LIMBURGS ONCOLOGISCH CENTRUM vzw

Update stadium III melanoma

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Melanoompunt meeting
Crowne Plaza 25/1/2020

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Inhoud voordracht

- Wat is stadium III?
- Quid heelkunde van de LN?
- Adjuvant beleid
  - Lokaal
  - Systemisch

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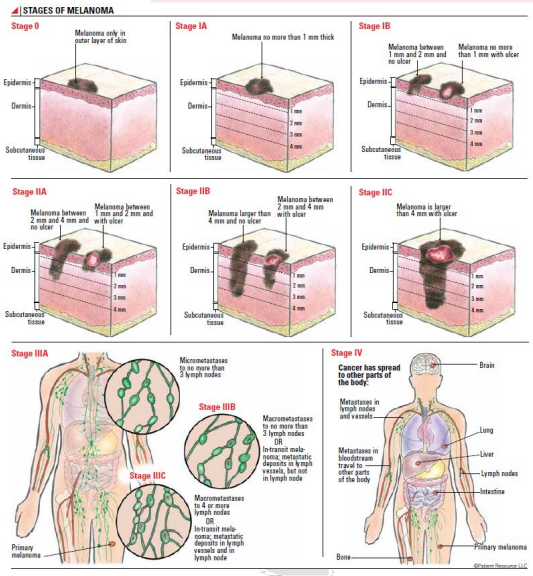
Wat is stadium III melanoma?



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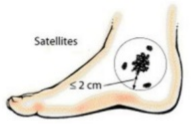
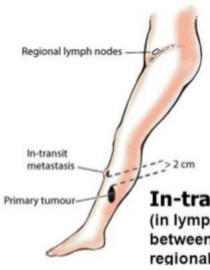
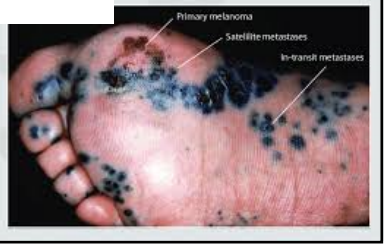
Satelliet lesie versus in-transit lesie



Satellite nodules/lesions
(tumor nests or nodules in dermis or subq tissue)



In-transit mets
(in lymph channels between primary and regional nodes)



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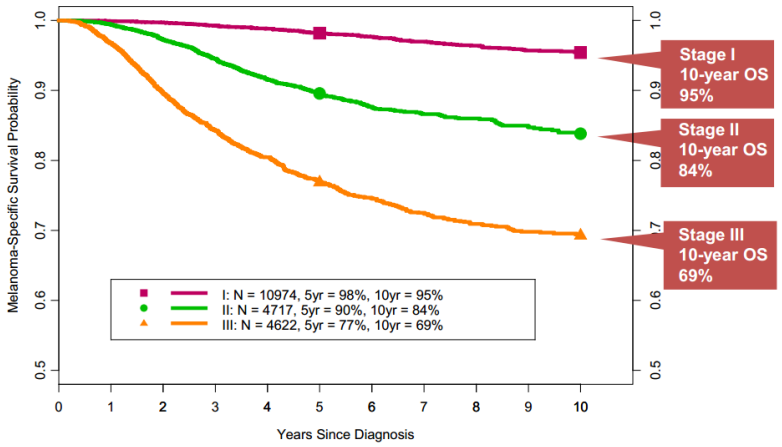
Melanoma AJCC 8th Edition
Stage specific Survival



Jeffrey E. Gershenwald,CA CANCER J CLIN 2017;00:00–00

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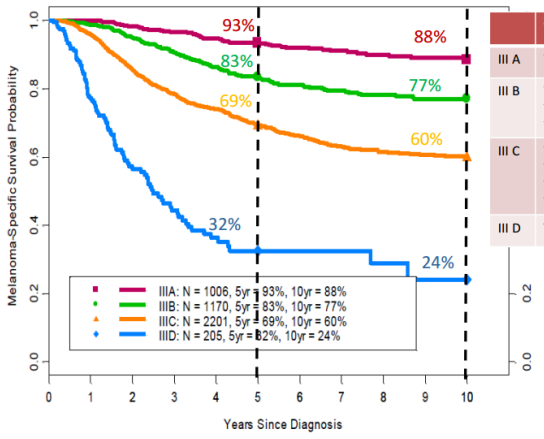
Stadium III Overall Survival

AJCC 2017



	T	N	M
III A	T1a/T1b/T2a	N1a/2a	M0
III B	T0 T1a/T1b/T2a T2b/T3a	N1b/N1c N1b/N1c/N2b N1a-N2b	M0 M0 M0
III C	T0 T1a-T3a T3b/T4a T4b	N2b-c/N3b-c N2c/N3a-c ≥N1 N1a-N2c	M0 M0 M0 M0
III D	T4b	N 3a-c	M0

Balch CM, et al. *J Clin Oncol* 2009;27(36):6199–206; Gershenwald J, et al. Melanoma Prevention and Staging: Election Day 2016 Update. Presented at: the Society for Melanoma Research 2016 Congress; November 6-9, 2016; Boston, MA.

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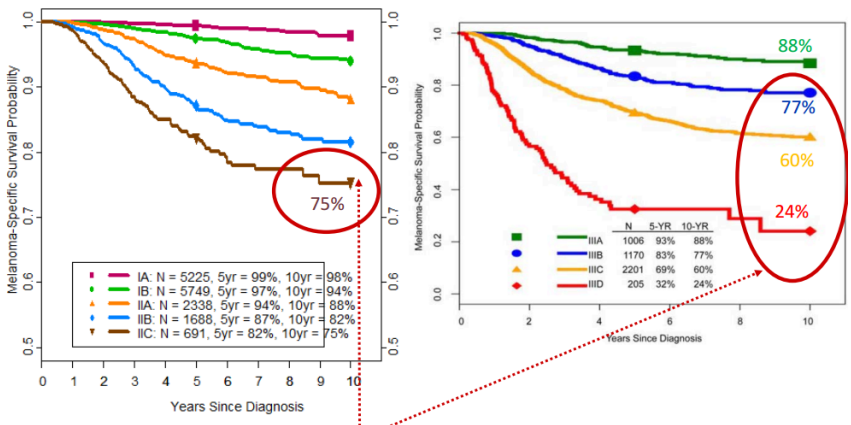
Who is at risk?



High Risk Patients:

Higher Recurrence Rate and Relatively Poor Survival

Jeffrey E. Gershenwald,CA CANCER J CLIN 2017;00:00–00

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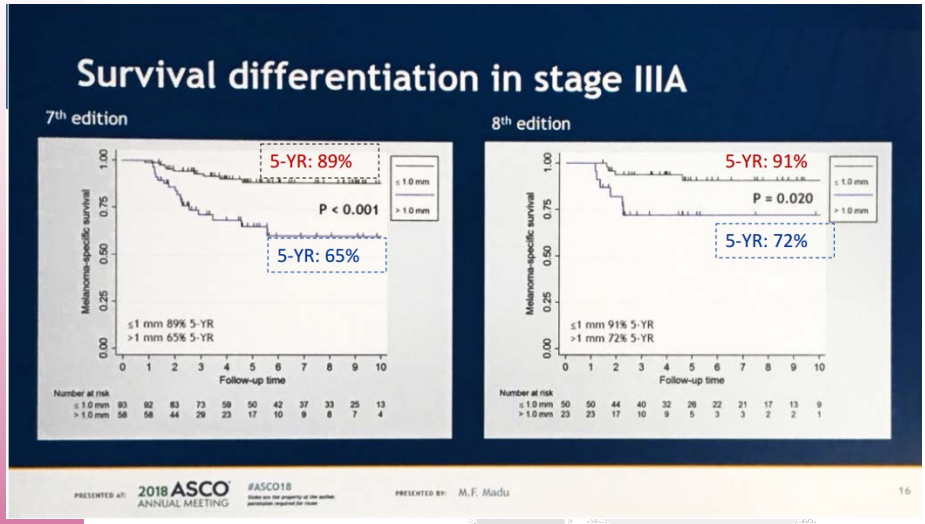

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Heelkunde van de LN: update

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 8, 2017 VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

M.B. Faries, J.F. Thompson, A.J. Cochran, R.H. Andtbacka, N. Mozzillo, J.S. Zager, T. Jahkola, T.L. Bowles, A. Testori, P.D. Beitsch, H.J. Hoekstra, M. Moncrieff, C. Ingvar, M.W.J.M. Wouters, M.S. Sabel, E.A. Levine, D. Agnese, M. Henderson, R. Dummer, C.R. Rossi, R.I. Neves, S.D. Trocha, F. Wright, D.R. Byrd, M. Matter, E. Hsueh, A. MacKenzie-Ross, D.B. Johnson, P. Terheyden, A.C. Berger, T.L. Huston, J.D. Wayne, B.M. Smithers, H.B. Neuman, S. Schneebaum, J.E. Gershenwald, C.E. Ariyan, D.C. Desai, L. Jacobs, K.M. McMasters, A. Gesierich, P. Hersey, S.D. Bines, J.M. Kane, R.J. Barth, G. McKinnon, J.M. Farma, E. Schultz, S. Vidal-Sicart, R.A. Hoefer, J.M. Lewis, R. Scheri, M.C. Kelley, O.E. Nieweg, R.D. Noyes, D.S.B. Hoon, H.-J. Wang, D.A. Elashoff, and R.M. Elashoff

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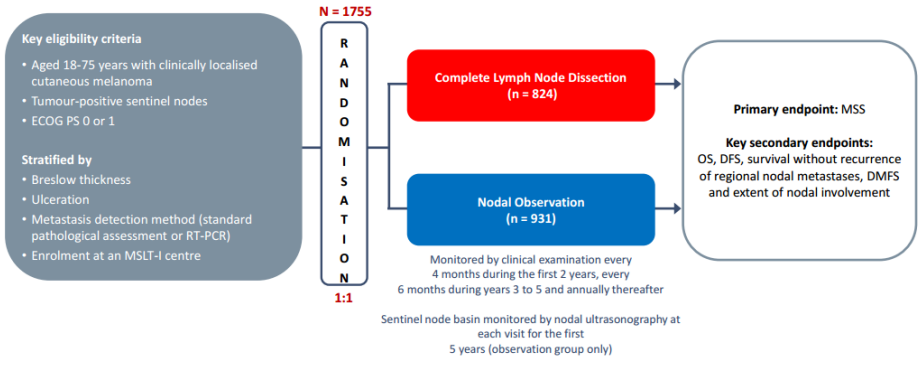
MSLT-II: STUDY DESIGN

PHASE 3 TRIAL EVALUATING CLND VS OBSERVATION WITH NODAL ULTRASONOGRAPHY IN NODE-POSITIVE INTERMEDIATE-THICKNESS MELANOMA



Faries et al. NEJM 2017

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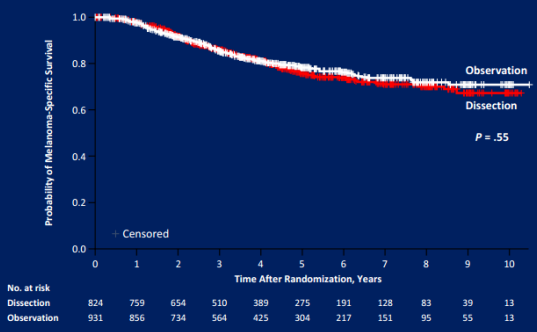
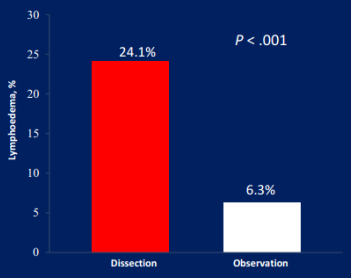
MSLT-II: KEY RESULTS

CLND WAS NOT ASSOCIATED WITH IMPROVED MELANOMA-SPECIFIC SURVIVAL VS OBSERVATION IN PATIENTS WITH SENTINEL NODE METASTASES





Faries et al. NEJM 2017

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- No indication for CLND
- Exception: ? Unable to undergo US FU
  - Eg: remote areas, stress

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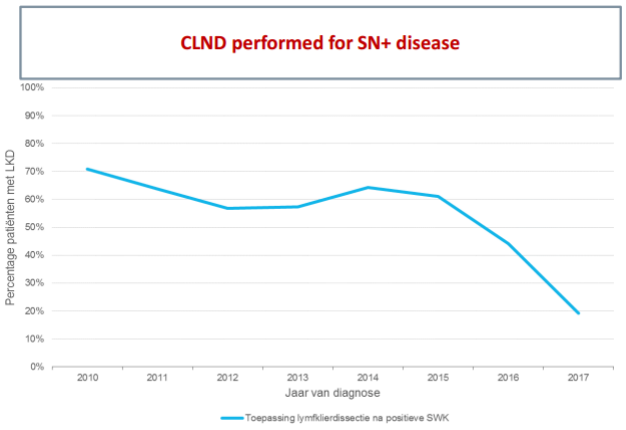
Situatie in Nederland



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Adjuvant therapies

- Radiotherapy
  - Could be useful for local lymph node- field control
  - No improvement of OS and RFS

ANZMTG01,02 trial

Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial

Michael A Henderson*, Bryan H Burmeister*, Jill A Ainslie, Richard Fisher, Juliana Di Iulio, B Mark Smithers, Angela Hong, Kerwin Shannon, Richard A Scolyer, Scott Carruthers, Brendon J Coventry, Scott Babington, Joao Duprat, Harald J Hoekstra, John F Thompson

⇒ Adjuvant systemic therapy might be first option!!

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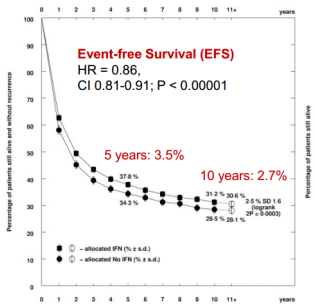
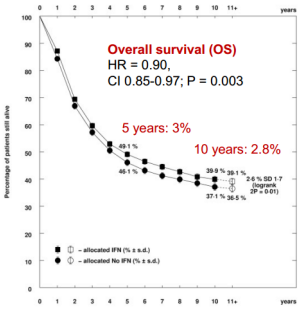
Adjuvant therapies

- Chemotherapy: no
- Immunotherapy
  - Interferon

Low benefit

- **Recent meta-analysis 2017:** 15 clinical trials





Ives et al, EJC 2017

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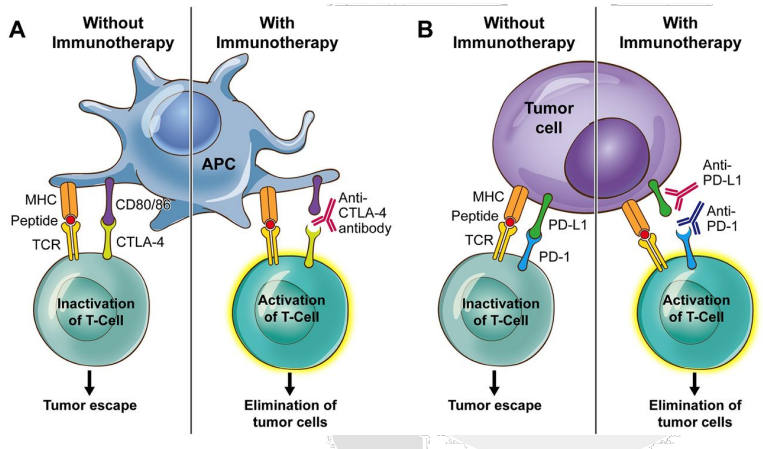
Adjuvant therapies

- Check point-inhibitoren



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Adjuvant therapies

- Immunotherapy
  - CPI
    - Ipilimumab 10 mg vs Placebo
    - Ipilimumab 10 mg vs Nivolumab 3 mg
    - Pembrolizumab 200 mg vs placebo

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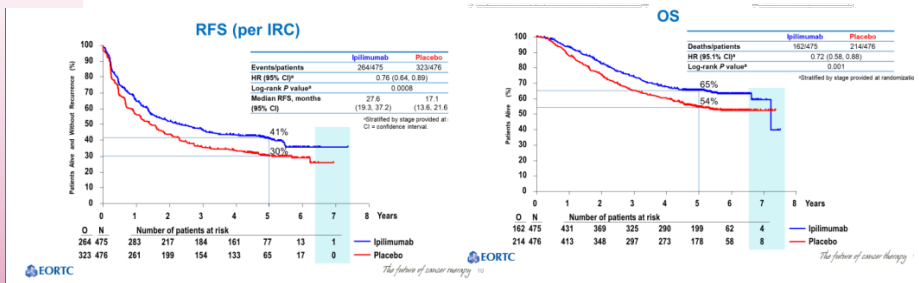
Adjuvant therapies

- Ipi 10 mg vs placebo



At 5 yrs: 10% advantage of RFS and OS; high toxicity
Not in EU

Eggermont et al, NEJM 2016 EJC 2017

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Tarhini AA, Lee SJ, Hodi FS, *et al*. Phase III study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma: North American Intergroup E1609 . *J Clin Oncol*; Advance online publication 27 December 2019. doi: 10.1200/JCO.19.01381

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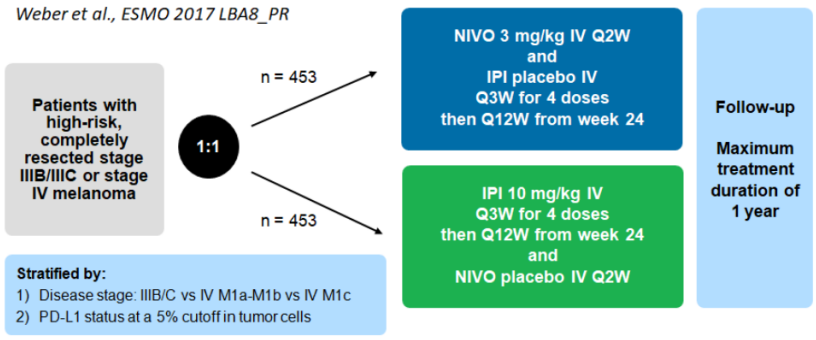
Adjuvant therapies

- Ipilimumab 10 mg versus Nivolumab 3 mg: checkmate 238



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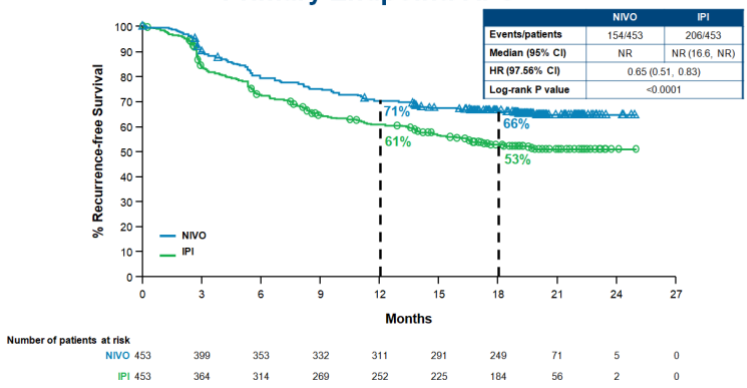
Adjuvant therapies

Primary Endpoint: RFS



	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank P value	<0.0001	

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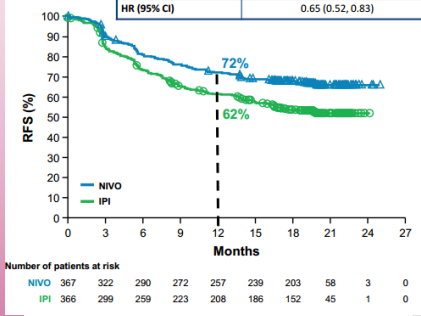
Subgroup Analysis of RFS: Disease Stage

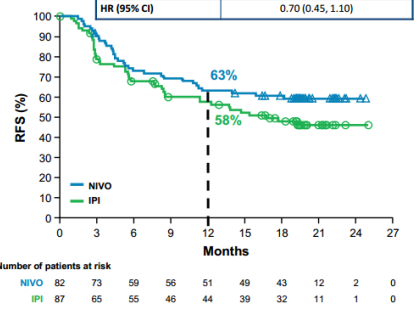
Stage III

	NIVO	IPI
Events/patients	120/367	163/366
Median (95% CI)	NR	NR (16.6, NR)
HR (95% CI)	0.65 (0.52, 0.83)	



Stage IV

	NIVO	IPI
Events/patients	33/82	43/87
Median (95% CI)	NR (15.9, NR)	16.8 (8.5, NR)
HR (95% CI)	0.70 (0.45, 1.10)	



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- Improvement of RFS for nivo vs ipi
- 1yr RFS: 71 vs 61%
- Benefit across all subgroups
- Significant more toxicity and death for ipi
- EMA approval since July 2018

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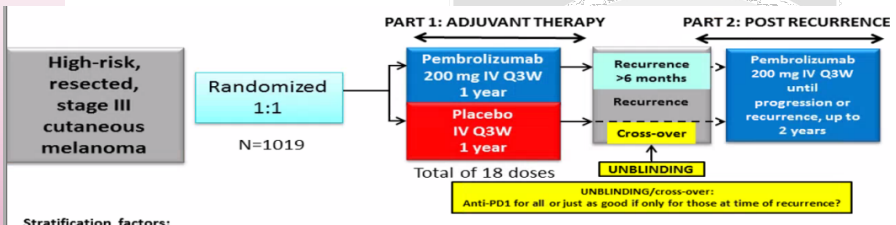
Adjuvant therapies

- Pembrolizumab 200 mg vs placebo: Keynote 054



Stratification factors:
- ✓ **Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:
- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:
- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

EORTC *The future of cancer therapy*

Eggermont, AACR 2018

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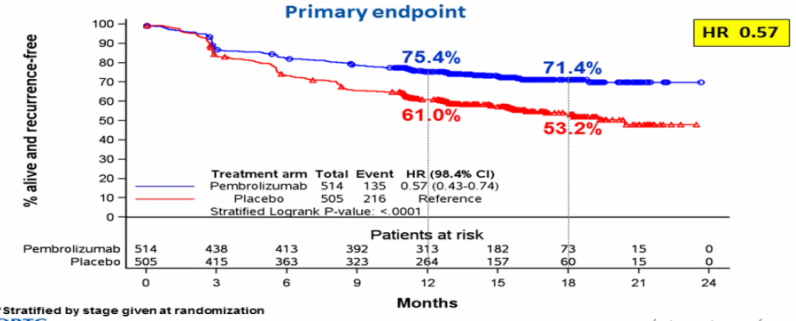
Pembrolizumab adjuvant EORTC 1325/Keynote 054

L. Eggermont AACR 2018

Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

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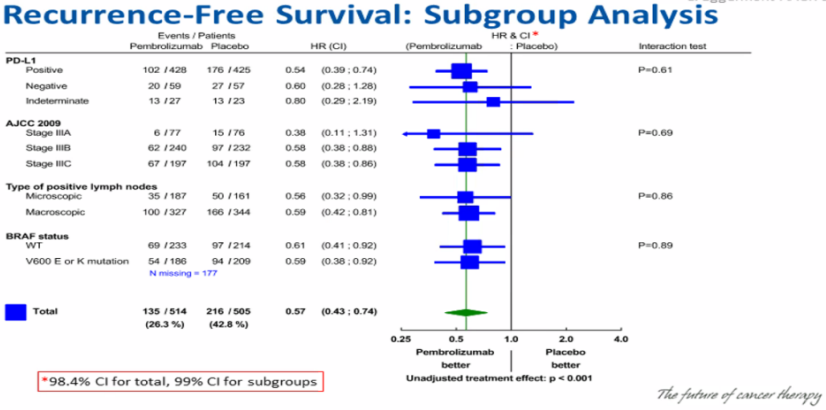
L. Eggermont AACR 2018

Recurrence-Free Survival: Subgroup Analysis



*98.4% CI for total, 99% CI for subgroups

The future of cancer therapy

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- RFS: Pembro better than placebo
- Pembro gr 3-5AEs: 15%, 1 death (myositis)
- EMA approval: 12/2018

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JAMA Network

From: **Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial**
JAMA Oncol. Published online January 02, 2020. doi:10.1001/jamaoncol.2019.5570

Table 3. Treatment Effect in the Presence and Absence of Immune-Related Adverse Events

Immune-Related Adverse Event Status and Treatment Arm	Recurrence-Free Survival, HR (95% CI)[a]	*P* Value[a,b]
Any irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.62 (0.49-0.78)	.03
Pembrolizumab after irAE onset	0.37 (0.24-0.57)	
Endocrine irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.60 (0.48-0.75)	.03
Pembrolizumab after irAE onset	0.34 (0.20-0.57)	
Vitiligo		
Placebo	1	
Pembrolizumab without/before irAE	0.57 (0.46-0.70)	.15
Pembrolizumab after irAE onset	0.13 (0.02-0.95)	
Any severe (grade 3-4) irAE		
Placebo	1	
Pembrolizumab without/before irAE	0.55 (0.44-0.68)	.43
Pembrolizumab after irAE onset	0.78 (0.32-0.91)	

Abbreviations: HR, hazard ratio; irAE, immune-related adverse event.

[a] A Cox model, which included a time-varying covariate for irAEs, the product of this covariate and the treatment indicator, and the patients' cancer stage, sex, and age, was used (model 2, see Statistical Methods).

[b] *P* value was calculated for the test of a difference in the effect of the randomized treatment in the presence and absence of irAEs among the pembrolizumab-treated patients (ie, the difference between the 2 HRs).

Treatment Effect in the Presence and Absence of Immune-Related Adverse Events

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Adjuvant therapies

- Targeted therapies
  - BRAFi dabrafenib + MEKi trametinib

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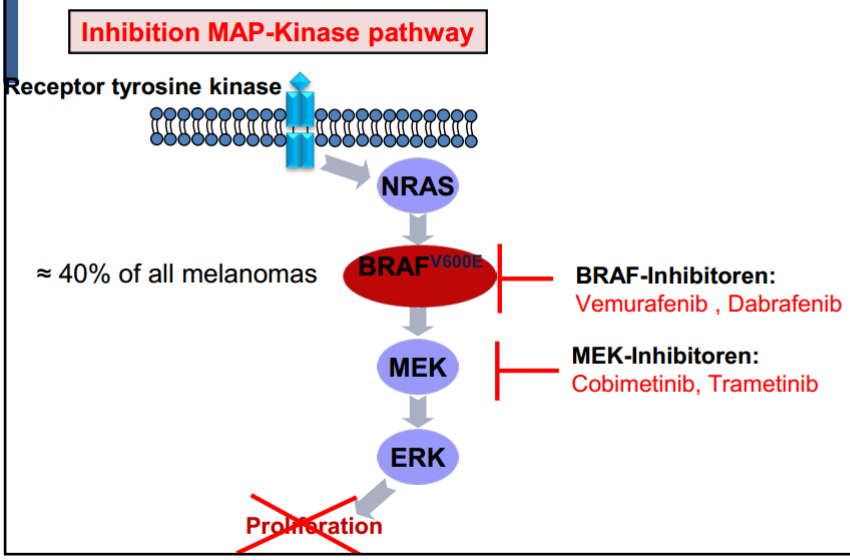
BRAF-Mutation

Universitätsklinikum Ess



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MADRID 2017 ESMO congress

COMBI-AD: STUDY DESIGN

Key eligibility criteria
- Completely resected, high-risk stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- Surgically free of disease ≤ 12 weeks before randomization
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy

Stratification
- *BRAF* mutation status (V600E, V600K)
- Disease stage (IIIA, IIIB, IIIC)

RANDOMIZATION

N = 870

1:1

Treatment: 12 months[a]

Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 438)

2 matched placebos (n = 432)

Follow-up[b] until end of study[c]

- **Primary endpoint: RFS[d]**
- **Secondary endpoints: OS, DMFS, FFR, safety**

BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival. [a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b] Patients were followed for disease recurrence until the first recurrence and thereafter for survival; [c] The study will be considered complete and final OS analysis will occur when ≈ 70% of randomized patients have died or are lost to follow-up; [d] New primary melanoma considered as an event.

Inclusion of st IIIA (sentinel >1mm), IIIB or IIIc

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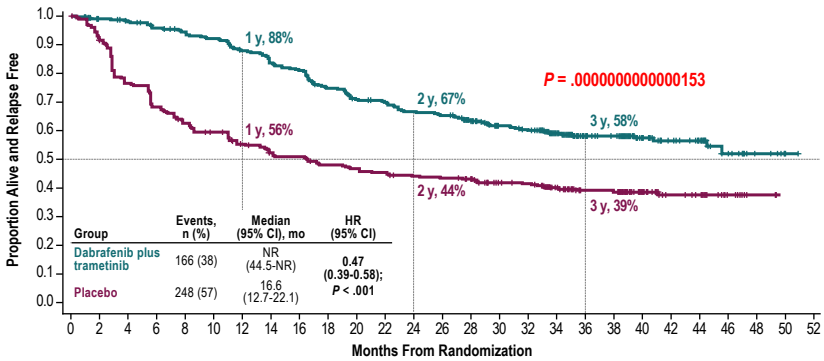
MADRID 2017 ESMO congress

RELAPSE-FREE SURVIVAL (PRIMARY ENDPOINT)



NR, not reached.

RFS benefit for all subgroups

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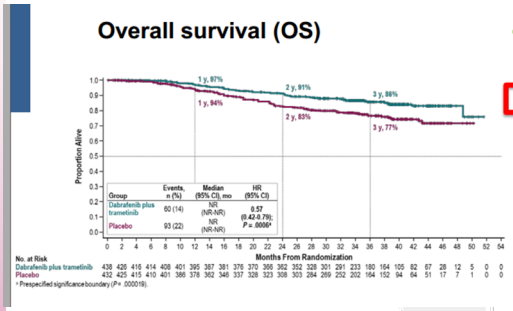
Combi-AD: OS



Post-recurrence Therapy	Dabra plus Trametinib (n=163)	Placebo (n=247)
Any systemic	74%	74%
Immunotherapy	55%	42%
Anti–CTLA-4	33%	28%
Anti–PD-1/PD-L1	44%	28%
BRAFi ± MEKi	39%	55%
Chemotherapy	12%	9%

Improvement in OS
Aes: Fever, fatigue and nausea
No treatment-related deaths
EMA: 8/2018

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- At 3-years: better RFS and OS
- Manageable side-effects

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Adjuvant trials: comparison of stage subgroups

	Study	Design	Stage - AJCC 7th Edition (All patients NED) IIC	IIIA	IIIB	IIIC	IV
FDA 11.15	EORTC 18071	Ipi 10 vs. placebo		✓ SN > 1mm	✓	✓ no in transit mets	
	EORTC 1325	Pembro vs. placebo		✓ SN > 1mm	✓	✓ no in transit mets	
FDA 12.17	Checkmate 238	Ipi 10 vs. nivo			✓	✓	✓
	ECOG 1609	Ipi 10 vs ipi 3 vs. HD INF-α2b			✓	✓	✓ M1a-b
	BRIM-8	Vem vs. placebo	✓	✓ SN > 1mm	✓	✓	
FDA 04.18	COMBI-AD	Dabra + trame vs. placebo		✓ SN > 1mm	✓	✓	

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Olivier Michielin, MD-PhD

NA, Not Available; NE, Not Estimated
[1] AJCC 8th Edition staging

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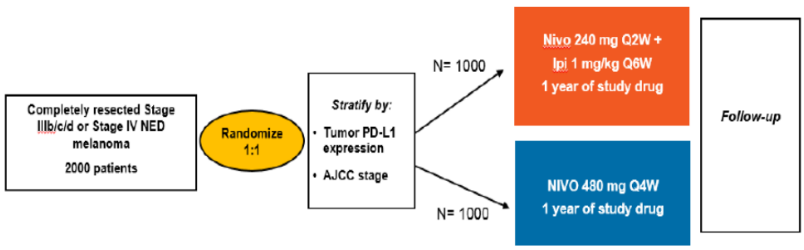
New trial

CA209-915

Randomized, Double-blind Phase III Study to Compare NIVO + IPI to NIVO



Primary Endpoint: RFS
Secondary Endpoints: OS; Association between PD-L1 and RFS
Exploratory: Safety, PROs, DMFS, PK & IG, Biomarkers

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Quid neo-adjuvant?

Comparison of relapse rate in patients with pCR and non-pCR in few selected trials of neoadjuvant therapy in locally/regionally advanced melanoma.

Reference	Study	Time of surgical resection after neoadjuvant therapy initiation	pCR rate	Median follow-up time	Durability of pCR	Durability of non-pCR
Immunotherapy						
Moschos *et al.*[30]	Moschos, HDI	4 weeks	15% (3/20)	18.5 months	Not given	Not given
Tarhini *et al.*[34,35]	Tarhini, ipi mono	⩾6 weeks	0	42 months	Not applicable	23/33 relapsed
Tarhini *et al.*[36]	Tarhini, ipi + HDI	6–8 weeks	39% (11/28)	32 months	1/11 relapsed	11/17 SD/PR/CR relapsed
Tarhini *et al.*[38]	Tarhini, pembro + HDI	6 weeks	35%	11 months	None relapsed	Not given
Blank *et al.*[39]	OpAcin, blank, nivo + ipi	6 weeks	30% (3/10)	25.6 months	None relapsed	2/10 relapsed
Blank *et al.*[40]	OpAcin neo, Arm A: Ipi (3 mg/kg) + Nivo (1 mg/kg) Arm B: Ipi (1 mg/kg) + Nivo (3 mg/kg) Arm C: Ipi (3 mg/kg) Q3W for 6 wks followed immediately by NIVO 3 mg/kg Q2W for 4 wks	6 weeks	47% in Arm A, 47% in Arm B, and 23% in arm C	7.7 months	None relapsed	9/21 relapsed
Amaria *et al.*[41]	Amaria, nivo + ipi Arm A: Neoadjuvant Nivo 3 mg/kg i.v. q2wks × 4 doses, followed by adjuvant Nivo 3 mg/kg i.v. q2wks × 13 doses Arm B: Neoadjuvant Nivo 1 mg/kg + Ipi 3 mg/kg q3wks × 3 doses, followed by adjuvant Nivo 3 mg/kg i.v. q2wks × 13 doses	8–9 weeks	Arm A- 25% pCR Arm B- 45% pCR	15.6 months	None relapsed at 20.5 mon	71% RFS at 16 mon
Targeted therapy						
Menzies *et al.*[42]	Menzies, dabrafenib + trametinib	12 weeks	17/33 (52%) had pCR	12.1 months	6 with pCR relapsed	6 with non-pCR relapsed
Amaria *et al.*[43]	Combi-Neo, Amaria, dabrafenib + trametinib	8 weeks	7/12 (pCR rate of 58%)	18.6 months	1 pt with pCR relapsed	3 pts with non-pCR relapsed

HDI, high-dose interferon-α2b; Ipi, ipilimumab; i.v. intravenous; Nivo, nivolumab; pCR, pathologic complete response; pembro, pembrolizumab; qxwks, every x weeks; QxW, x times a week.

Khunger et al, Ther Adv Med Onc; 2019

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Conclusions stage III

- Staging!
- Ptn met Sn+: consider adjuvant systemic therapy, not CLND
  - Cave N1b+: CLND is SOC
- Approval for dabrafenib-trametinib, nivolumab and pembrolizumab in the adjuvant setting
- IFN has no role
- What about PD in adjuvant setting?

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Dank voor uw aandacht

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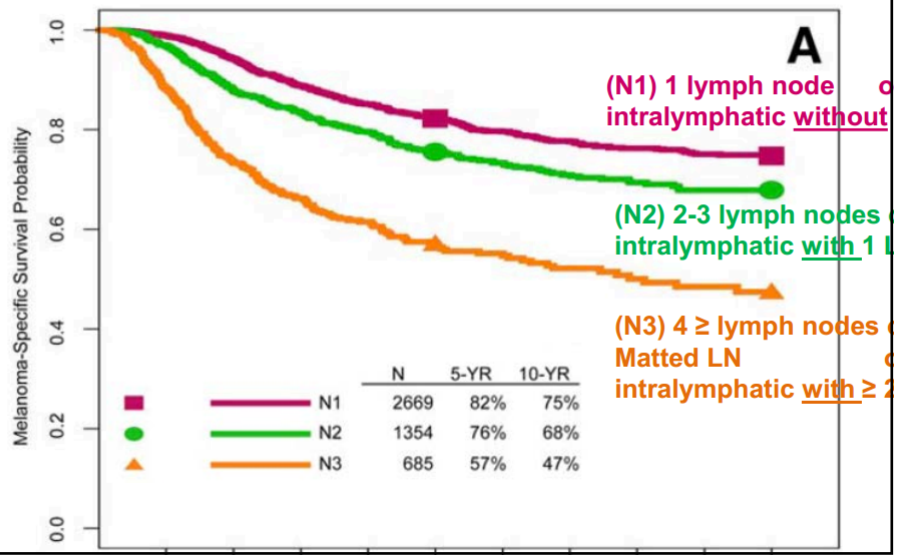
AJCC classification 2017

(N-category = regional LN and microsatellites, satellite and in-transit)



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