3,4], Phillip Wong[3], Mariaelena Capone[5], Gabriele Madonna[5], Amir Khammari[6], Bastian Schilling[7,8], Antje Sucker[7,8], Dirk Schadendorf[7,8], Peter Martus[9], Brigitte Dreno[6], Paolo A. Ascierto[5], Jedd D. Wolchok[3,4], Graham Pawelec[2,10], Claus Garbe[1], and Benjamin Weide[1]

Changes in blood counts and the frequency of circulating immune cell populations analyzed by flow cytometry were investigated in 82 patients to compare baseline values with different time-points after starting ipilimumab. Endpoints were overall survival (OS) and best clinical response.

Martens et al., CCR 2016

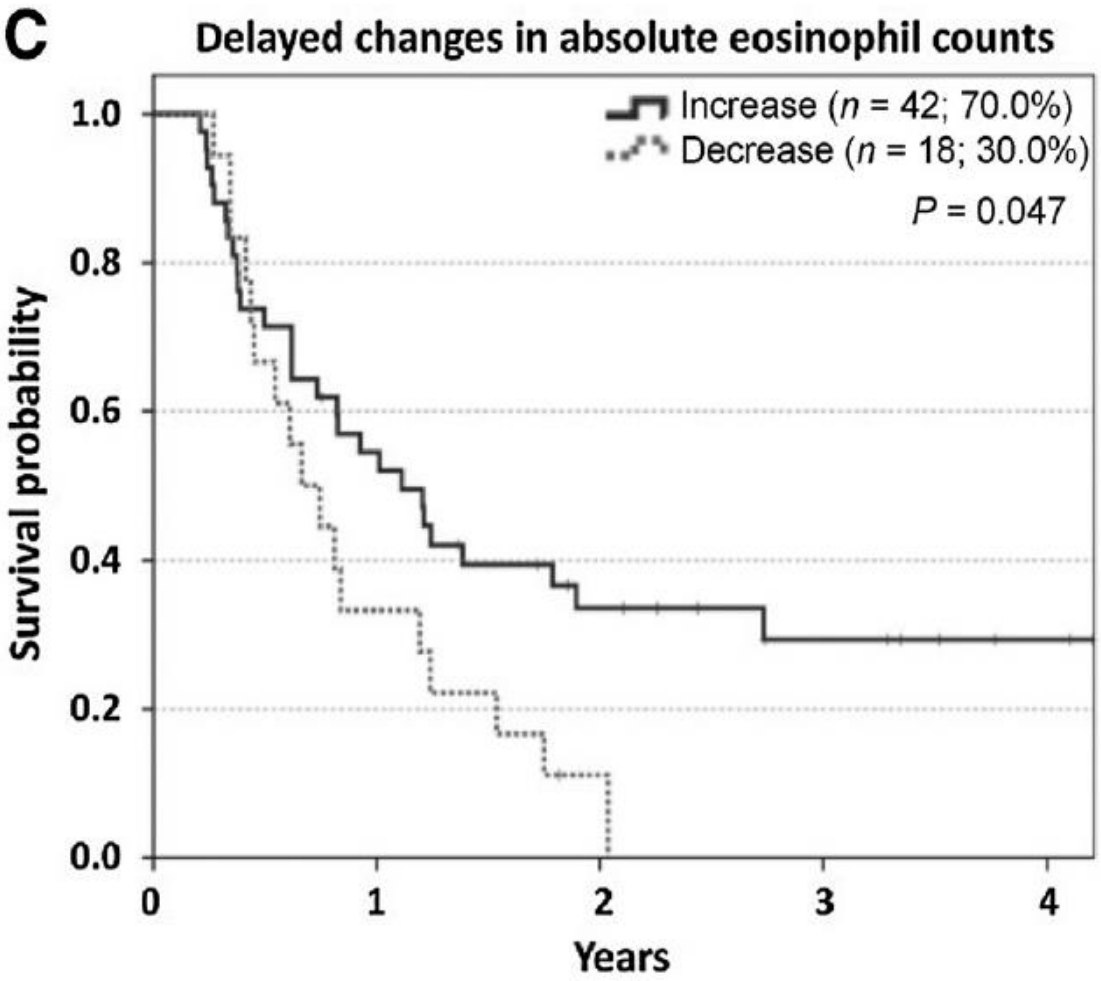
Increase in peripheral blood cells under ipilimumab treatment

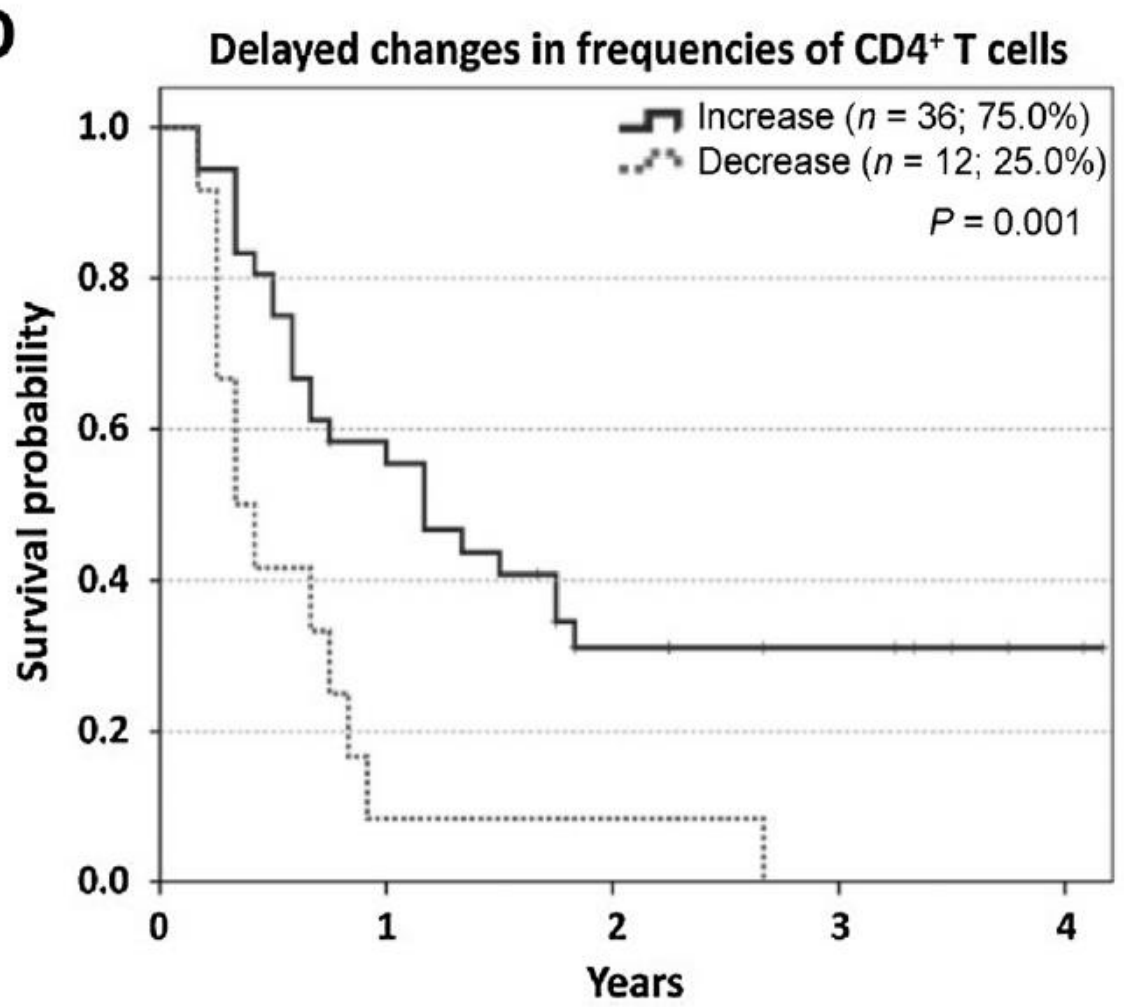




Martens et al., CCR 2016

Increase in peripheral blood cells under ipilimumab treatment





Martens et al., CCR 2016

Personalized Medicine and Imaging

Clinical Cancer Research

Baseline Biomarkers for Outcome of Melanoma Patients Treated with Pembrolizumab

Benjamin Weide[1,2], Alexander Martens[1], Jessica C. Hassel[3,4], Carola Berking[4,5], Michael A. Postow[6,7], Kees Bisschop[8], Ester Simeone[9], Johanna Mangana[10], Bastian Schilling[4,11], Anna Maria Di Giacomo[12], Nicole Brenner[13], Katharina Kähler[14], Lucie Heinzerling[15], Ralf Gutzmer[16], Armin Bender[17], Christoffer Gebhardt[4,18,19], Emanuela Romano[20], Friedegund Meier[4,21], Peter Martus[22], Michele Maio[12], Christian Blank[23], Dirk Schadendorf[4,11], Reinhard Dummer[10], Paolo A. Ascierto[9], Geke Hospers[8], Claus Garbe[1,4], and Jedd D. Wolchok[6,7]

Serum lactate dehydrogenase (LDH), routine blood count parameters, and clinical characteristics were investigated in 616 patients.
Endpoints were OS and best overall response following pembrolizumab treatment

Weide et al., CCR 2016

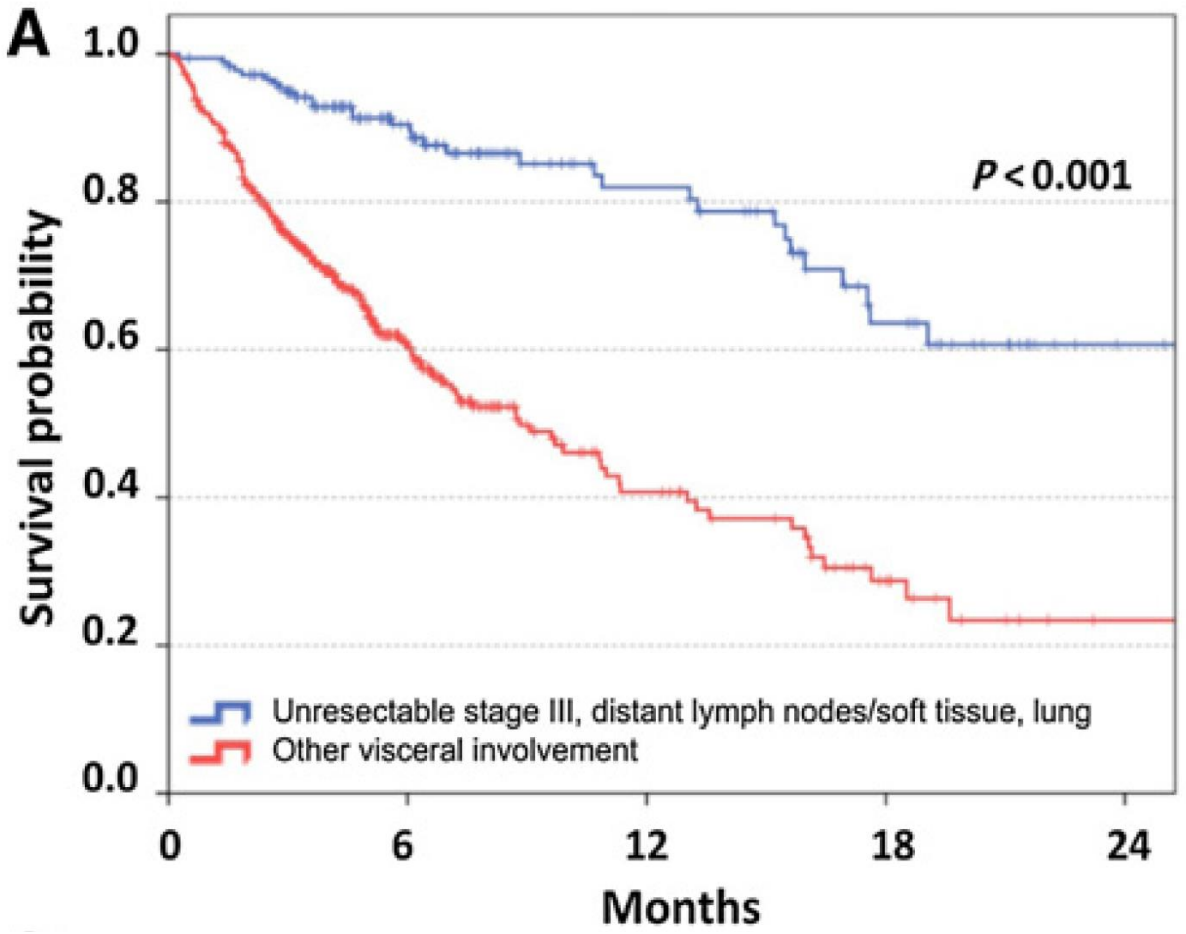
Biomarkers for pembrolizumab

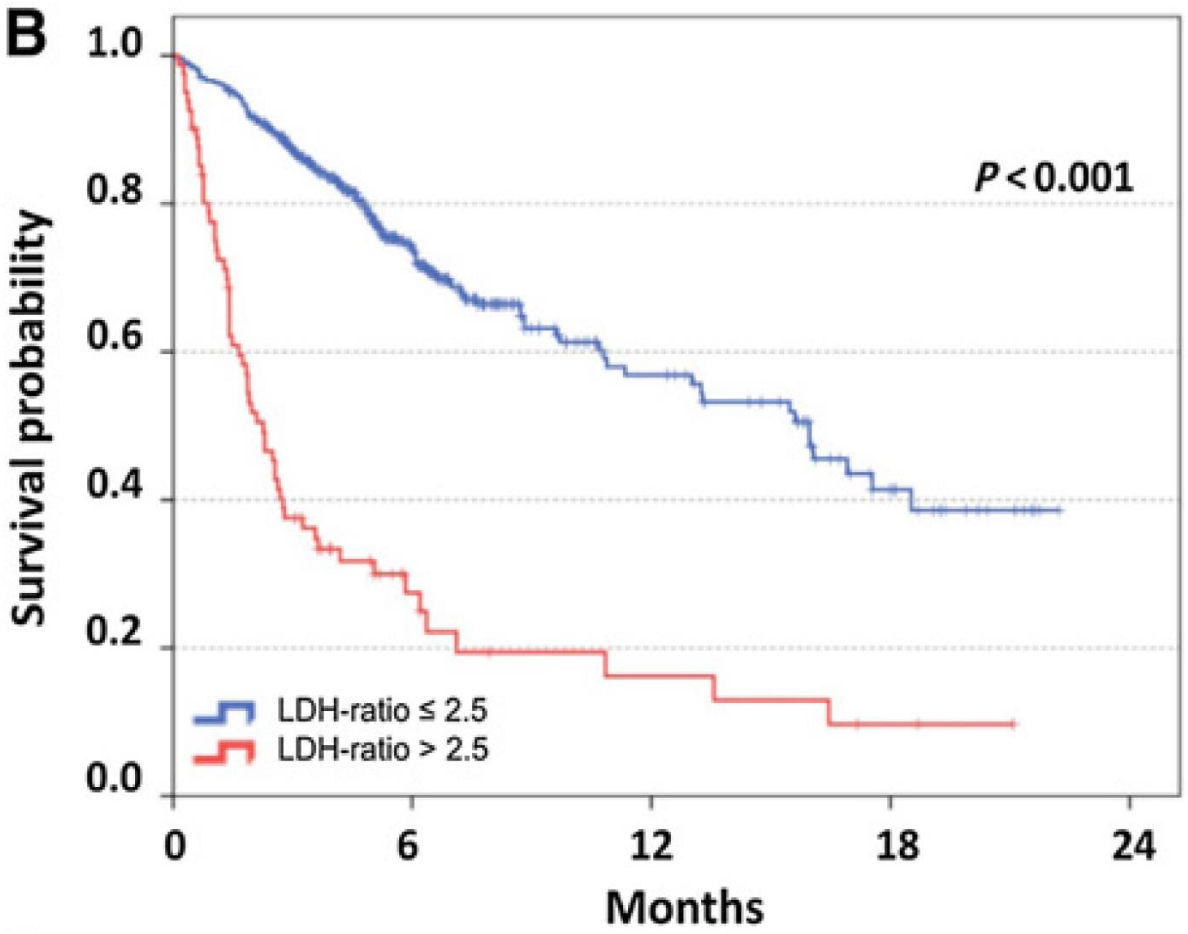
Multivariate model with Cox regression analysis for overall survival

- Stage III-IVB/IVC
- Lactate dehydrogenase
- Relative lymphocyte counts;
- Relative eosinophil counts;

Weide et al., CCR 2016

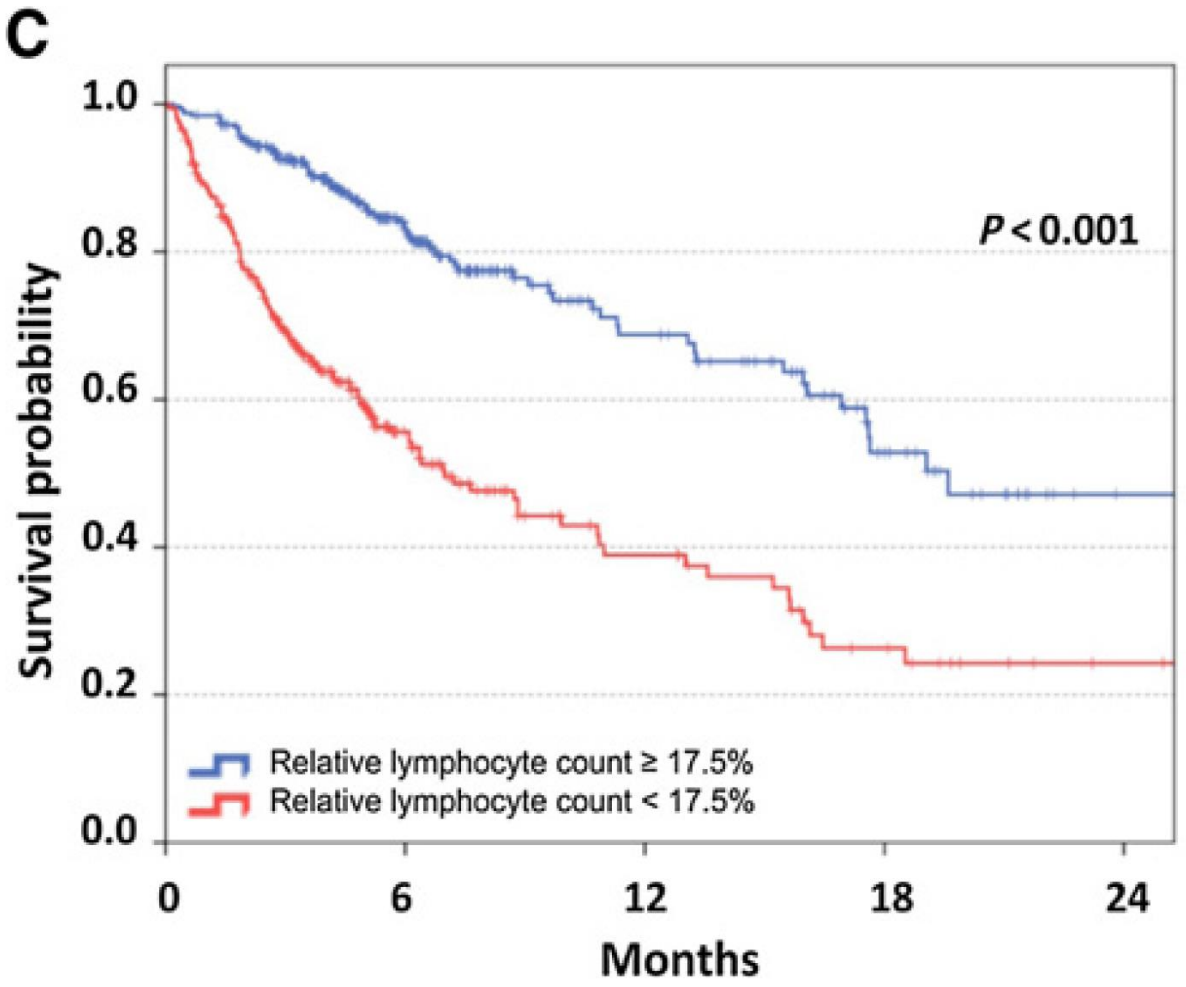
Biomarkers for pembrolizumab

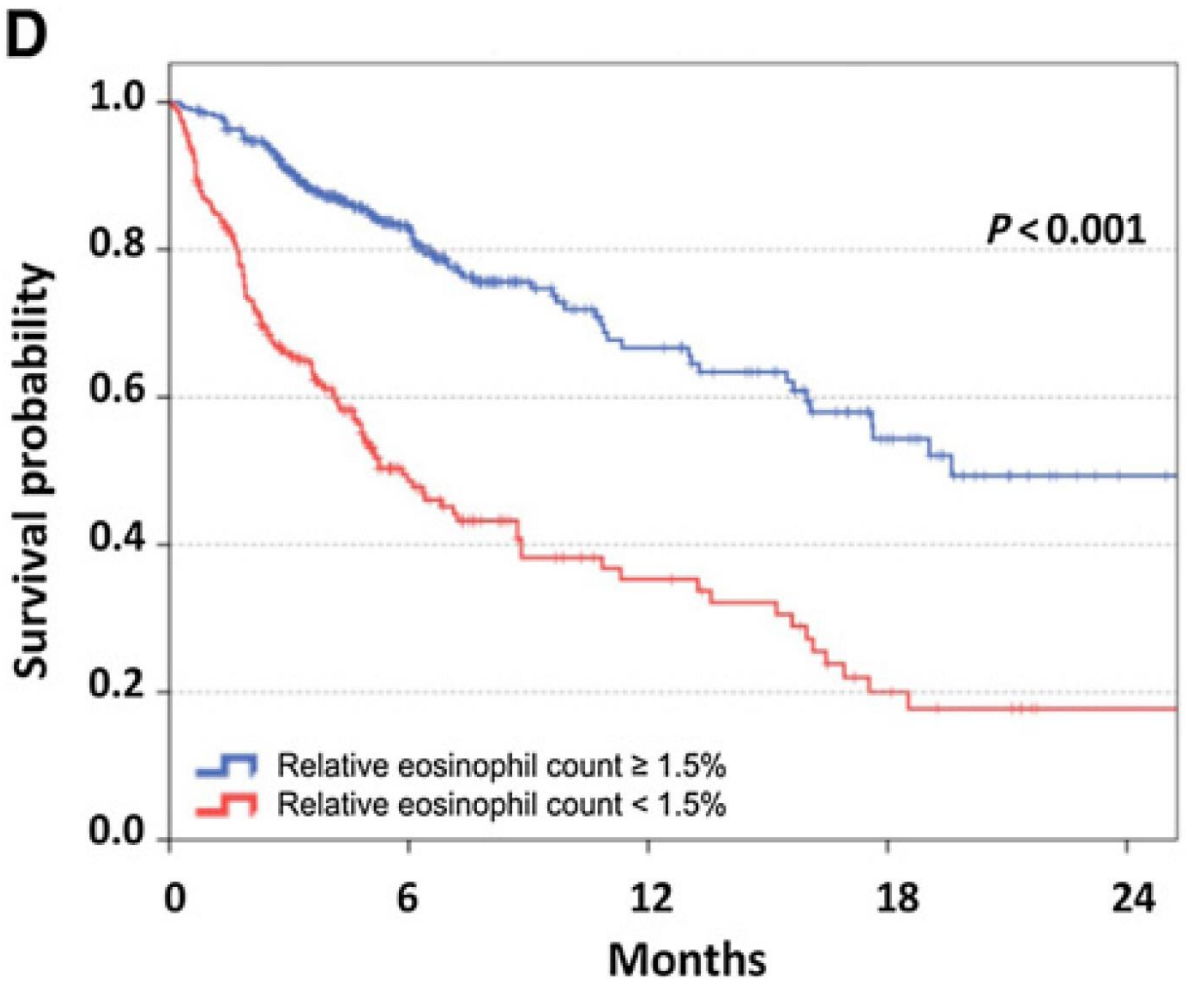




Weide et al., CCR 2016

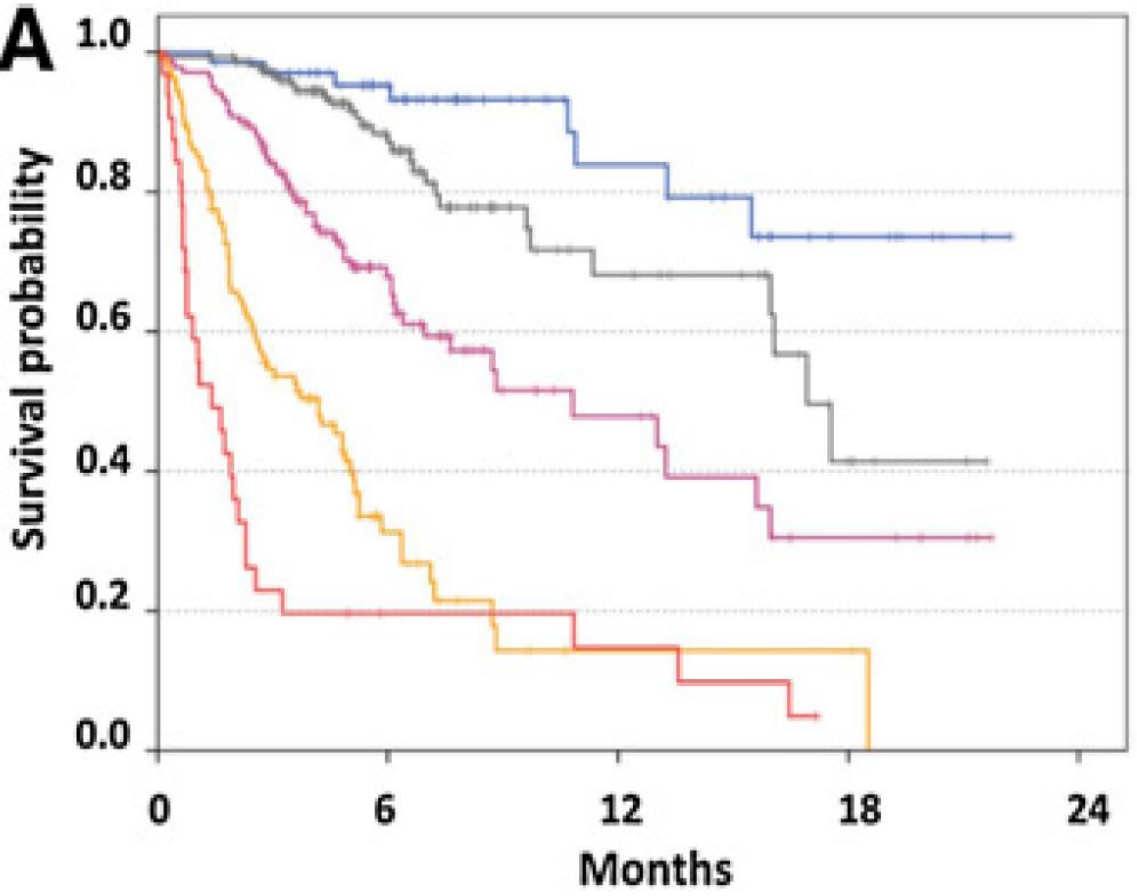
Biomarkers for pembrolizumab

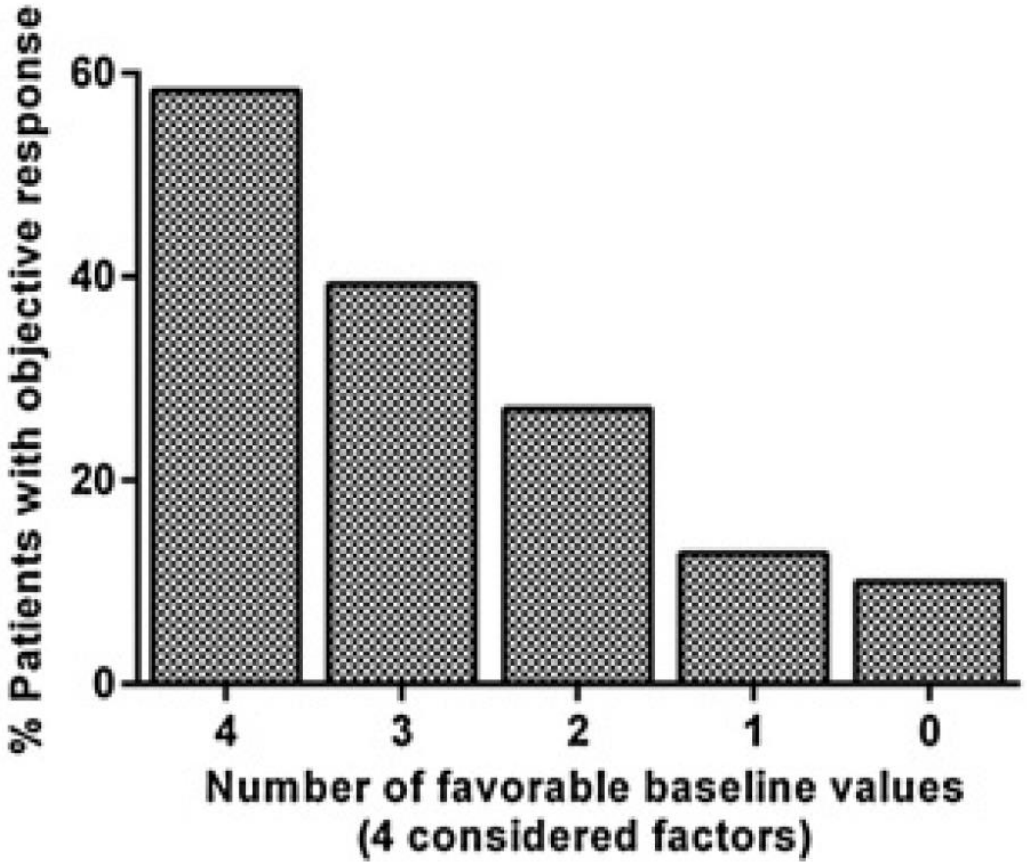




Weide et al., CCR 2016

Biomarkers for pembrolizumab

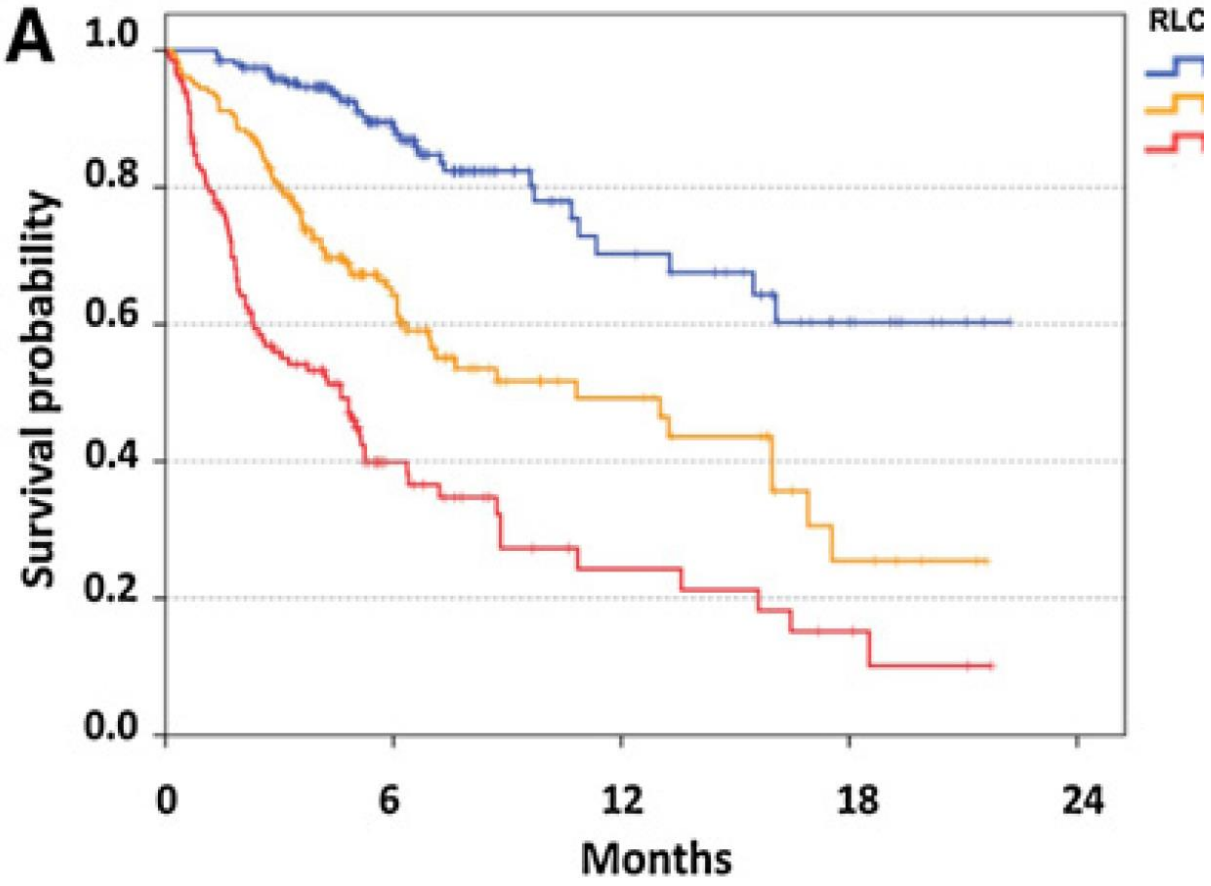


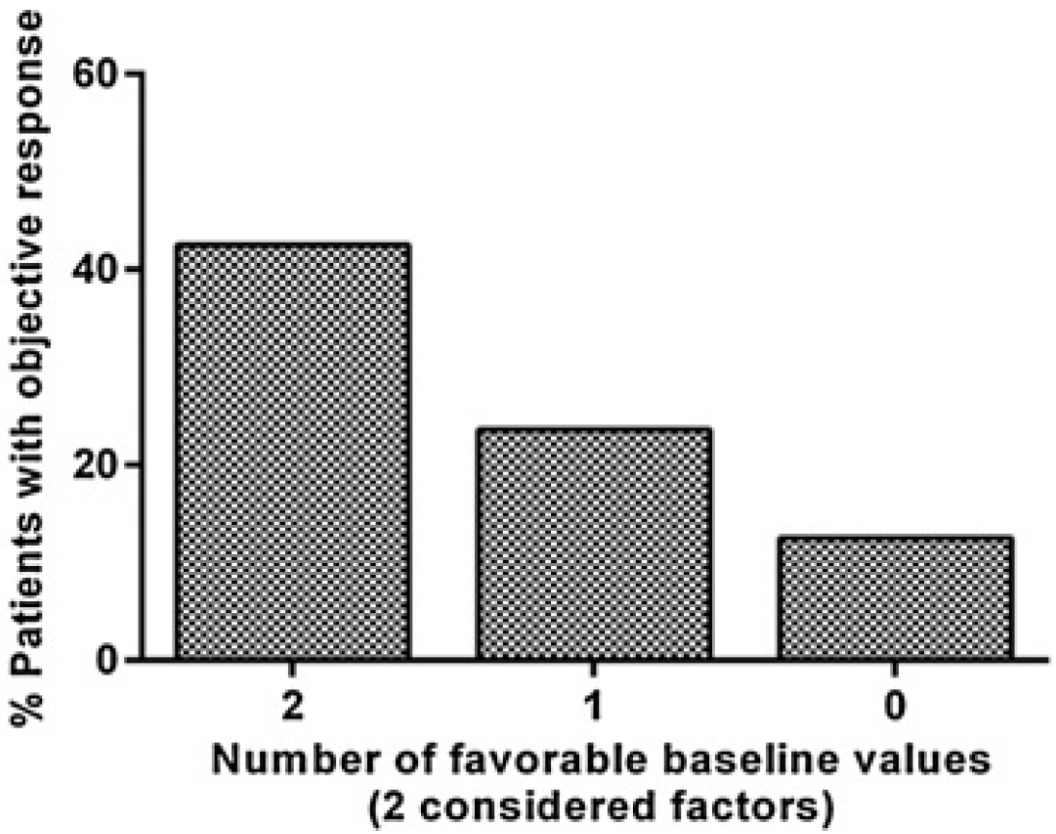


Prognostic score based on:
Stage III-IVB/IVC, lactate dehydrogenase
Relative lymphocyte counts, relative eosinophil counts

Weide et al., CCR 2016

Biomarkers for pembrolizumab





Prognostic score based only on:
Relative lymphocyte counts, relative eosinophil counts

Weide et al., CCR 2016

Biomarkers for checkpoint inhibitors

Ipilimumab

- Lactate dehydrogenase
- Relative lymphocyte counts;
- Absolute eosinophil counts;
- Absolute monocyte counts;
- ~~Tregs~~
- ~~MDSC~~
- γδ T-cells?
- Increase CD4+ CD8+ T cells?

Pembrolizumab

- Stage III-IVB/IVC
- Lactate dehydrogenase
- Relative lymphocyte counts;
- Relative eosinophil counts;

Functional T cell responses

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Study before checkpoint inhibition

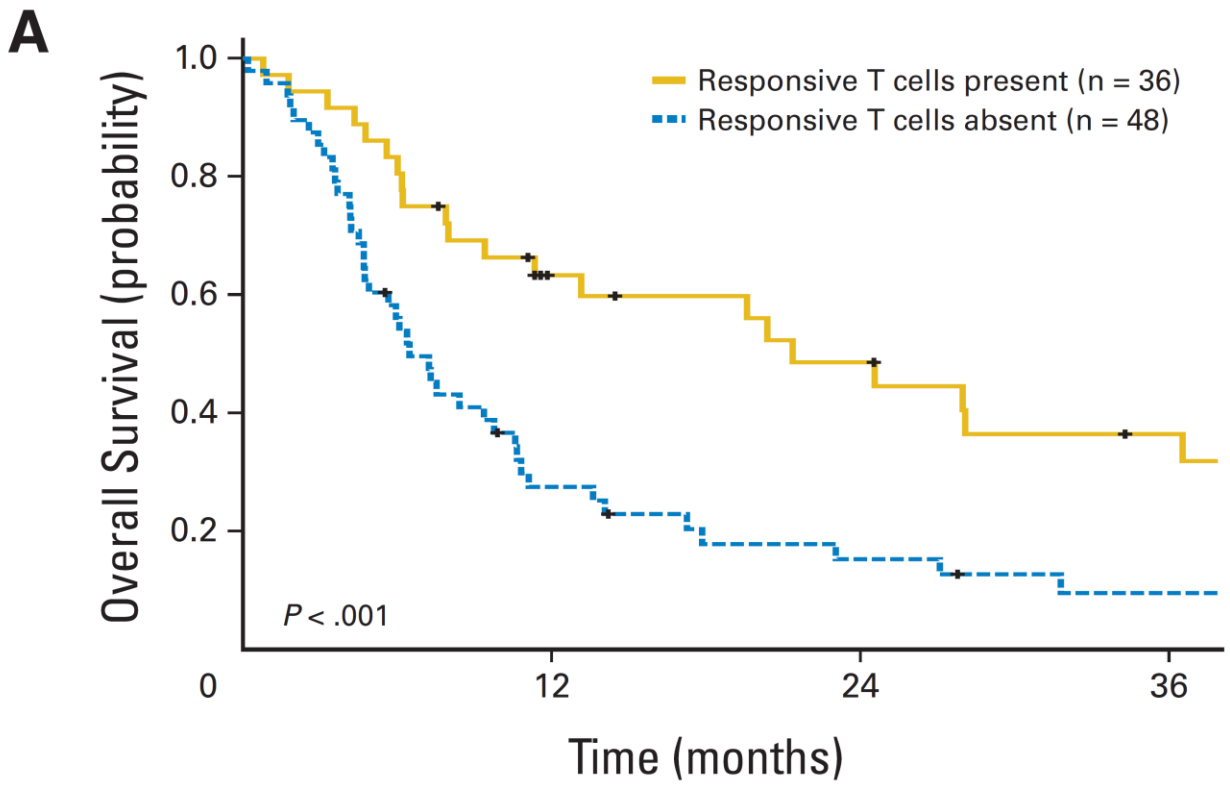
Functional T Cells Targeting NY-ESO-1 or Melan-A Are Predictive for Survival of Patients With Distant Melanoma Metastasis

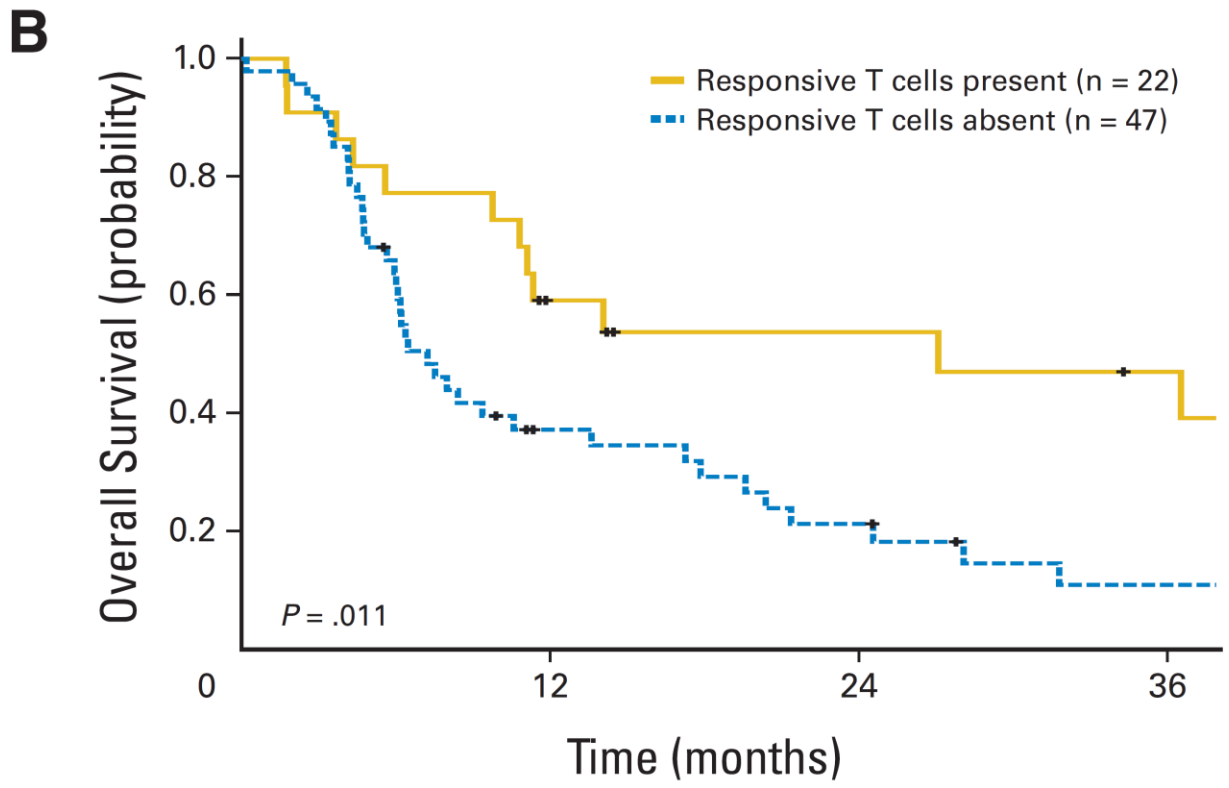
Benjamin Weide, Henning Zelba, Evelyna Derhovanessian, Annette Pflugfelder, Thomas K. Eigentler, Anna Maria Di Giacomo, Michele Maio, Erik H.J.G. Aarntzen, I. Jolanda M. de Vries, Antje Sucker, Dirk Schadendorf, Petra Büttner, Claus Garbe, and Graham Pawelec

We examined 84 patients with follow-up after analysis (cohort A), 18 long-term survivors with an extraordinarily favorable course of disease before analysis (24 months survival after first occurrence of distant metastases; cohort B), and 14 healthy controls. Circulating antigen-reactive T cells were characterized by intracellular cytokine staining after in vitro stimulation

Weide et al., JCO 2012

Functional T cell responses in patients with distant melanoma metastasis





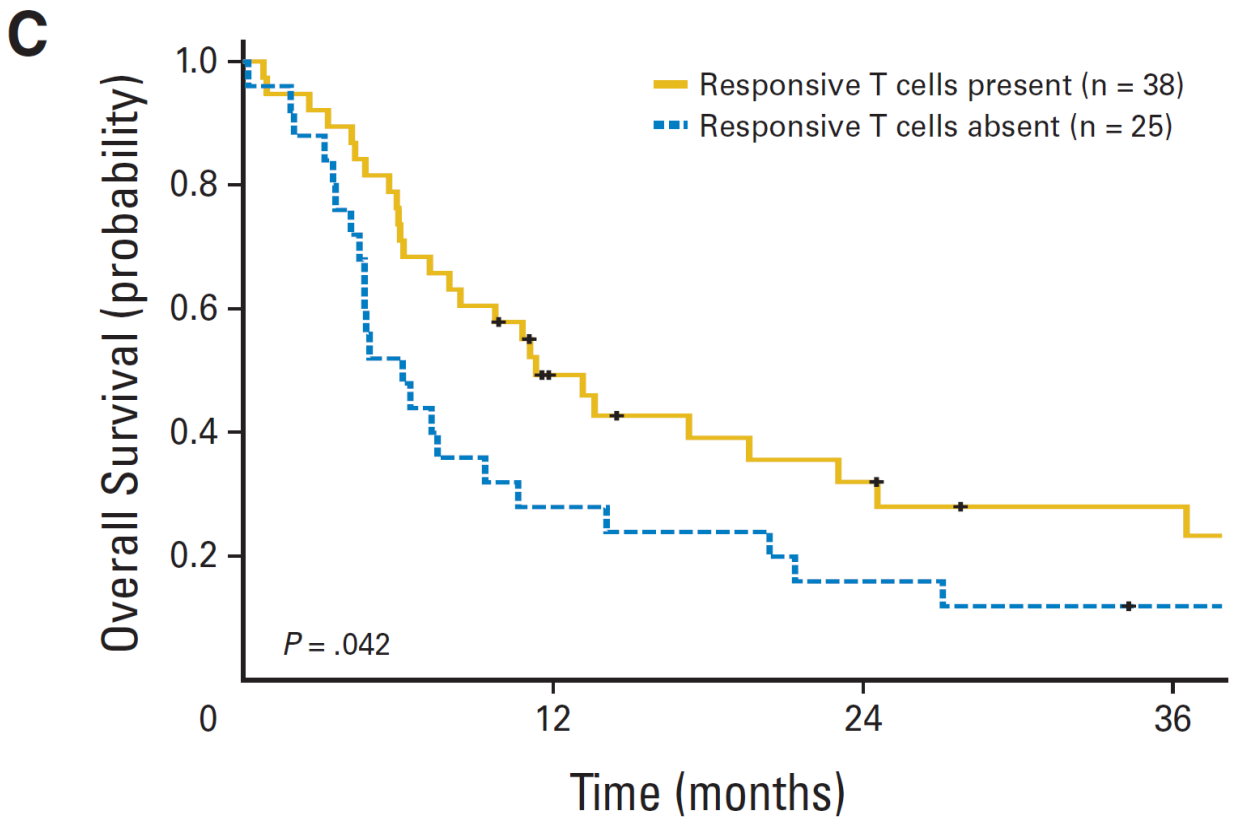
NY-ESO-1

Melan-A

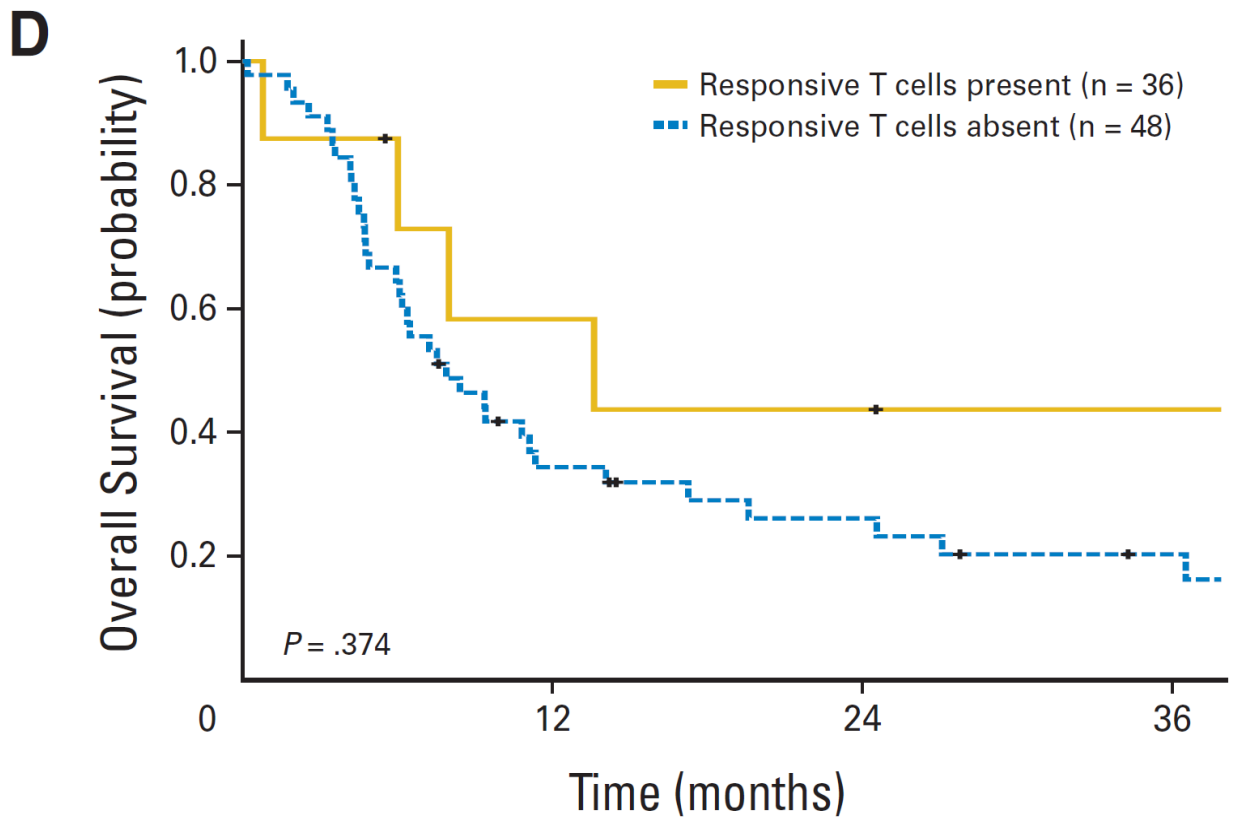
Strong prognostic markers independently of kind of treatment

Weide et al., JCO 2012

Functional T cell responses in patients with distant melanoma metastasis



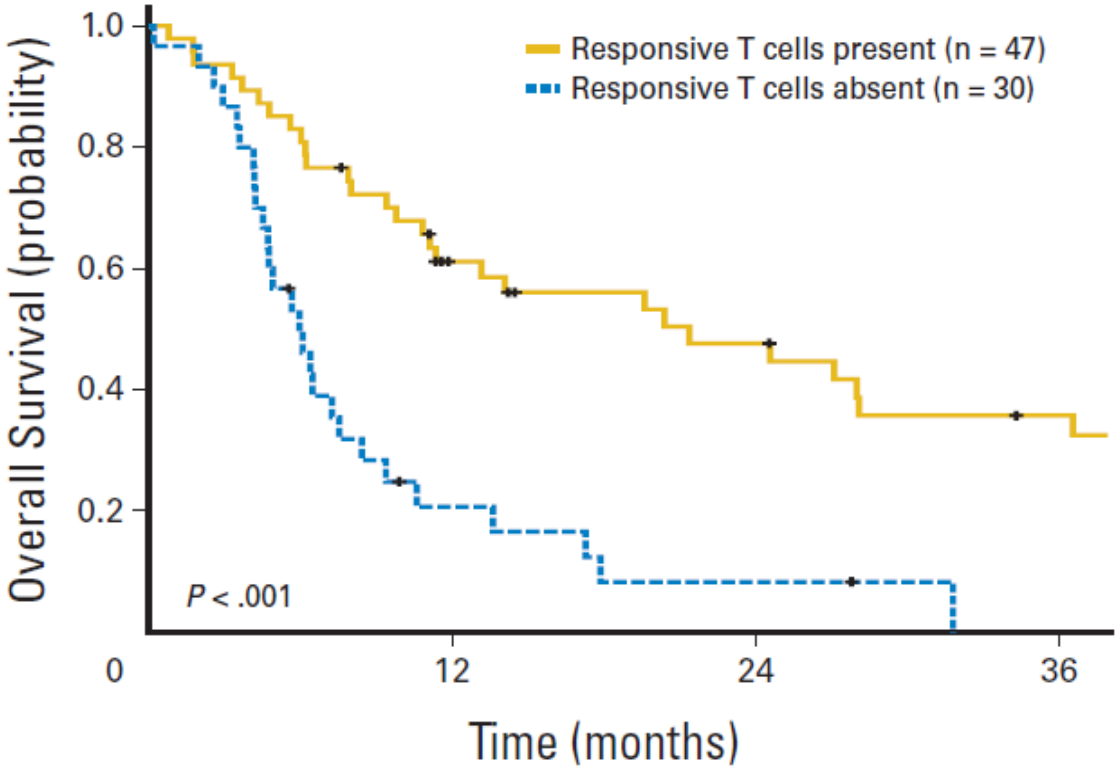
MAGE-3



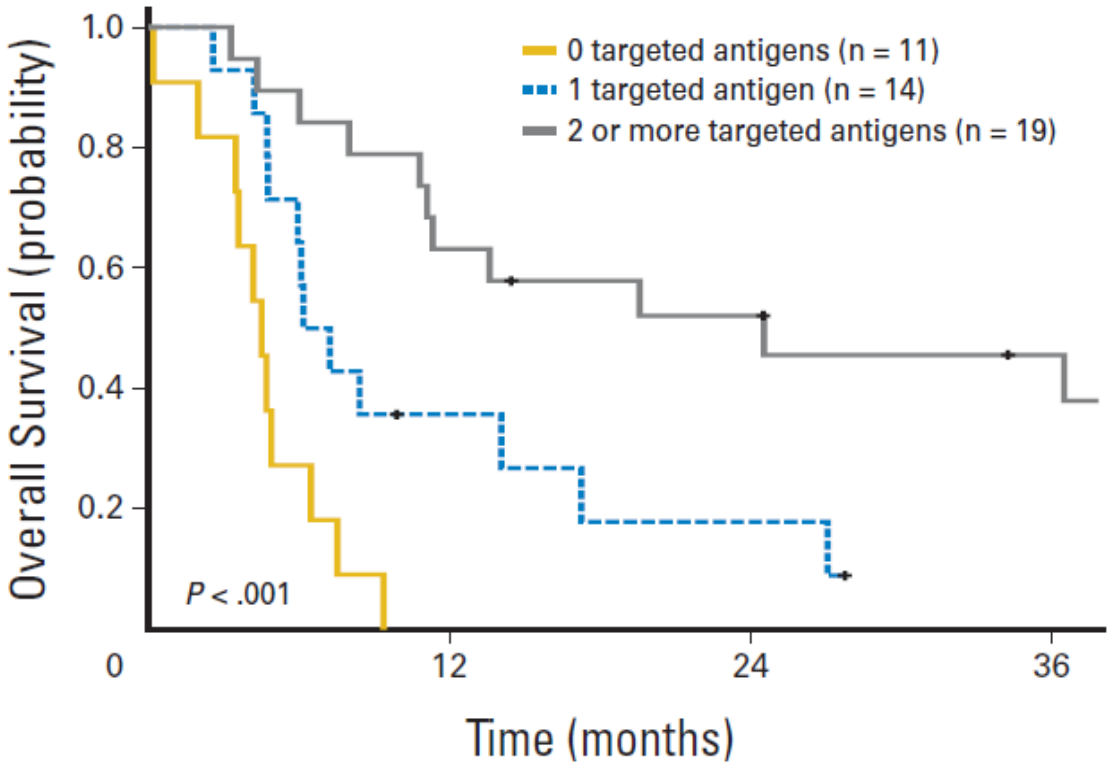
Survivin

Weide et al., JCO 2012

Functional T cell responses in patients with distant melanoma metastasis



Responsive/non-resp.



Number of responses

Weide et al., JCO 2012

Functional T cell responses: >100 tumor antigens in patients with HLA-A0201

Prognostic and predictive markers for patients treated with CTLA-4 and PD-1 inhibitors

- Outcome of first shot may be the most relevant biomarker
- Established prognostic markers like tumor-stage and LDH are valid in checkpoint inhibitor therapy
- Lymphocyte and eosinophil counts may have predictive value
- Preexisting functional antitumor T cell responses should be better analyzed

Co-workers and collaborations

Center of Dermatooncology Tübingen
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Laboratory Team Tübingen
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Immunology Department Tübingen
Hans-Georg Rammensee, Stefan Stevanovic, Gundram Jung

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Frankfurt: Michel Mittelbronn, Patrick Harter
Heidelberg: Jessica Hassel
Mannheim: Christoffer Gebhardt
Nantes: Brigitte Dreno, Amir Khammari
Neapel: Paolo Ascierto, Marielena Capone, Ester Simeone
New York: Jedd Wolchok, Jianda Yuan, Mike Postow
Paris: Laurance Zitvogel, Emanuela Romano
Siena: Michele Maio, Anna-Maria Di Giacomo
Würzburg: Jörg Wischhusen

ZDO
Zentrum für Dermatoonkologie Tübingen

TATI
Tübingen Ageing and Tumour Immunology Group

Thank you for your attention!