Malignt melanom

Immunterapi

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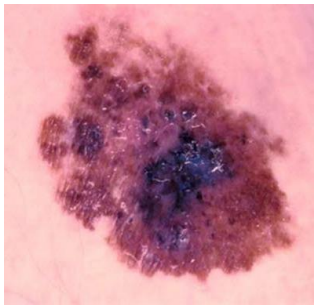
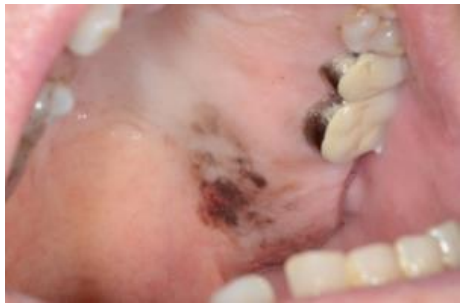
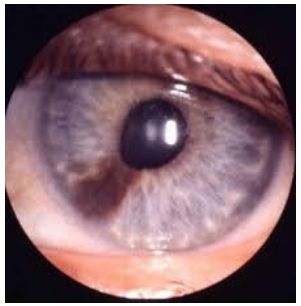
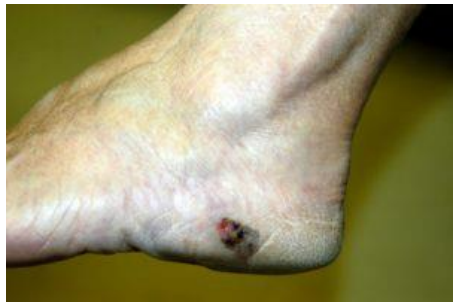
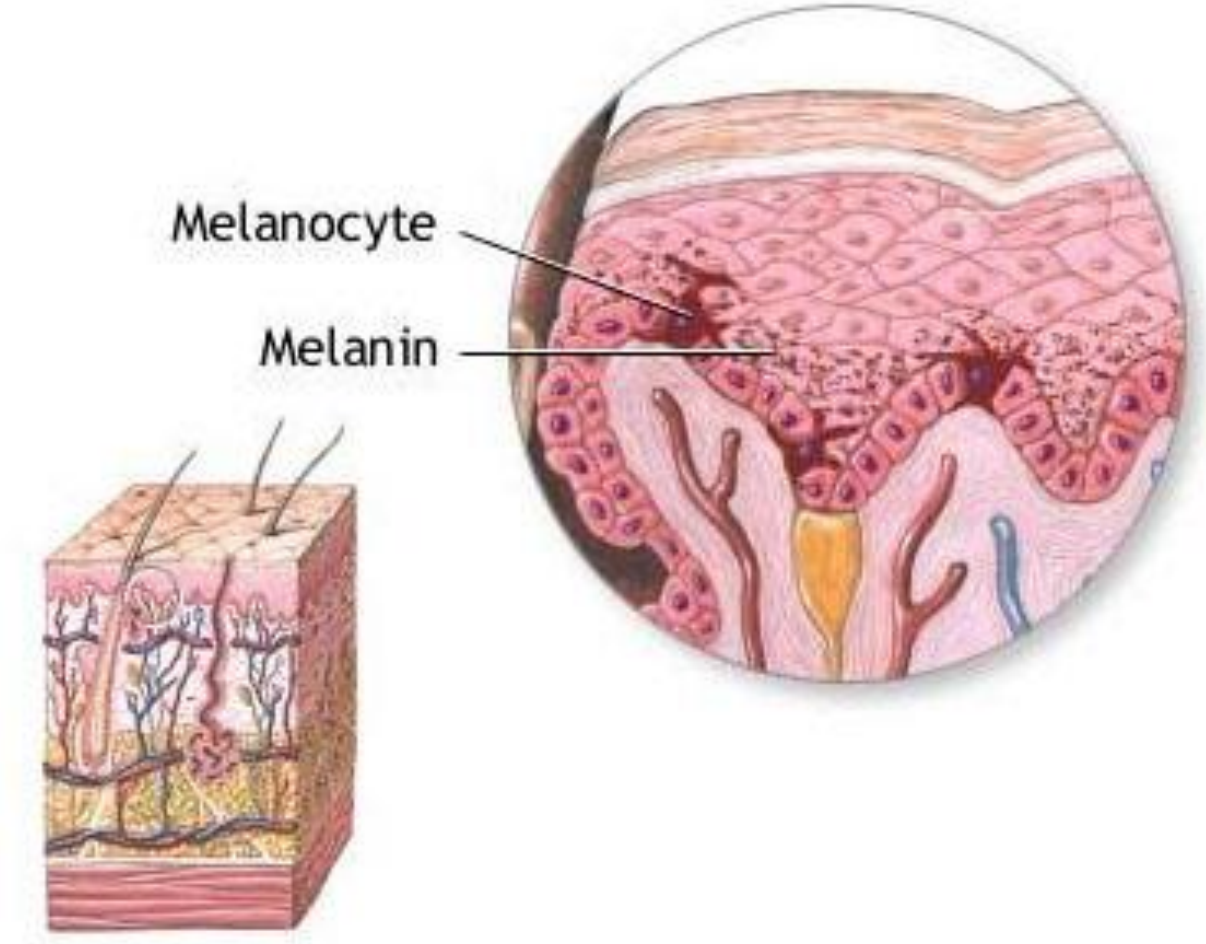
OnkoLIS 29.12.2021

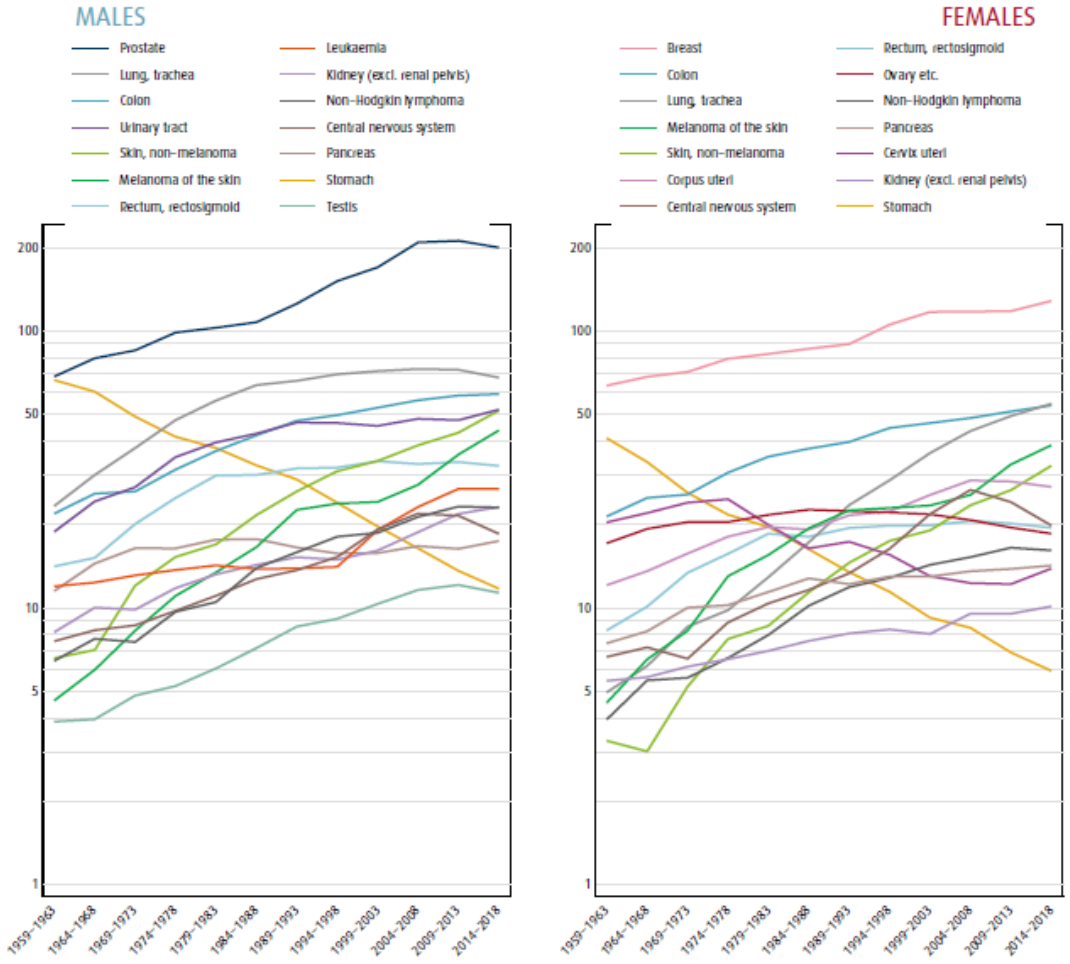






Oversikt

- Bakgrunn
- Klassifisering
- Virkningsmekanisme
- Adjuvant behandling
- Metastatisk behandling
- Hvor går veien videre



Epidemiologi



Incidens 2019

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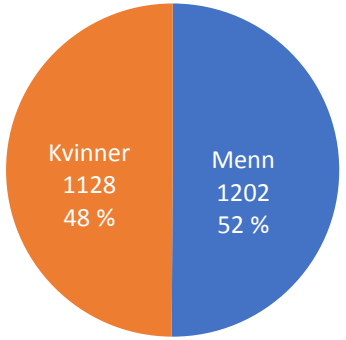
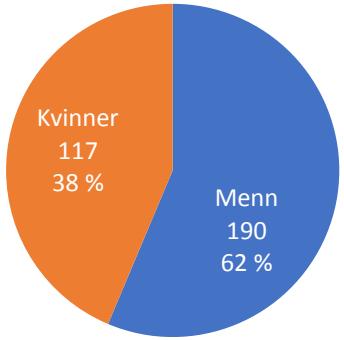


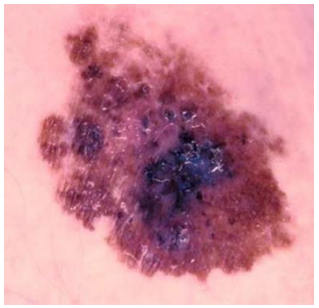
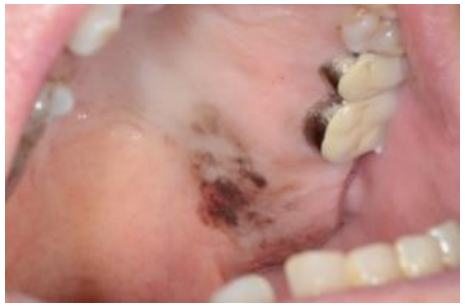
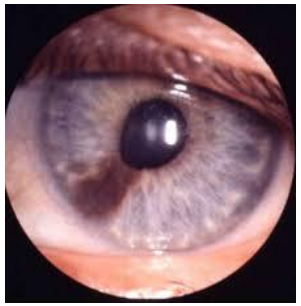
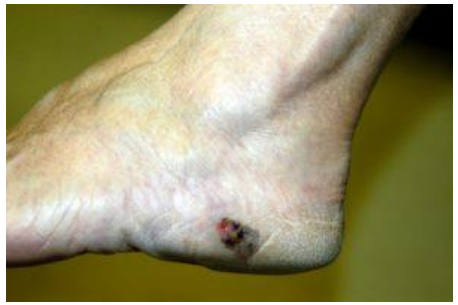
Døde 2019

N=307



Melanom

- Kutant Melanom
  - Superficielt spredende 70%
  - Nodulært melanom 15-30%
  - Lentigo maligna 4-10%
  - Acrale >5%
- Ikke-kutant melanom
  - Okkulære ca 5 %
  - Mucosale 1-2%


WHO classifisering

Pathway	Low UV Radiation Exposure/CSD I	High UV Radiation Exposure/CSD II	III
Endpoint of pathway	Low-CSD melanoma/SSM	High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (nevi)	Nevus	? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia, BIN, DBN	? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade MIS		
Malignant neoplasms	Low-CSD melanoma (VGP)		
Common mutations	***BRAF* p.V60** or ***NRAS***[b]		
	TERT[d]; CDK *TP53*[a]; *PT*		

Abbreviations: BIN, *BAP1*-inactivated nevu proliferation without atypia; LMM, lentigo uncertain malignant potential; MIS, melano or mitogenic melanoma).

Reprinted from Bastian et al[37] with permissi *Skin Tumours*. 4th ed. Lyon, France: IARC;

[a] For example, *CDKN2A*, loss-of-function
[b] For example, *BRAF*, gain-of-function mut
[c] For example, *PRKCA*, rearrangement.
[d] For example, *TERT*, promoter mutation.
[e] For example, *ERBB2*, amplification.

Pathway	Low to No (or Variable/Incidental) UV Radiation Exposure/CS IV	V	VI	
Endpoint of pathway	Malignant Spitz tumor/ Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanon
Benign neoplasms (nevi)	Spitz nevus	? Acral nevus	? Melanosis	CN
Intermediate/low-grade dysplasias/ melanocytomas	Atypical Spitz tumor (melanocytoma)	IAMPUS/dysplasia	Atypical melanosis/dysplasia/ IAMPUS	Nodule i (melar
Intermediate/high-grade dysplasias	STUMP/MELTUMP	Acral MIS	Mucosal MIS	MIS in C
Malignant neoplasms	Malignant Spitz tumor/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanon (tumor
Mutations	***HRAS***[b]; ***ALK***[e]; ***ROS1***[e]; ***RET***[e]; ***NTRK1***[e]; ***NTRK3***[e]; ***BRAF***[e]; or ***MET***[e]	***KIT***[b]; ***NRAS***[b]; ***BRAF***[b]; ***HRAS***[b]; ***KRAS***[b]; ***NTRK3***[e]; ***ALK***[e]; or ***NF1***[a]	***KIT***[b]; ***NRAS***[b]; ***KRAS***[b]; or ***BRAF***[b]	***NRAS***[b]; I (small
	CDKN2A[a]	*CDKN2A*[a]; *TERT*[f]; *CCND1*[d]; *GAB2*[d]	***NF1***[b]; *CDKN2A*[a]; *SF3B1*[a]; *CCND1*[d]; *CDK4*[d]; *MDM2*[d]	

Abbreviations: BN, blue nevus; CBN, cellular blue nevus; CN, congenital nevus; CSD, cumulative solar damage; IAMPUS, intraepidermal atypica melanocytic proliferation of uncertain MELTUMP, melanocytic tumor of uncertain malignant potential; MIS, melanoma in situ; STUMP, spitzoid tumor of uncertain malignant potential; UV, ultraviolet; VGP, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Reprinted from Bastian et al[37] with permission. International Agency for Research on Cancer. World Health Organization. Elder DE, Massi D, Scolyer RA, Willemze R, eds. 2018. *WHO Classification of Skin Tumours*. 4th ed. Lyon, France: IARC; 2018.

Common mutations in each pathway are listed; mutations already identified in benign or borderline low lesions are shown in bold.

[a] For example, *CDDN2A*, loss-of-function mutation.
[b] For example, *BRAF*, gain-of-function mutation.
[c] For example, *SF3B1*, change-of-function mutation.
[d] For example, *CCND1*, amplification.
[e] For example, *ALK*, rearrangement.
[f] For example, *TERT*, promoter mutation.

Table 1. Classification of Melanoma (Modified From 2018 WHO Classification)

A. Melanomas typically associated with CSD
- Pathway I. Superficial spreading melanoma/low-CSD melanoma
- Pathway II. Lentigo maligna melanoma/high-CSD melanoma
- Pathway III. Desmoplastic melanoma

B. Melanomas not consistently associated with cumulative solar damage (no CSD)
- Pathway IV. Spitz melanomas
- Pathway V. Acral melanoma
- Pathway VI. Mucosal melanomas
- Pathway VII. Melanomas arising in congenital nevi
- Pathway VIII. Melanomas arising in blue nevi
- Pathway IX. Uveal melanoma (not considered further in this review)

C. Nodular melanoma (may occur in any or most of the pathways)

Abbreviation: CSD, cumulative solar damage.

Melanom TNM classifisering AJCC 8

T category		Thickness	Ulceration status
	TX (Tumor thickness not as	NA	NA
	T0 (Nc primar		
	Tis (m		
	T1		
	T2		
	T3		
	T4		

N category		Number of tumor involved lymph nodes	Metastatic burden
	NX (Regional nodes not assessed)		N/
	N0 (No regio metastasis d		
	N1		
	N2		
	N3		

M category	
	M0
	M1
	M1a
	M1a (0)
	M1a (1)
	M1b
	M1b (0)
	M1b (1)
	M1c
	M1c (0)
	M1c (1)
	M1d
	M1d (0)
	M1d (1)

Clinical stage[1]				Patological stage[2]			
	T	N	M		T		
0	Tis	N0	M0	0	Tis		
IA	T1a	N0	M0	IA	T1a		
IB	T1b	N0	M0	IA	T1b		
	T2a	N0	M0	IB	T2a		
IIA	T2b	N0	M0	IIA	T2b		
	T3a	N0	M0		T3a		
IIB	T3b	N0	M0	IIB	T3b		
	T4a	N0	M0		T4a		
IIc	T4b	N0	M0	IIc	T4b		
III	Any T	≥N1	M0	IIIA	T1a/b		
					T2a		
IV	Any T	Any N	M1a-d	IIIB	T0		
					T1a/b		
					T2a		
					T2b/T		
					a		
				IIIC	T0		
					T1a-T		
					T3b/T		
					a		
					T4b	N1a-N2c	M0
				IIID	T4b	N3a/b/c	M0
				IV	Any T included Tis	Any N	M1a-d

1) After clinical findings, 2) After pathological findings

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

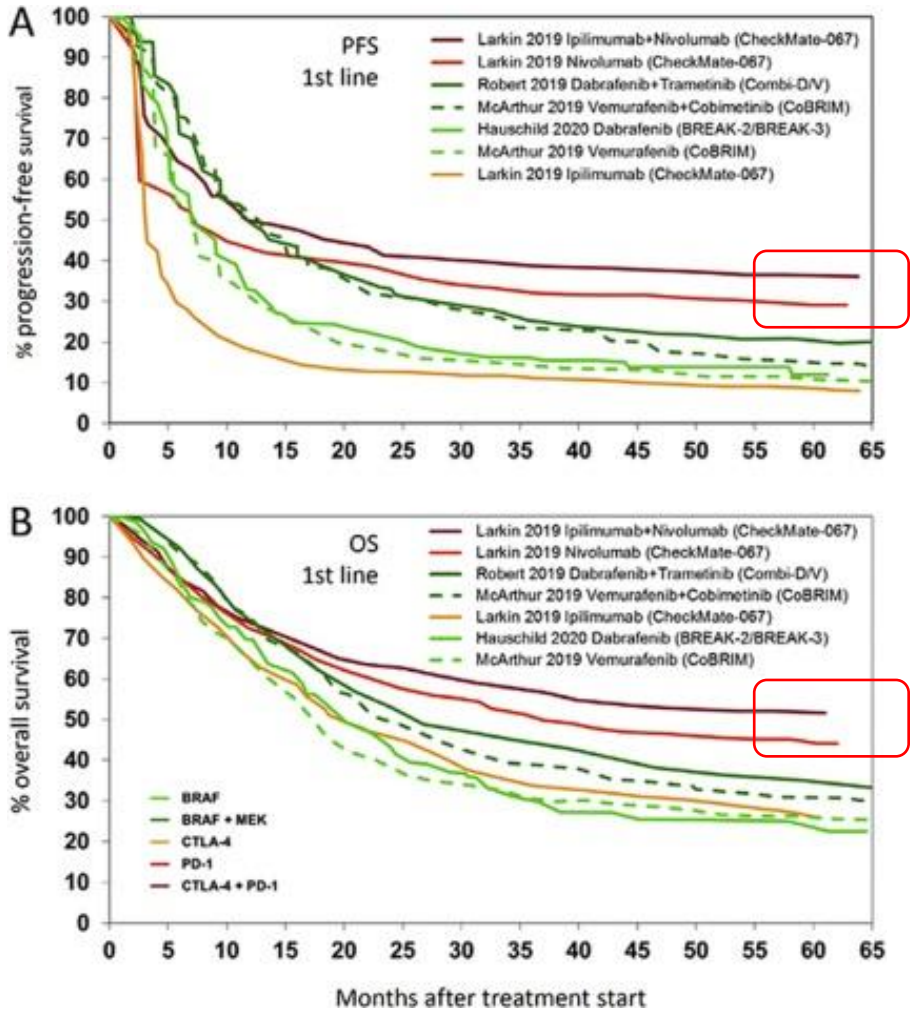
N/A=Not assigned, please see manual for details.[4]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

Gershenwald, J.E. et l CA Cancer J Clin 2017

Behandling metastatisk melanom

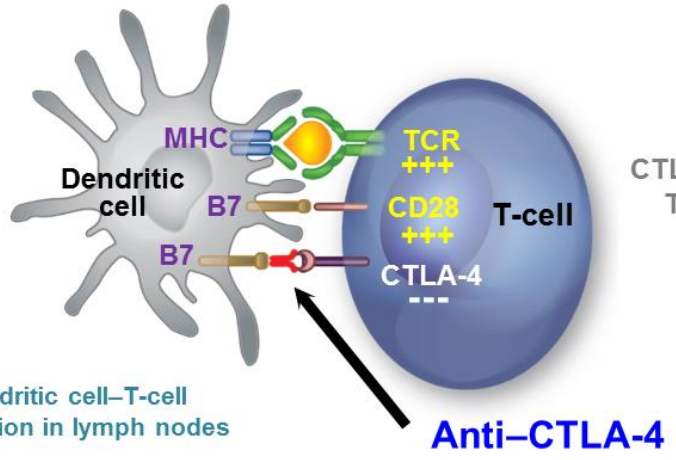


Ugurel, S. et all. Eur J of Cancer 2020

Metastatisk melanom behandling

Ipilimumab (anti–CTLA-4)

- **Induces *de novo* anti-tumor T-cell responses[1,2]**
- Enables adaptation to evolving tumor[2,3]
- Promotes emergence of memory T cells[4]
- Causes compensatory increase in tumor PD-L1[2]



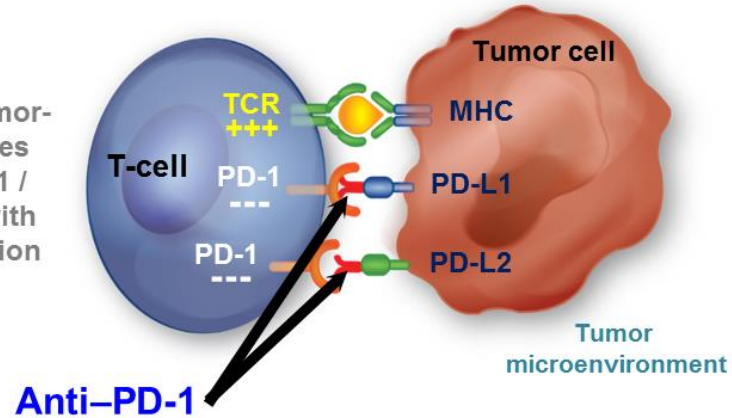
Dendritic cell–T-cell interaction in lymph nodes

CTLA-4 is expressed on T cells and inhibits T-cell activation[1]

Nivolumab (anti–PD-1)

- **Restores anti-tumor T-cell function[5,6]**
- Enhances pre-existing T-cell response[5]
- Increases cytokine production[7]

PD-1 expression on tumor-infiltrating lymphocytes interacting with PD-L1 / PD-L2 is associated with reduced effector function

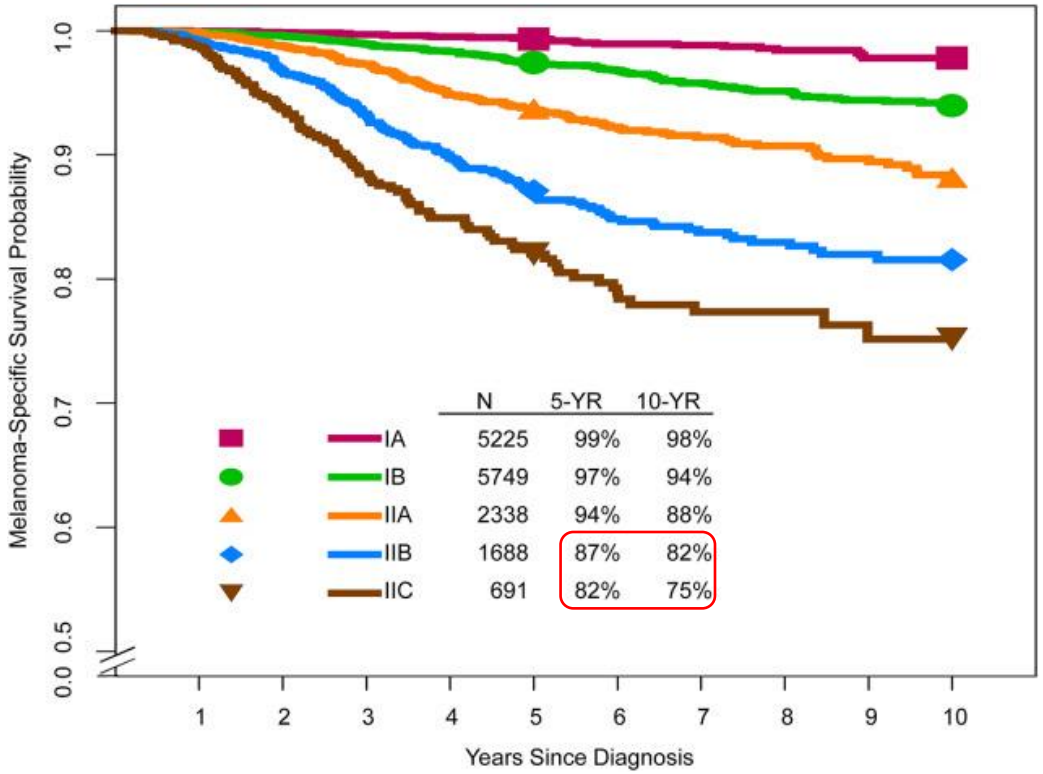


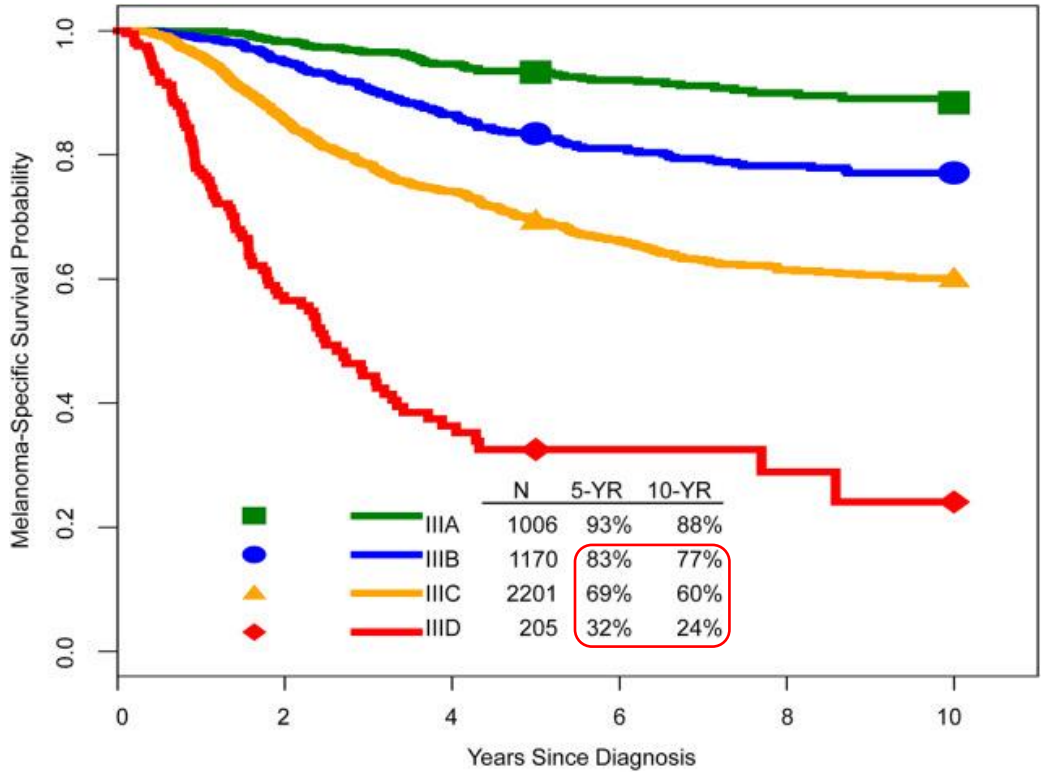
Tumor microenvironment

1. Pardoll DM. *Nat Rev Cancer* 2012; 2. Wei SC, et al. *Cancer Discov* 2018; 3. Wei SC, et al. *Immunity* 2019; 4. Das R, et al. *J Immunol* 2015; 5. Wang C, et al. *Cancer Immunol Res* 2014; 6. Brahmer JR, et al. *J Clin Oncol* 2010; 7. Hamanishi J, et al. *Proc Natl Acad Sci U S A* 2007

Oslo universitetssykehus

Hvorfor trenger vi adjuvant behandling?

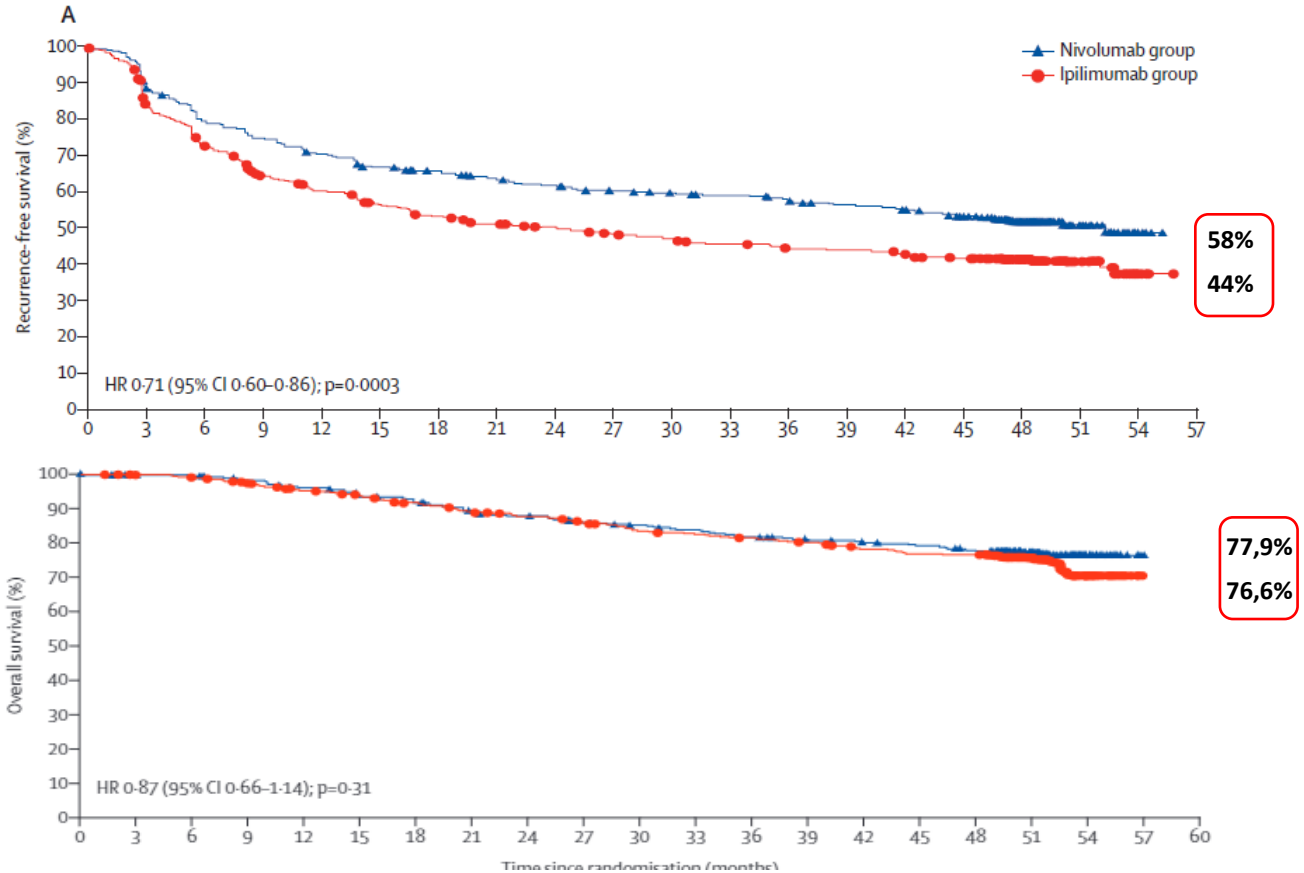




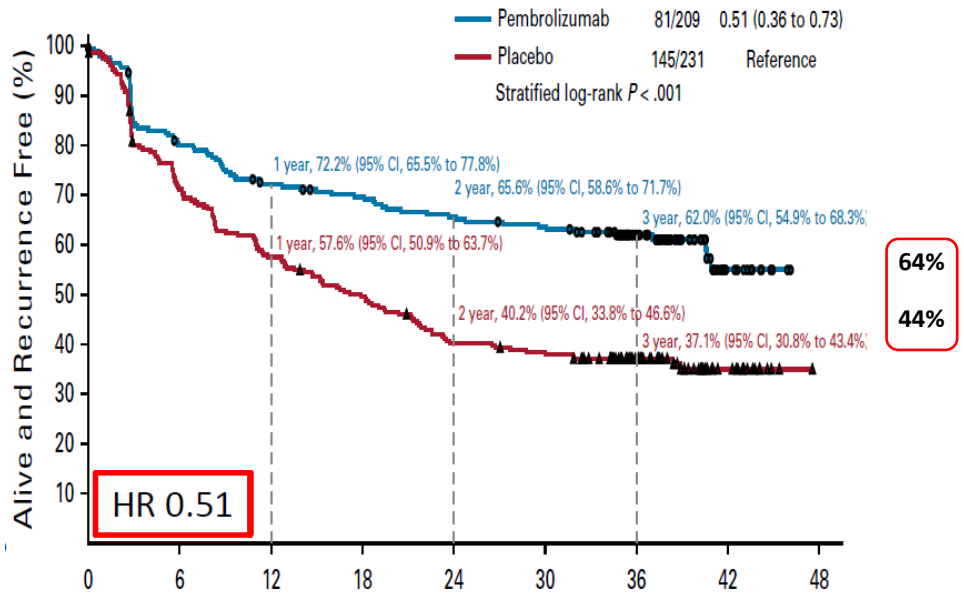
CA: A Cancer Journal for Clinicians, Volume: 67, Issue: 6, Pages: 472-492, First published: 13 October 2017, DOI: (10.3322/caac.21409)

Adjuvant melanom behandling RFS

CA209-238studien



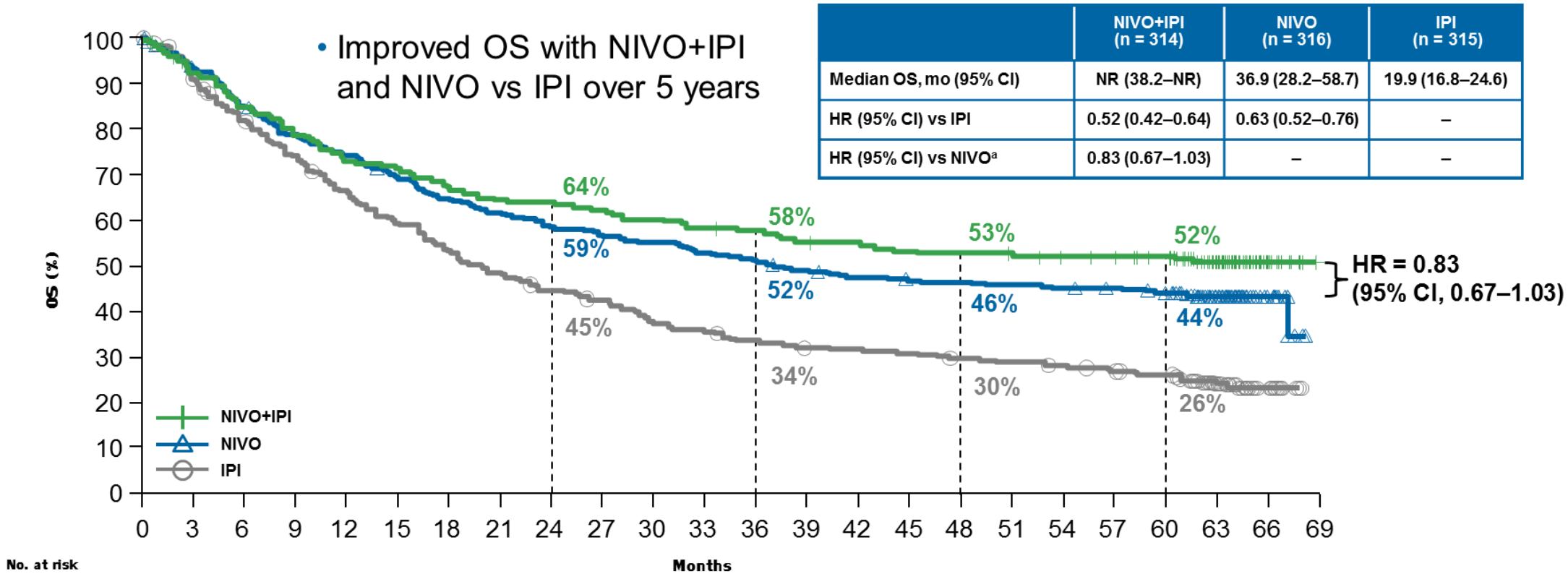
MK3475-054/EORTC 1325 studien



1.Ascierto, P. et al Lancet 2020; 2. Eggermont, A. et al JCO 2020

Metastatisk melanom behandling OS

CA209-067 studien



	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

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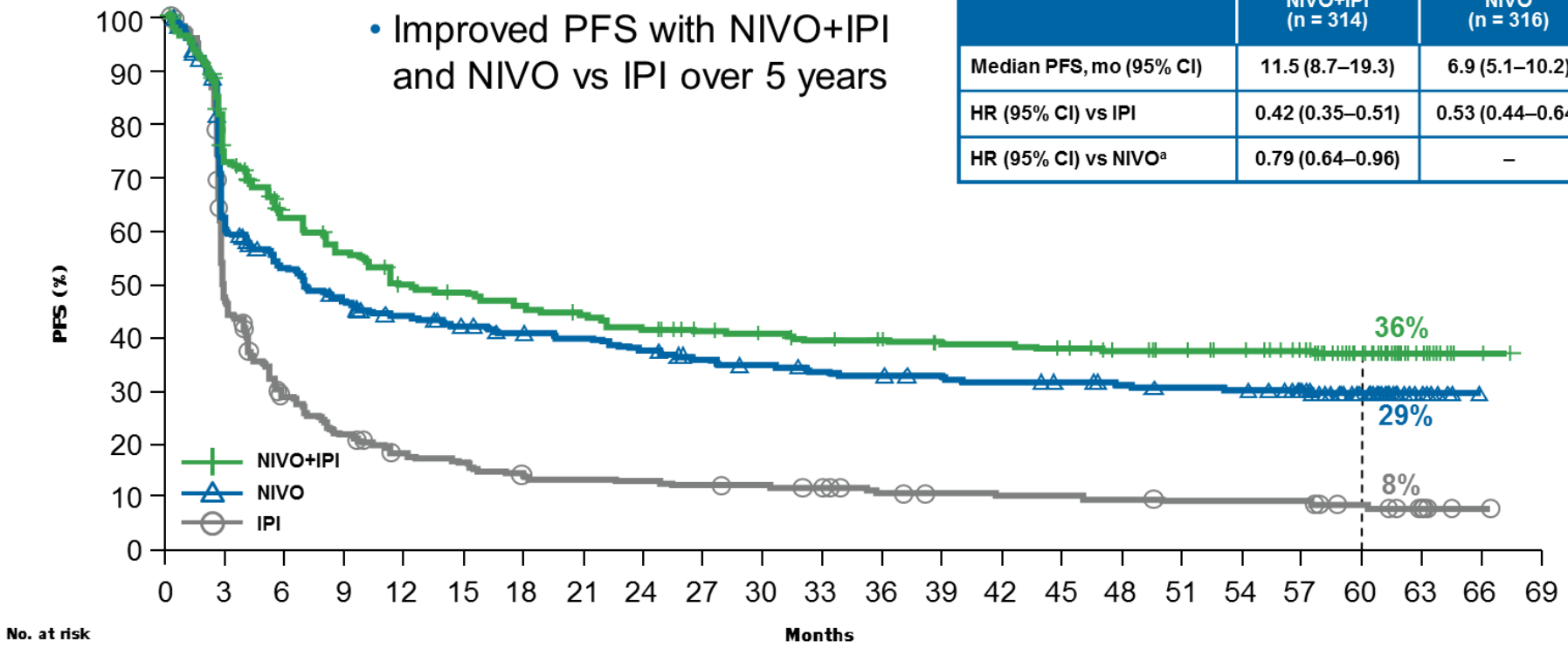
Larkin, J et al New Eng J Med 2019

Metastatisk melanom behandling PFS

CA209-067 studien

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–



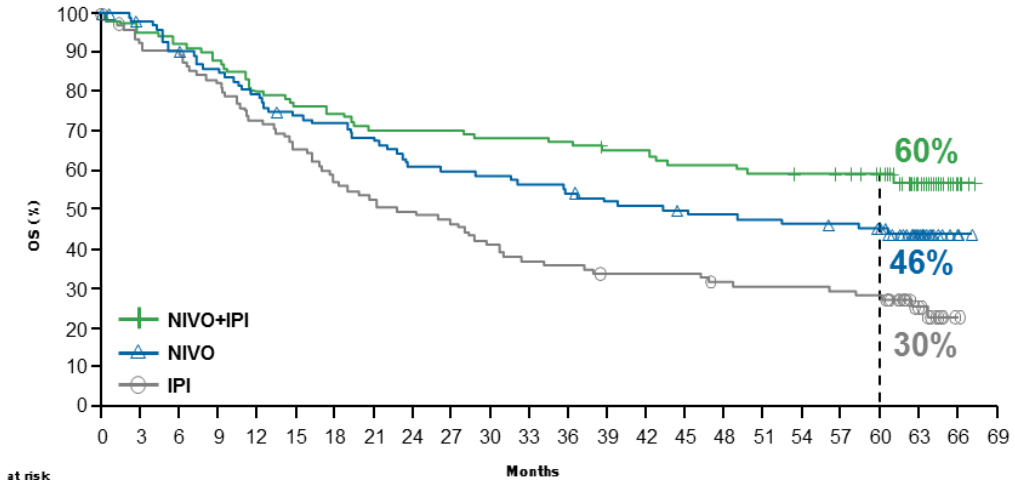
Larkin, J et al New Eng J Med 2019

Metastatisk melanom behandling

- Improved OS and PFS with NIVO+IPI and NIVO vs IPI regardless of *BRAF* mutation status

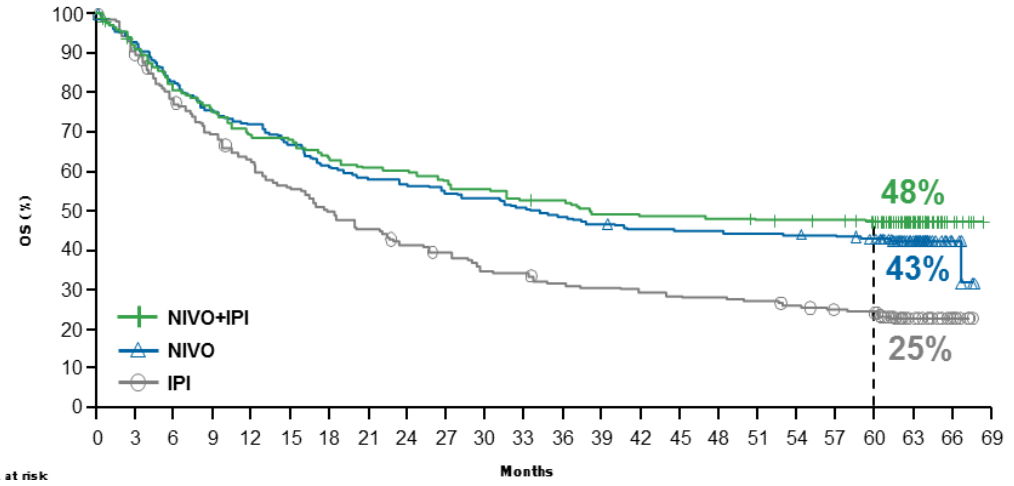
BRAF Mutant

	NIVO+IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median, mo (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs IPI	0.44 (0.30–0.64)	0.63 (0.44–0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46–1.05)	–	–



BRAF Wild-Type

	NIVO+IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1–59.2)	18.5 (14.1–22.7)
HR (95% CI) vs IPI	0.57 (0.45–0.73)	0.64 (0.50–0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69–1.15)	–	–



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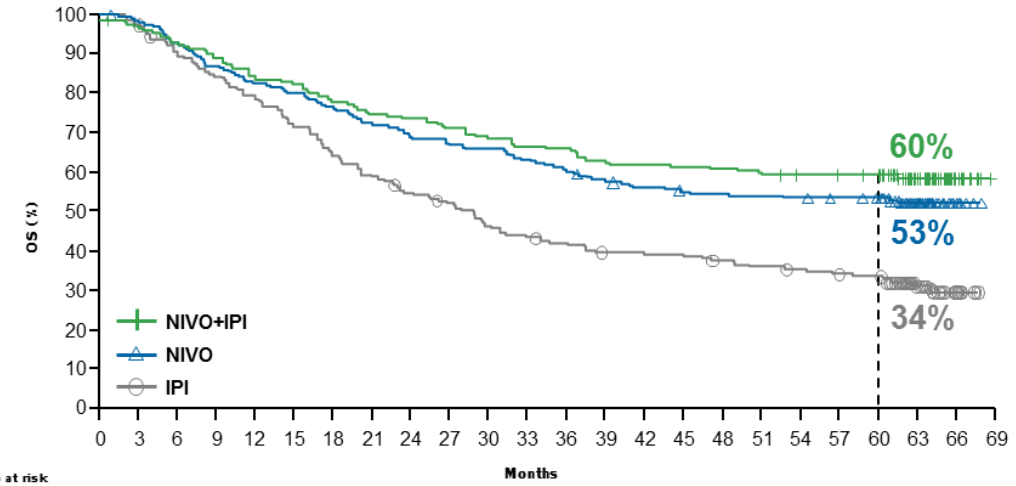
Metastatisk melanom behandling

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline LDH levels

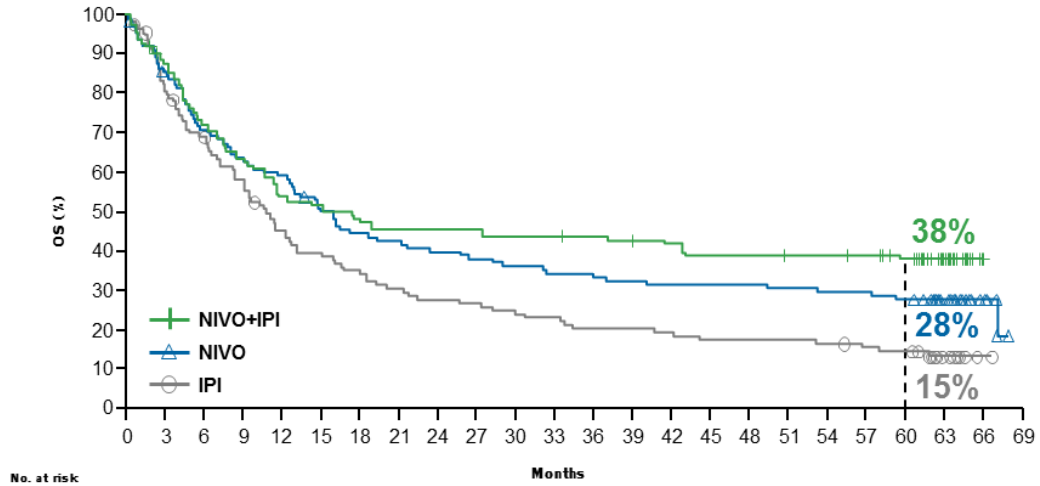
LDH ≤ ULN

	NIVO+IPI (n = 199)	NIVO (n = 197)	IPI (n = 194)
Median, mo (95% CI)	NR	NR (40.2–NR)	28.8 (22.7–34.0)
HR (95% CI) vs IPI	0.48 (0.37–0.64)	0.58 (0.44–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.62–1.12)	–	–



LDH > ULN

	NIVO+IPI (n = 114)	NIVO (n = 112)	IPI (n = 115)
Median, mo (95% CI)	17.4 (10.7–42.6)	16.0 (11.7–21.7)	10.9 (8.4–13.1)
HR (95% CI) vs IPI	0.58 (0.43–0.79)	0.71 (0.53–0.96)	–
HR (95% CI) vs NIVO[a]	0.82 (0.59–1.13)	–	–



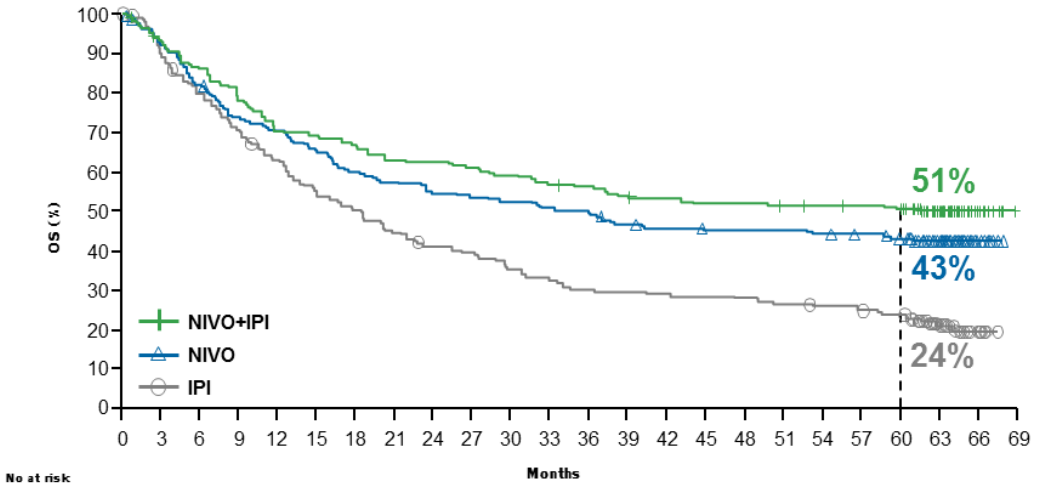
Larkin, J et al New Eng J Med 2019

Metastatisk melanom behandling

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline tumor PD-L1 expression

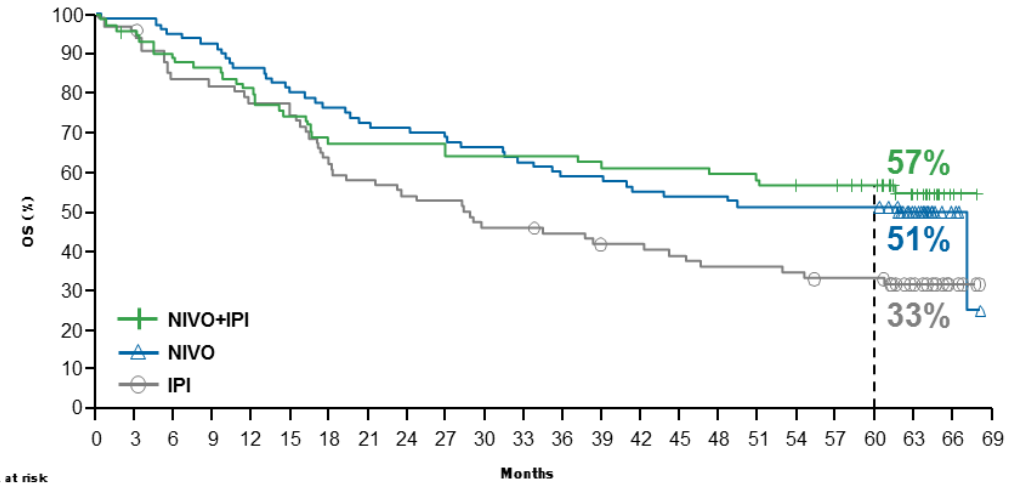
PD-L1 < 5%

	NIVO+IPI (n = 210)	NIVO (n = 208)	IPI (n = 202)
Median, mo (95% CI)	NR (32.7–NR)	35.9 (23.1–59.2)	18.4 (13.7–22.5)
HR (95% CI) vs IPI	0.50 (0.39–0.65)	0.62 (0.49–0.79)	–
HR (95% CI) vs NIVO[a]	0.81 (0.62–1.06)	–	–



PD-L1 ≥ 5%

	NIVO+IPI (n = 68)	NIVO (n = 80)	IPI (n = 75)
Median, mo (95% CI)	NR (39.1–NR)	61.6 (33.6–NR)	28.9 (18.1–44.2)
HR (95% CI) vs IPI	0.58 (0.37–0.91)	0.63 (0.42–0.96)	–
HR (95% CI) vs NIVO[a]	0.91 (0.57–1.46)	–	–



Larkin, J et al New Eng J Med 2019

Respons

CA209-067 studien

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NR[a]**	**NR (50.4–NR)**	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

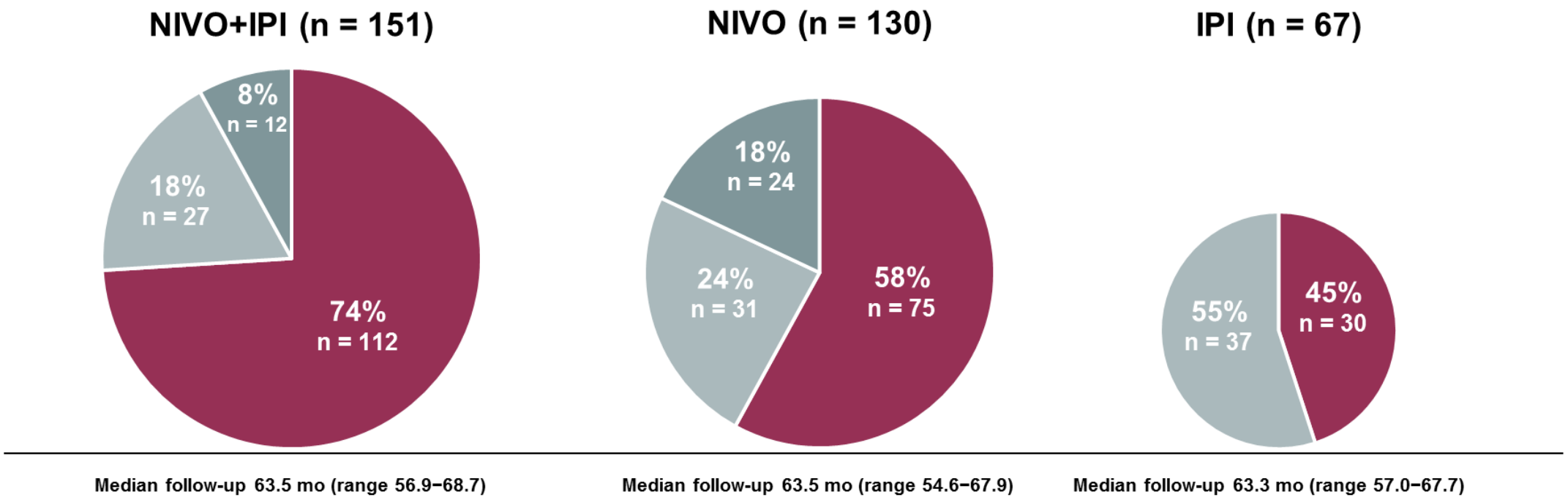
- While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]
  - 19%, 21%, and 22% for NIVO+IPI
  - 16%, 18%, and 19% for NIVO
  - 5%, 5%, and 6% for IPI

Larkin, J et al New Eng J Med 2019

Andel av pasienter i live og uten behandling på 5 år

On study therapy | Received subsequent systemic therapy | Treatment-free (off study treatment and never received subsequent systemic therapy)

CA209-067 studien



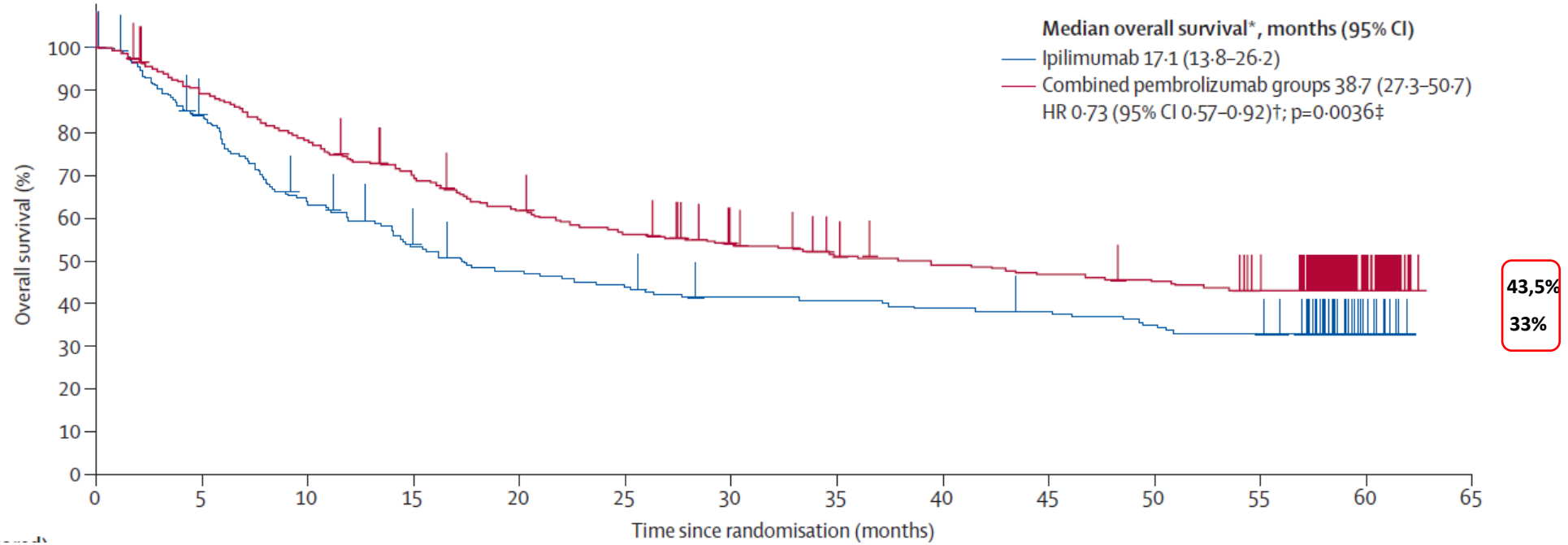
Median follow-up 63.5 mo (range 56.9–68.7)

Median follow-up 63.5 mo (range 54.6–67.9)

Median follow-up 63.3 mo (range 57.0–67.7)

Larkin, J et al New Eng J Med 2019

OS KeyNote-006 studien



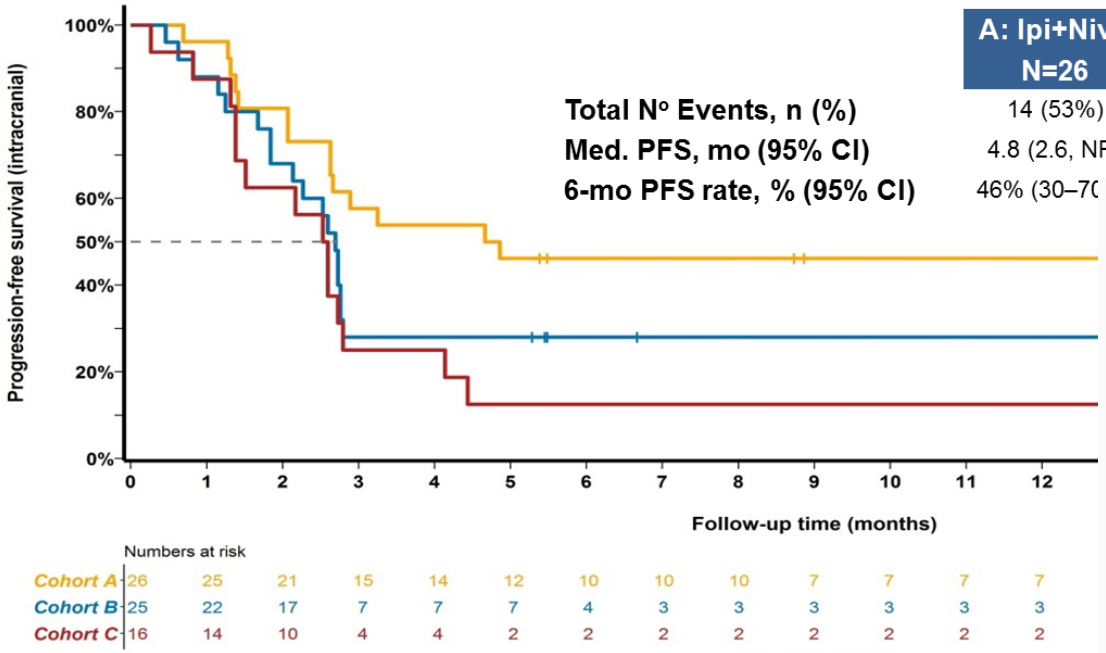
Hjernemetastaser

Study Design

Intracranial Progression Free Survival - ABC

- Melanoma Brain M
  ≥ 5mm & < 40mm
- No previous
  Anti-CTLA-4
  Anti-PD-1 or -Pl
- Previous BRAFi+M
- ECOG PS 0-2
- No serious autoim
- No corticosteroids
  (Cohort C < 10mg prednis

Primary Endpoint:
Secondary Endpoints:



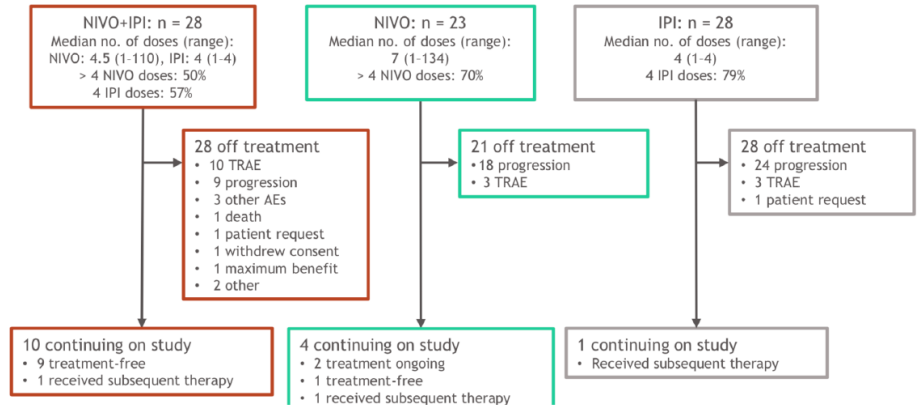
	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Total Nº Events, n (%)	14 (53%)	18 (72%)	14 (88%)
Med. PFS, mo (95% CI)	4.8 (2.6, NR)	2.7 (2.2, NR)	2.5 (1.4, NR)
6-mo PFS rate, % (95% CI)	46% (30–70		

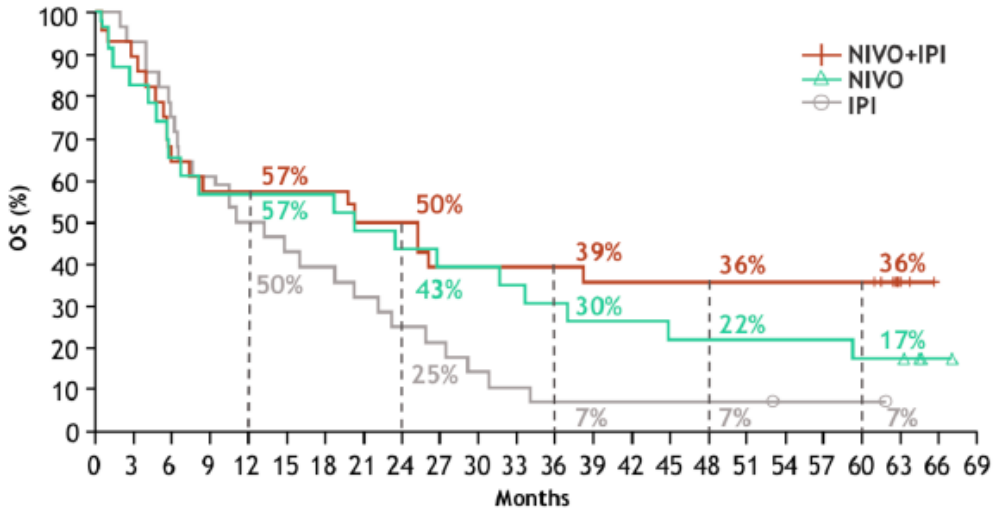
	A N = 25 nivo+ipi	B N = 25 nivo	C N = 16 nivo
ICR % (95% CI)	44 (24, 65)	20 (7, 41)	6 (0, 30)
ICR Complete Response	16 (24, 65)	12 (7, 41)	0
ECR % (95% CI)	38 (18, 62)	26 (10, 48)	21 (5, 50)
6-mo PFS % (95% CI)	50 (33, 75)	29 (15, 56)	0
6-mo OS % (95% CI)	76 (59, 97)	59 (41, 86)	44 (25, 76)

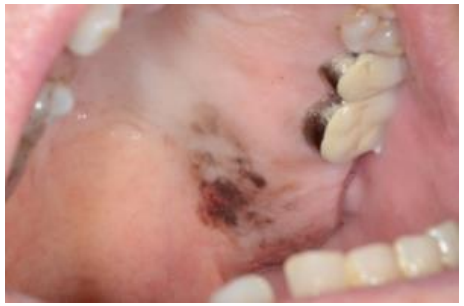
Long, G. et al JCO 2017/2019

Mucosale Melanom

CA209-067 studien





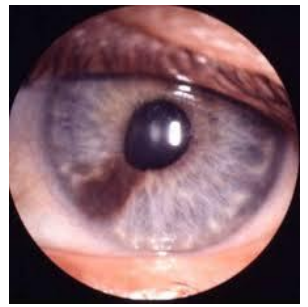


1.Larkin, J et al New Eng J Med 2019; 2.Shoushtari et al JCO 2019

Uveale Melanom

- ASCO/ESMO guide lines ingen anbefaling hverken for eller imot noen systemisk behandling
- Anbefales inklusjon i studier
- Responsrate rapportert er lave < 10% og OS under 1 år med single checkpunkt hemmer
- 2 phase II studier pågår med ipi/nivo:
  - NTC01585194 : 17% PR, 53% SD, med OS 1,6 år, 1 år OS 62%

(Pelster, M. et al J Clin Oncol 2019)



Hva med de eldre >70-75?

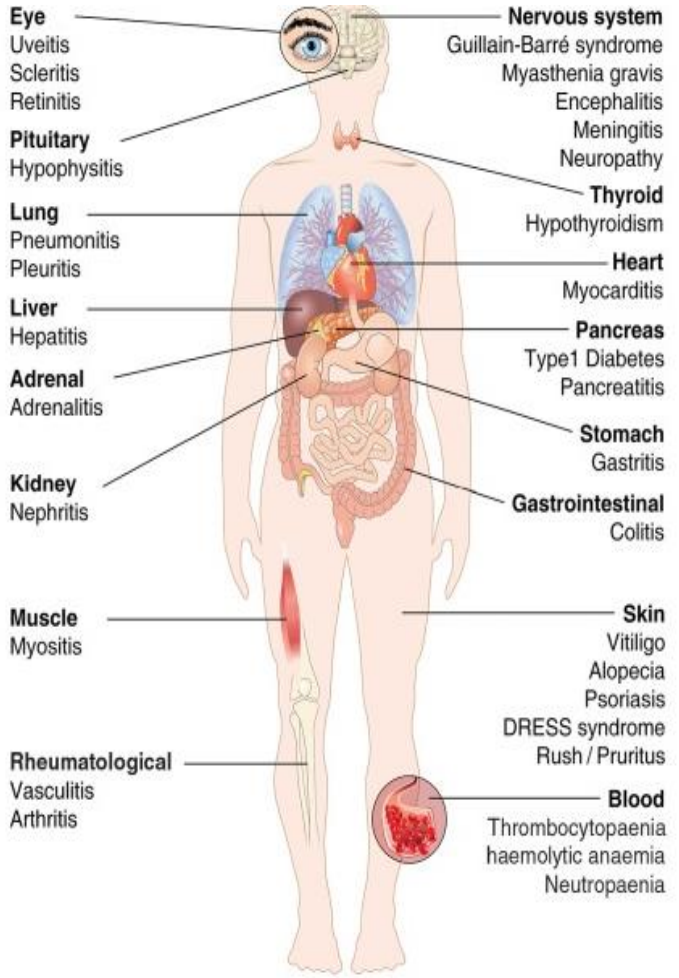
- Hvorfor eldre?
- Faktorer å tenke på
  - Kognitiv funksjon
  - ECOG status
  - Komorbiditet og vanlige plager
  - Polyfarmasi
  - Ernæring
- Aldrende immun forsvar
  - Endring T celle populasjon
  - Økning myeloid-derived suppressor cells (MDSCs)
- Hvordan gjennomføre behandling hos eldre

Bivirkninger

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	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
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)



[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

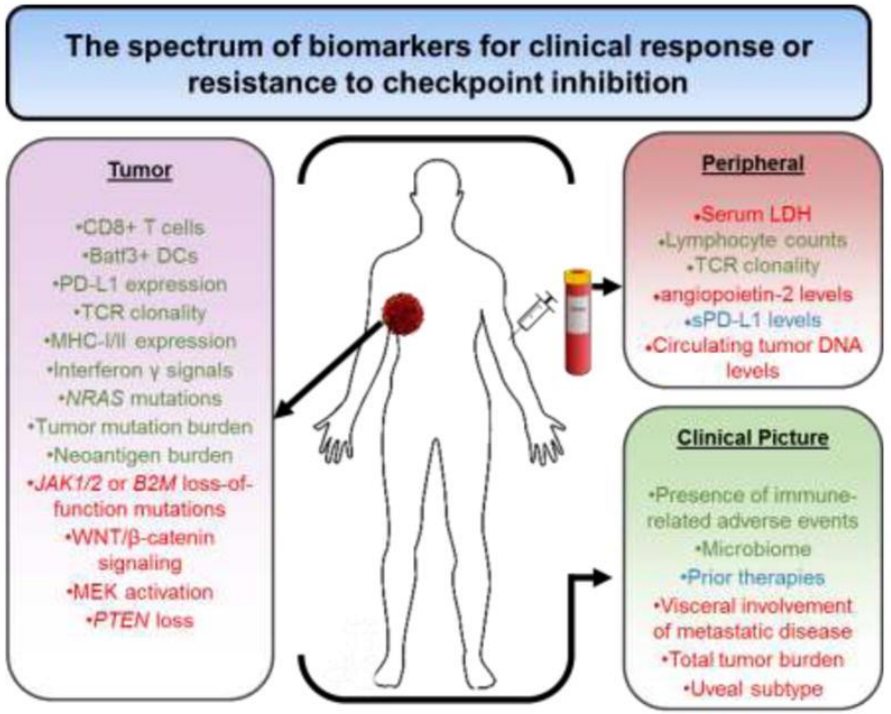
1. Larkin, J. et al NEJM 2019; 2. Varrachi, G. et al ESMO 2017

Faktorer vurdering kombinasjonsimmunterapi

- Vil pasienten tåle bivirkninger ?
- Ung pasient
- Asymptomatiske hjernemetastaser
- Forhøyet LD
- BRAF v600 mutasjon positiv
- Mucosalt melanom
- PD-1 utrykk?

Utfordringer

- RESISTENS
- Optimalisere integrering med ikke immunterapi behandling/sekvensering
- Biomarkører
  - BRAF
  - PD-L1?
  - TMB
  - IFN-ϒ/IL-6
- Forstå mekanismene for tox/unngå tox
- Optimalisere varighet av behandling



Axelrod, M.L et al. Sen Cancer Biol 2018

Nye strategier

Talimogene laherparepvec (T-VEC) for the treatment of advanced melanoma

Douglas B Johnson [1], Igor Puzanov [1], Mark C Kelley [2]

Affiliations + expand

PMID: 26098919 PMCID: PMC4519012 DOI: 10.2217/imt.15.35

Adoptive cell transfer as personalized immunotherapy for human cancer

Steven A Rosenberg [1], Nicholas P Restifo [1]

Affiliations + expand

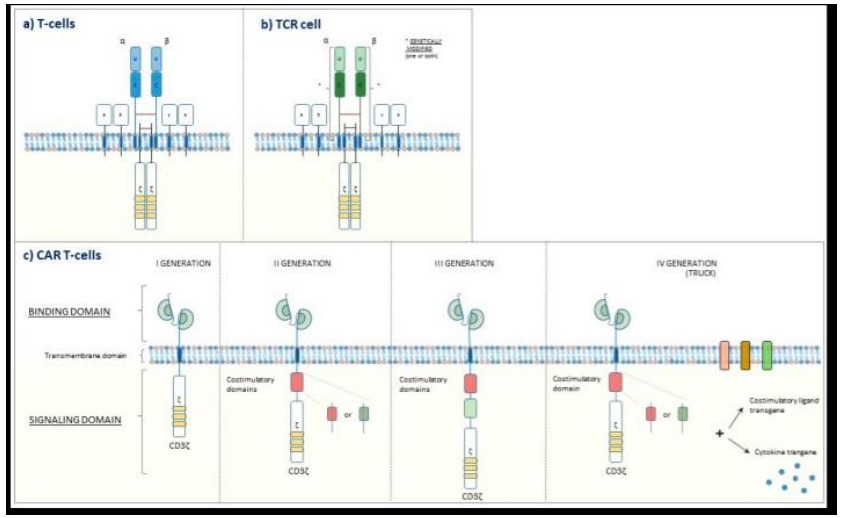
PMID: 25838374 PMCID: PMC6295668 DOI: 10.1126/science.aaa4967

The Emerging World of TCR-T Cell Trials Against Cancer: A Systematic Review

Jianxiang Zhang [1], Lingyu Wang [2]

Affiliations + expand

PMID: 30798772 PMCID: PMC6391541 DOI: 10.1177/1533033819831068



Review > Semin Cancer Biol. 2019 Dec;59:236-250. doi: 10.1016/j.semcancer.2019.08.002. Epub 2019 Aug 9.

Unraveling the crosstalk between melanoma and immune cells in the tumor microenvironment

Monica Marzagalli [1], Nancy D Ebelt [2], Edwin R Manuel [3]

ELSEVIER

Annals of Oncology

Volume 28, Issue 6, June 2017, Pages 1368-1379

Original articles

Melanoma

Editor's Choice

Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab

N. Chaput [1, 2, †], P. Lepage [3, †], C. Coutzac [1, 4], E. Soularue [1, 4, 5], K. Le Roux [3], C. Monot [3], L. Boselli [1], E. Routier [6], L. Cassard [1], M. Collins [4, 5], T. Vaysse [4, 5], L. Marthey [4, 5], A. Eggermont [6, 7], V. Asvatourian [8, 9], E. Lanoy [8, 9], C. Mateus [4], C. Robert [4, 6, †], F. Carbonnel [4, 5, *, †]

Review > Genes Dev. 2019 Oct 1;33(19-20):1295-1318. doi: 10.1101/gad.329771.119.

Melanoma plasticity and phenotypic diversity: therapeutic barriers and opportunities

Florian Rambow [1, 2], Jean-Christophe Marine [1, 2], Colin R Goding [3]

Oslo universitetssykehus

Takk for oppmerksomheten

- Spørsmål?