Prognose en medische behandeling van het niet-gemetastaseerd melanoom

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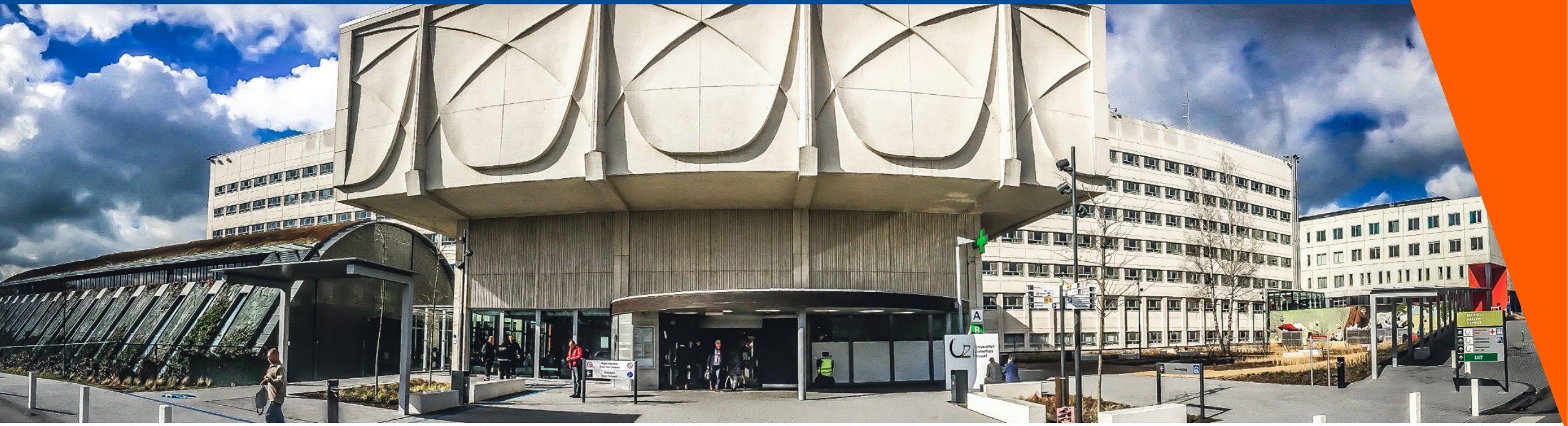

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DISCLOSURES

- **Personal financial compensation** from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, and Novartis for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received **research funding** related to research projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono

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AJCC Melanoma of the Skin Staging 8th Edition

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- **T0** No evidence of primary tumor
- **Tis** Melanoma in situ
- **T1** Melanomas 1.0 mm or less in thickness
- **T2** Melanomas 1.1 - 2.0 mm
- **T3** Melanomas 2.1 - 4.0 mm
- **T4** Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and thickness as shown belowt:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Regional Lymph Nodes (N)

- **NX** Patients in whom the regional nodes cannot be assessed (for example previously removed for another reason)
- **N0** No regional metastases detected
- **N1-3** Regional metastases based on the number of metastatic nodes, number of palpable metastatic nodes on clinical exam, and presence or absence of MSI[2]

NOTE: N1-3 and a-c subcategories assigned as shown below:

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult[1], no MSI[2] b: clinically detected[1], no MSI[2] c: 0 nodes, MSI present[2]
N2	1-3 nodes	a: 2-3 nodes clinically occult[1], no MSI[2] b: 2-3 nodes clinically detected[1], no MSI[2] c: 1 node clinical or occult[1], MSI present[2]
N3	>1 nodes	a: >3 nodes, all clinically occult[1], no MSI[2] b: >3 nodes, ≥1 clinically detected[1] or matted, no MSI[2] c: >1 nodes clinical or occult[1], MSI present[2]

Distant Metastasis (M)

- **M0** No detectable evidence of distant metastases
- **M1a** Metastases to skin, sub cutaneous, or distant lymph nodes
- **M1b** Metastases to lung
- **M1c** Metastases to all other visceral sites
- **M1d** Metastases to brain

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	Serum LDH
M1a-d	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Not assessed
M1a-d(0)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Normal
M1a-d(1)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0		0	Tis	N0	M0
Stage IA	T1a	N0	M0		IA	T1a	N0	M0
Stage IB	T1b	..	..			T1b	..	..
	T2a	..	..		IB	T2a	..	..
Stage IIA	T2b	N0	M0		IIA	T2b	M0	M0
	T3a	..	..			T2a	..	..
Stage IIB	T3b	..	..		IIB	T3b	..	..
	T4a	..	..			T4a	..	..
Stage IIC	T4b	..	..		IIC	T4b	..	..
Stage III	Any T	≥N1	M0		IIIA	T1-2a	N1a	M0
	..	..	..			T1-2a	N2a	..
	..	..	..		IIIB	T0	N1b-c	M0
	..	..	..			T1-2a	N1b-c	..
	..	..	..			T1-2a	N2b	..
	..	..	..			T2b-3a	N1a-2b	..
	..	..	..		IIIC	T0	N2b-c	M0
	..	..	..			T0	N3b-c	..
	..	..	..			T1a-3a	N2c-3c	..
	..	..	..			T3b-4a	Any N	..
	..	..	..			T4b	N1a-2c	..
	..	..	..		IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1		IV	Any T	Any N	M1

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases	T Category								
			T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
			No evidence of primary tumor	<0.8 mm without ulceration	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration	>1.0-2.0 mm without ulceration	>1.0-2.0 mm with ulceration	>2.0-4.0 mm without ulceration	>2.0-4.0 mm with ulceration	>4.0 mm without ulceration	>4.0 mm with ulceration
N0	No regional metastases detected	No	-	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

T0 — no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); **Tis** — melanoma in situ;
Tx — thickness cannot be assessed. (Tis and Tx are not included in the table but are part of the staging system.)
Nx — Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason).
Exception: pathological N category is not required for T1 melanomas, use clinical N information. (If an SLNB was performed, the results can and *should* be used for pathological evaluation.)

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases	T Category								
			T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
			No evidence of primary tumor	<0.8 mm without ulceration	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration	>1.0-2.0 mm without ulceration	>1.0-2.0 mm with ulceration	>2.0-4.0 mm without ulceration	>2.0-4.0 mm with ulceration	>4.0 mm without ulceration	>4.0 mm with ulceration
N0	No regional metastases detected	No	-	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

T0 — no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); **Tis** — melanoma in situ;
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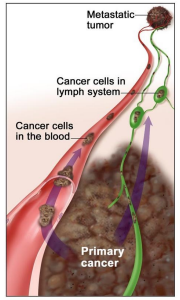
Exception: pathological N category is not required for T1 melanomas, use clinical N information. (If an SLNB was performed, the results can and *should* be used for pathological evaluation.)

Standard Therapeutic interventions

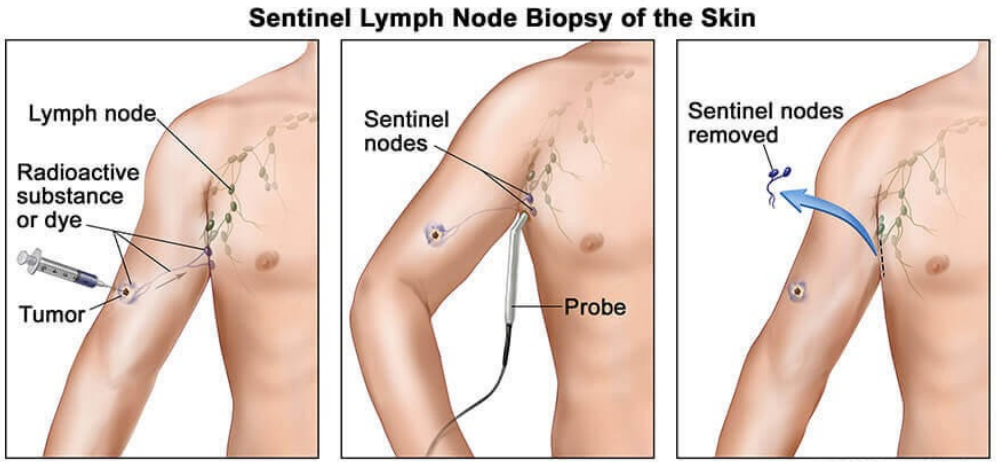
Resection of primary (and satellites/ITM)	Sentinel node procedure	CLND	Adjuvant medical therapy

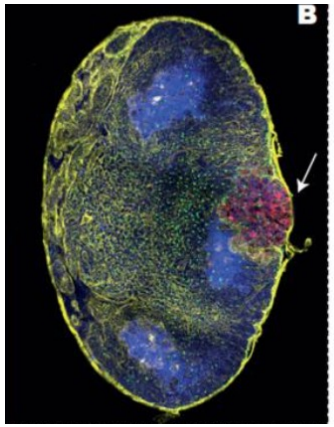
The Evolving Treatment Landscape for pT1b-4b cN0M0 Melanoma of the Skin

2016



- Sentinel Node Biopsy
  - Most important prognostic information in pT1b-3a melanoma
  - Negligible therapeutic benefit (no impact on RFS, DMFS or OS)
- CLND indicated in case of micrometastasis to the sentinel node
- Adjuvant therapy (IFNa) not widely accepted





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2016

Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial

Ulrike Leiter, Rudolf Stadler*, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Klaus-Werner Schulte, Percy Lehmann, Thomas Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Peter Martus, Claus Garbe, for the German Dermatologic Cooperative Oncology Group (DeCOG)*

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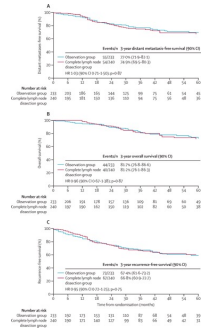

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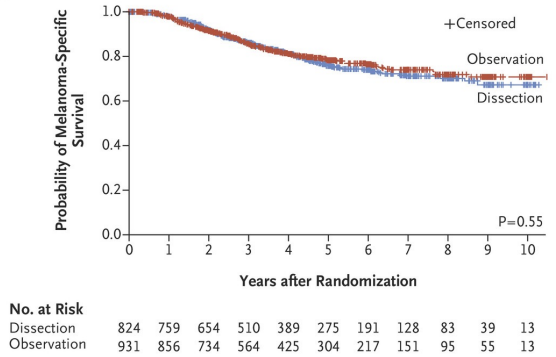
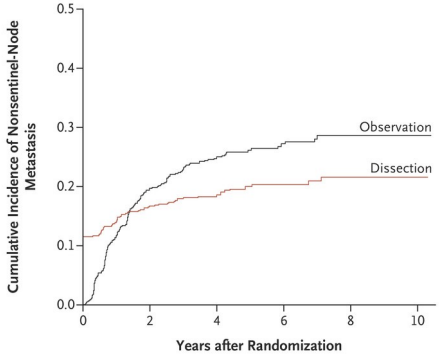
Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

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





- Sentinel Node Biopsy
  - Most important prognostic information in pT1b-3a melanoma
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The Evolving Treatment Landscape for pT1b-4b cN0M0 Melanoma of the Skin

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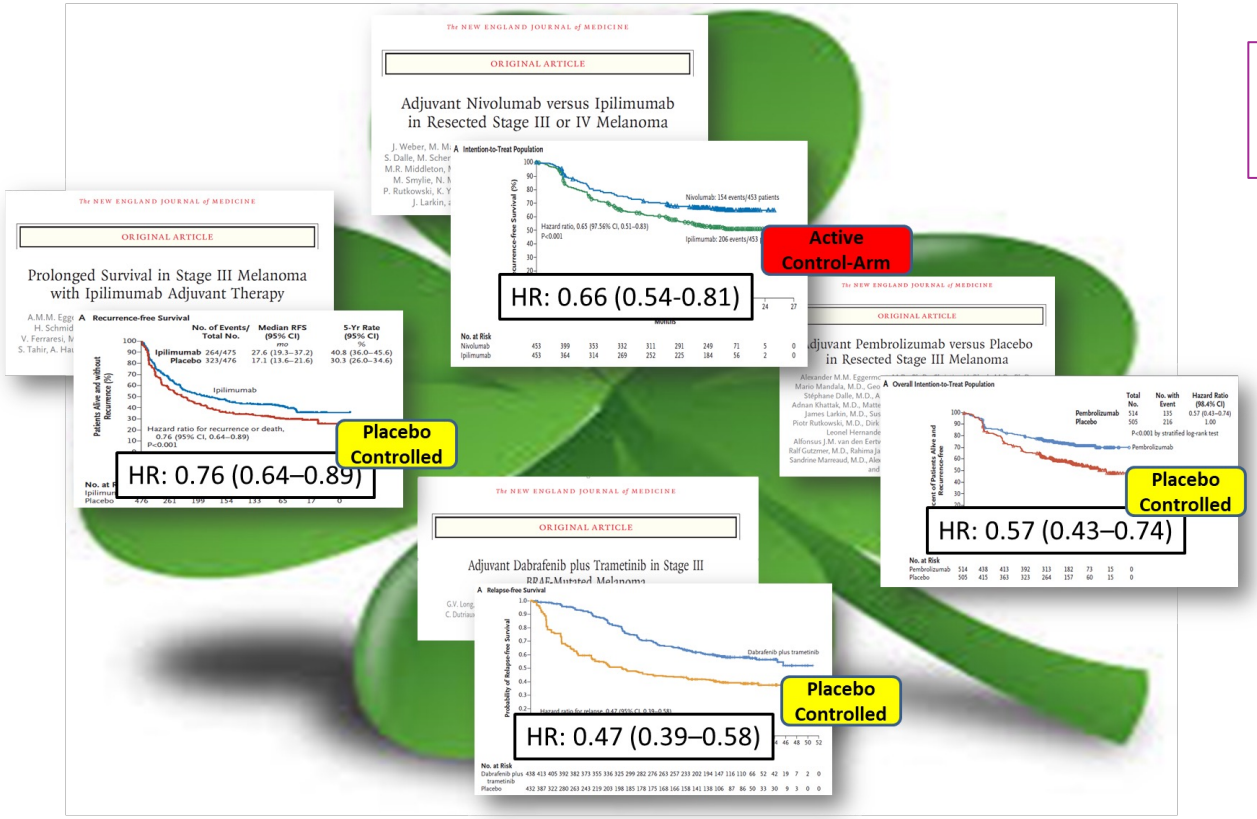
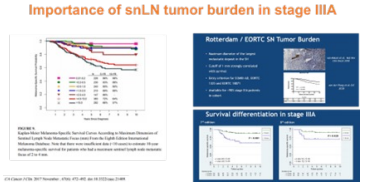
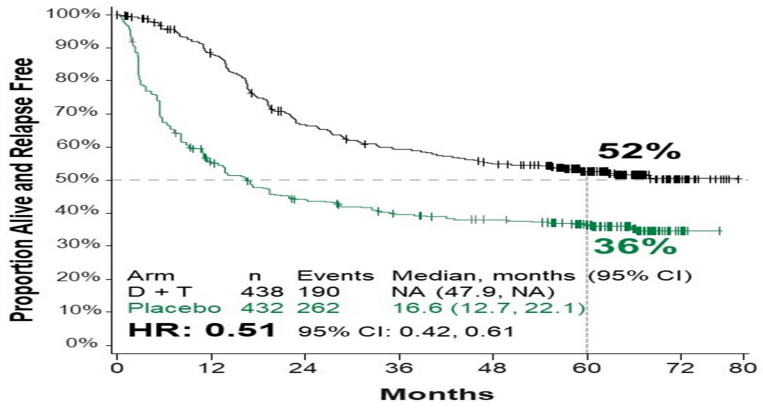
2017



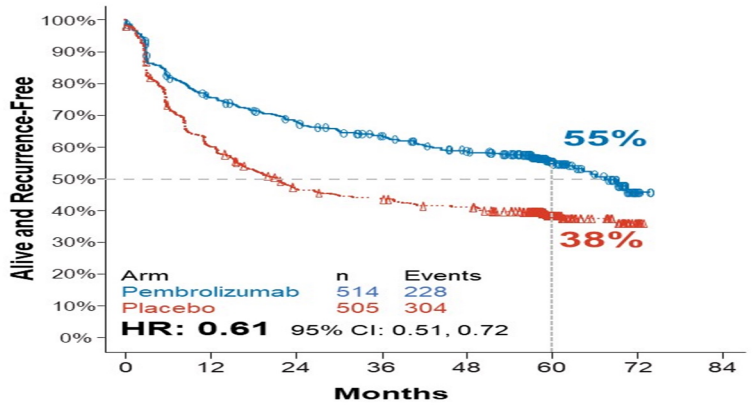
Eligibility : >1mm SLN metastasis



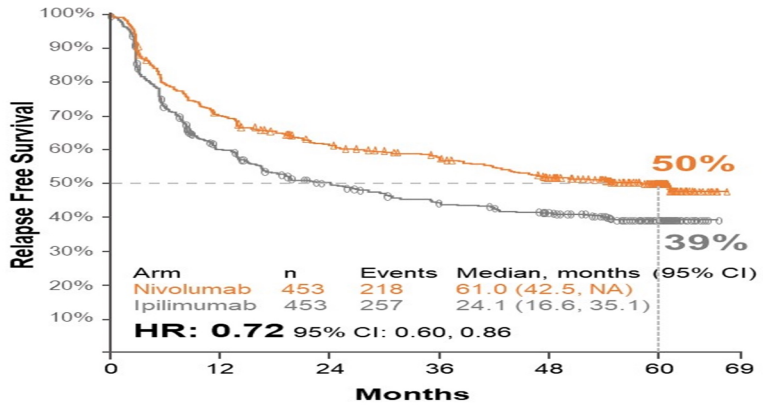
RFS following adjuvant medical therapy in resected AJCC 7th stage III melanoma (with SLNB >1mm)



COMBI-AD[1]
Dabrafenib plus trametinib vs placebo



KEYNOTE-054[2]
Pembrolizumab vs placebo



CHECKMATE-238[3]
Nivolumab vs ipilimumab

Endpoint	COMBI-AD[1]	KEYNOTE-054[2]	CHECKMATE-238[3]
Population	Dabrafenib + trametinib (n=438) vs placebo (n=432) *BRAF* V600E/K only	Pembrolizumab (n=514) vs placebo (n=505)	Nivolumab (n=453) vs ipilimumab (n=453)
Melanoma stage	AJCC 7th edition Stage IIIA-C	AJCC 7th edition Stage IIIA-C	AJCC 7th edition Stage IIIB-C/IV
RFS	52% vs 36% HR: 0.51 95% CI: 0.42, 0.61	55% vs 38% HR: 0.61 95% CI: 0.51, 0.72	50% vs 39% HR: 0.72 95% CI: 0.60, 0.86
DMFS	65% vs 54% HR: 0.55 95% CI: 0.44, 0.70	61% vs 44% HR: 0.62 95% CI: 0.52, 0.75	58%[a] vs 51%[b] HR: 0.79 95% CI: 0.63, 0.99
OS	Not analyzed[c]	Not analyzed	76% vs 72% HR: 0.86 95% CI: 0.66, 1.12

[a]n=370; [b]n=366; [c]Inadequate number of events to trigger the final analysis.

1. Dummer R, et al. *N Engl J Med*. 2020;383:1139-1148. 2. Eggermont A, et al. *NEJM Evidence*. 2022;1:EVIDoa2200214. 3. Larkin J, et al. *Clin Cancer Res*. 2023;29:3352-3361.

Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915)

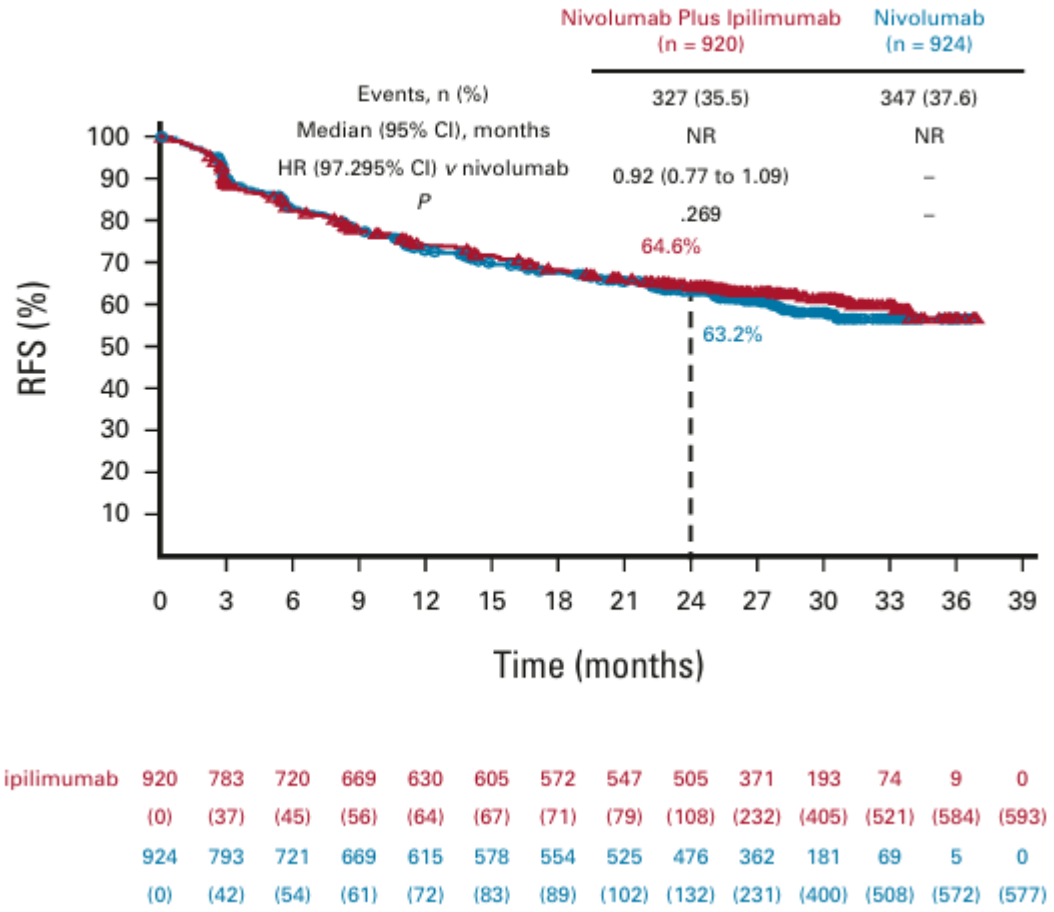
Jeffrey S. Weber, MD, PhD[1]; Dirk Schadendorf, MD[2]; Michele Del Vecchio, MD[3]; James Larkin, PhD, FRCP[4]; Victoria Atkinson, MD[5]; Michael Schenker, MD[6]; Jacopo Pigozzo, MD[7]; Helen Gogas, MD, PhD[8]; Stéphane Dalle, MD, PhD[9]; Nicolas Meyer, MD, PhD[10]; Paolo A. Ascierto, MD[11]; Shahneen Sandhu, MBBS[12]; Thomas Eigentler, MD[13]; Ralf Gutzmer, MD[14]; Jessica C. Hassel, MD[15]; Caroline Robert, MD, PhD[16]; Matteo S. Carlino, MBBS, PhD[17]; Anna Maria Di Giacomo, MD, PhD[18]; Marcus O. Butler, MD[19]; Eva Muñoz-Couselo, MD[20]; Michael P. Brown, MBBS, PhD[21]; Piotr Rutkowski, MD[22]; Andrew Haydon, MD[23]; Jean-Jacques Grob, MD[24]; Jacob Schachter, MD, PhD[25]; Paola Queirolo, MD[26,27]; Luis de la Cruz-Merino, MD[28]; Andre van der Westhuizen, MBChB, MMed[29]; Alexander M. Menzies, MBBS, PhD[30]; Sandra Re, MD[31]; Tuba Bas, PhD[31]; Veerle de Pril, MSc[31]; Julia Braverman, PhD[31]; Daniel J. Tenney, PhD[31]; Hao Tang, PhD[31]; and Georgina V. Long, MBBS, PhD[30]

TABLE 2. Treatment-Related Adverse Events[a]

	Nivolumab Plus Ipilimumab (n = 916), No. (%)		Nivolumab (n = 917), No. (%)	
Event	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Any	863 (94.2)	299 (32.6)	788 (85.9)	117 (12.8)
Pruritus	303 (33.1)	2 (0.2)	194 (21.2)	0
Fatigue	279 (30.5)	10 (1.1)	276 (30.1)	2 (0.2)
Diarrhea	248 (27.1)	22 (2.4)	187 (20.4)	5 (0.5)
Rash	222 (24.2)	5 (0.5)	192 (20.9)	6 (0.7)
Hypothyroidism	202 (22.1)	2 (0.2)	133 (14.5)	1 (0.1)
Hyperthyroidism	178 (19.4)	4 (0.4)	93 (10.1)	0
Asthenia	134 (14.6)	3 (0.3)	122 (13.3)	1 (0.1)
Nausea	130 (14.2)	2 (0.2)	100 (10.9)	0
Headache	124 (13.5)	1 (0.1)	81 (8.8)	0
Increase in ALT level	121 (13.2)	30 (3.3)	72 (7.9)	4 (0.4)
Increase in lipase level	105 (11.5)	48 (5.2)	47 (5.1)	17 (1.9)
Arthralgia	105 (11.5)	7 (0.8)	120 (13.1)	3 (0.3)
Increase in AST level	99 (10.8)	15 (1.6)	59 (6.4)	1 (0.1)
Hypophysitis	96 (10.5)	19 (2.1)	15 (1.6)	4 (0.4)

[a]The safety population included all patients who had received at least one dose of trial drug. The investigators determined whether adverse events were related to a trial drug. The events listed here were any grade reported in at least 10% of the patients in either treatment group and occurred between the first dose and 30 days after the last dose. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

A



The Evolving Treatment Landscape for pT1b-4b cN0M0 Melanoma of the Skin

2016

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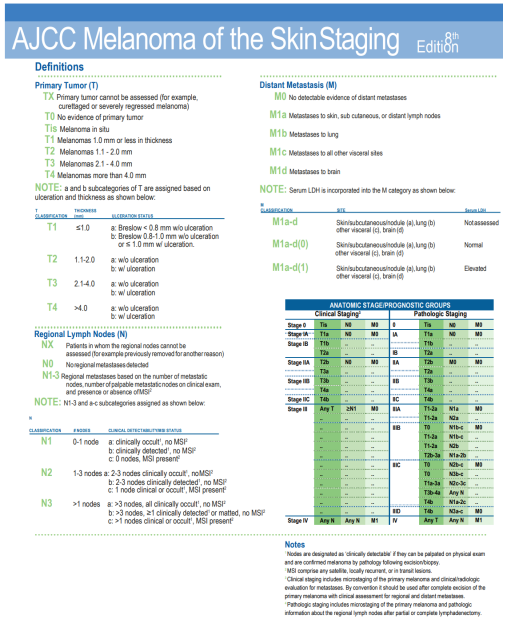
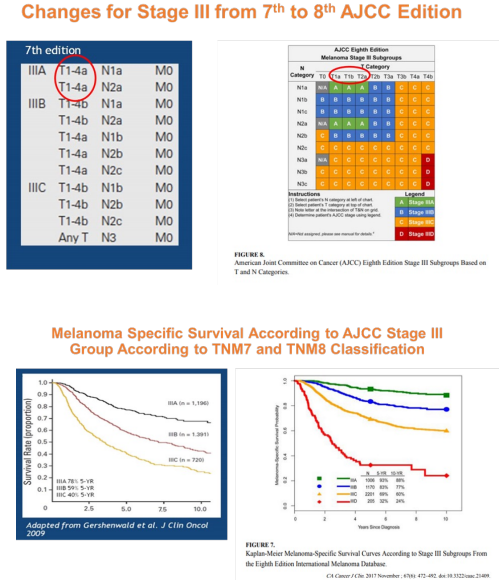
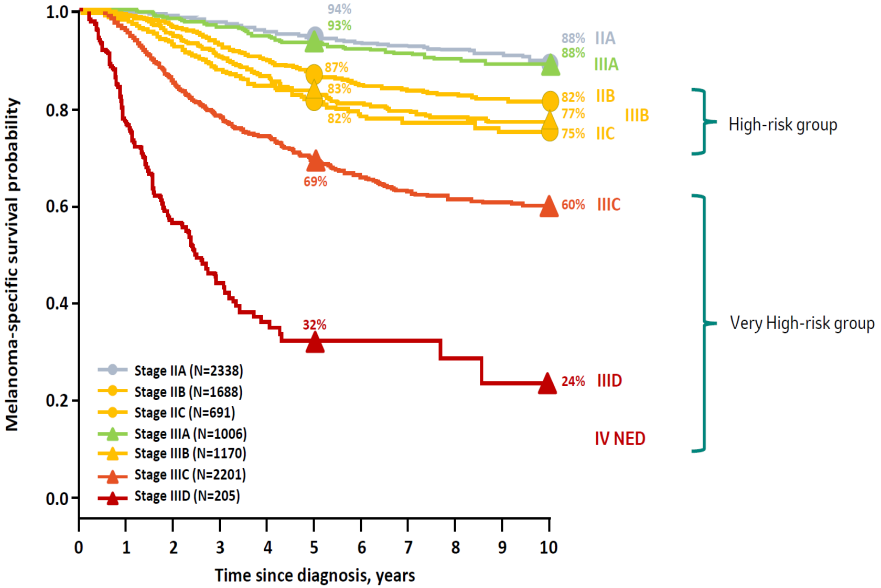
2017

- Anti-PD1 (nivolumab and pembrolizumab) and tafinlar/mekinist (in case of BRAF V600mut) approved for adjuvant therapy of stage III melanoma

2018







The Evolving Treatment Landscape for pT1b-4b cN0M0 Melanoma of the Skin

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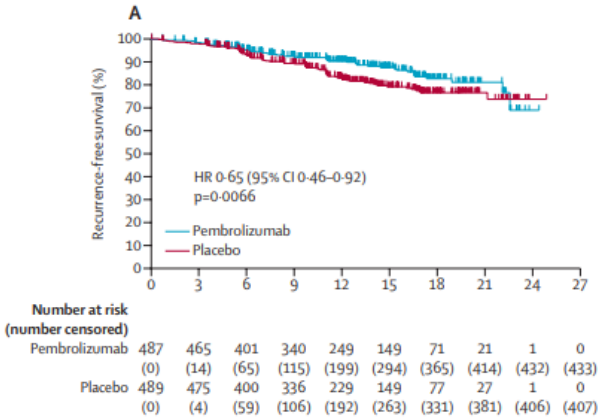
2018

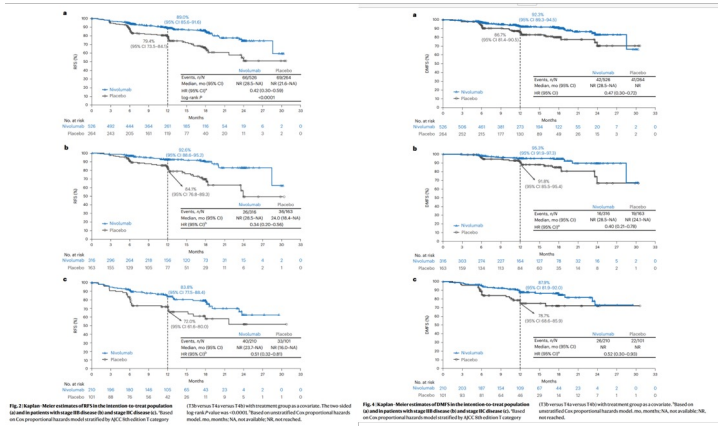
- AJCC 8th edition

2022

Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial

*Jason J Luke, Piotr Rutkowski, Paola Queirolo, Michele Del Vecchio, Jacek Mackiewicz, Vanna Chiarion-Sileni, Luis de la Cruz Merino, Muhammad A Khattak, Dirk Schadendorf, Georgina V Long, Paolo A Ascierto, Mario Mandala, Federica De Galitiis, Andrew Haydon, Reinhard Dummer, Jean-Jacques Grob, Caroline Robert, Matteo S Carlino, Peter Mohr, Andrew Poklepovic, Vernon K Sondak, Richard A Scolyer, John M Kirkwood, Ke Chen, Scott J Diede, Sama Ahsan, Nageatte Ibrahim, Alexander M M Eggermont, on behalf of the KEYNOTE-716 Investigators**





Ongoing debate = acceptable NNT and NNH to prevent 1 recurrence?

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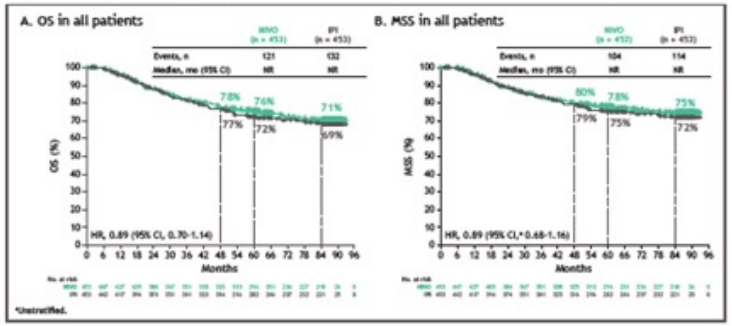


No OS-benefit demonstrated for any of the approved adjuvant therapies for Stage III or IIB/C melanoma (results of EORTC 1325-MG/KEYNOTE-054 pending)

10y survival data COMBI-AD (ASCO 2024)

PFS2 data of KN716 and CM 76K (ESMO 2024)

2024 ASCO ANNUAL MEETING

Long-Term Follow-Up for Adjuvant Dabrafenib Plus Trametinib in Stage III BRAF-Mutated Melanoma: Final Results of the COMBI-AD Study

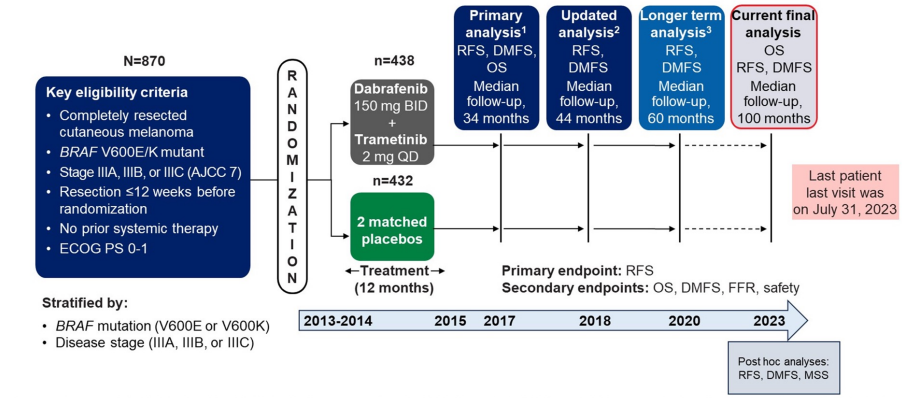
Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandala, Barbara Merelli, Vanna Chiarion-Sileni, Andrew Mark Haydon, Jacob Schachter, Dirk Schadendorf, Thierry Lesimple, Elizabeth Ruth Plummer, James Larkin, Monique Tan, Sachin Bajirao Adnaik, Paul Burgess, Tarveen Jandoo, Georgina V. Long

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

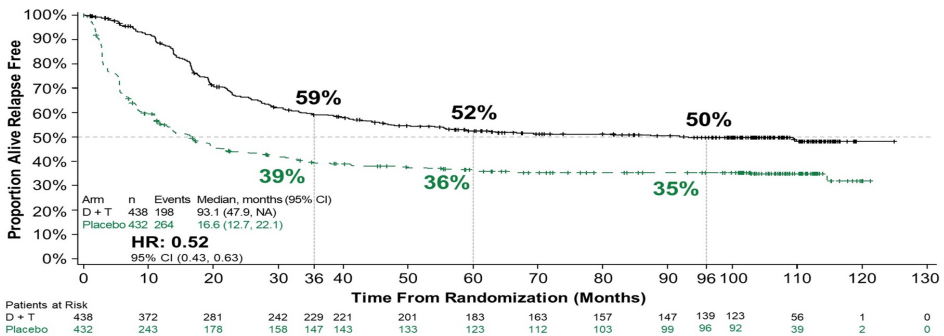
Final Results for Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma

G.V. Long, A. Hauschild, M. Santinami, J.M. Kirkwood, V. Atkinson, M. Mandala, B. Merelli, V.C. Sileni, M. Nyakas, A. Haydon, C. Dutriaux, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, J. Larkin, M. Tan, S.B. Adnaik, P. Burgess, T. Jandoo, and R. Dummer



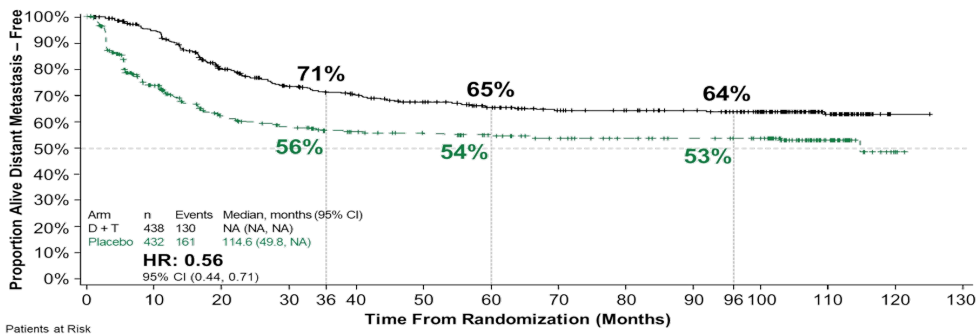
1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388; 3. Dummer R, et al. *N Engl J Med*. 2020;383:1139-1148.

Relapse-Free Survival (ITT)



End of study 31 July 2023. Median follow-up: D+T 100.0 (0–125) months; Placebo 82.5 (1–122) months.

Distant Metastasis-Free Survival* (ITT)



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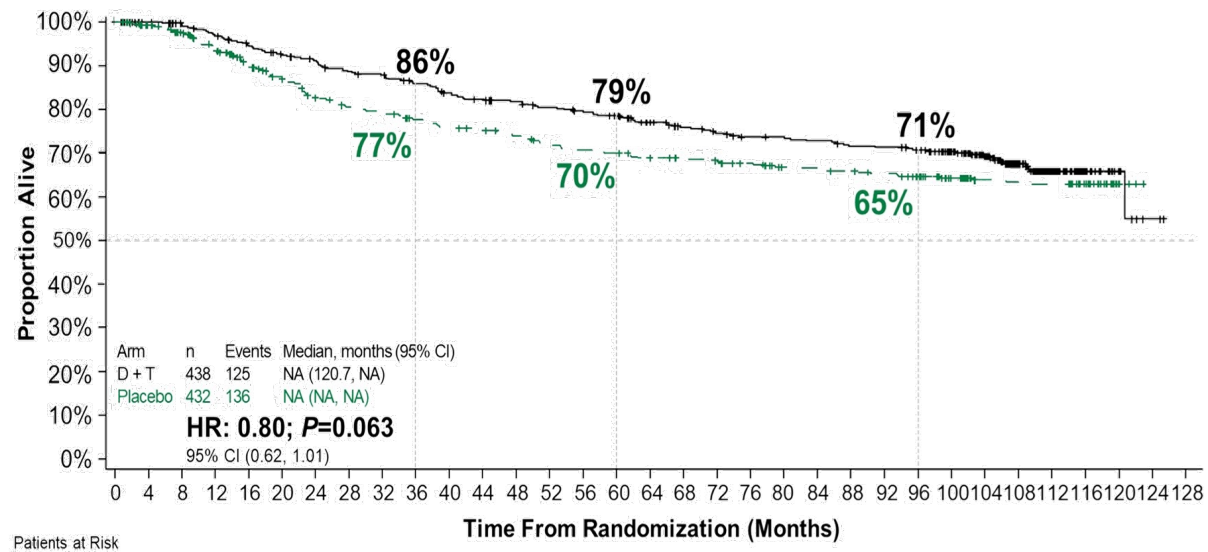
*Includes only first follow-up

Overall Survival (ITT)



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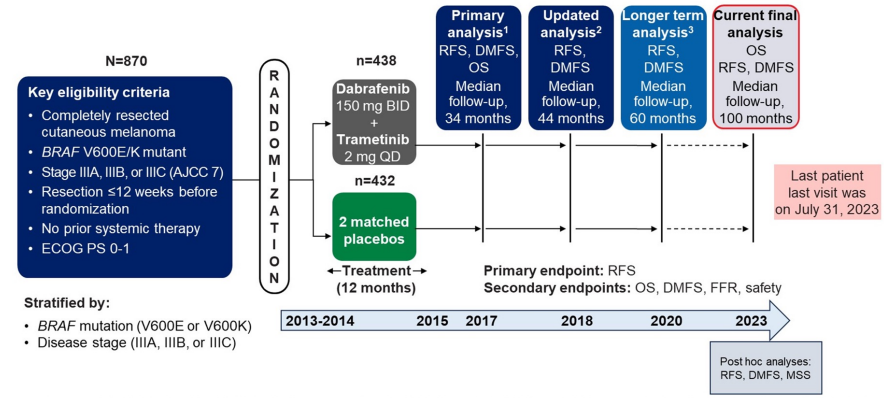

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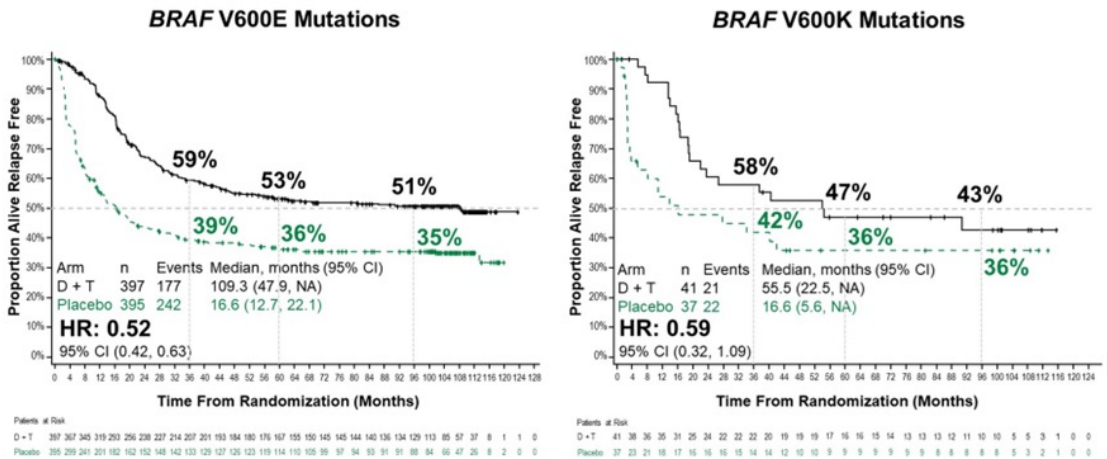
Subgroup Analysis: Effect of Treatment on RFS by *BRAF* V600 Mutations (ITT)



One patient had a *BRAF* V600E mutation and a *BRAF* V600K mutation and is included in the *BRAF* V600K subset

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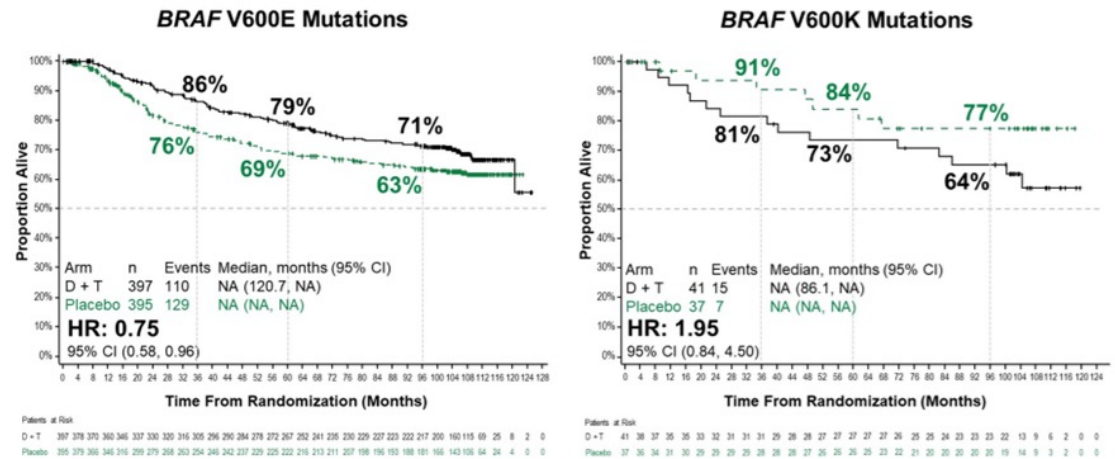
Subgroup Analysis: Effect of Treatment on Overall Survival by *BRAF* V600 Mutations (ITT)



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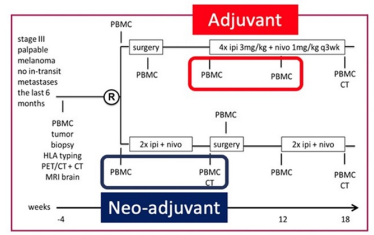
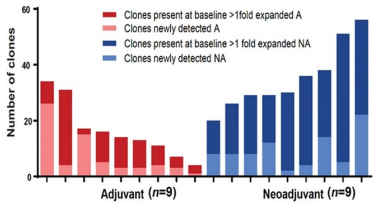
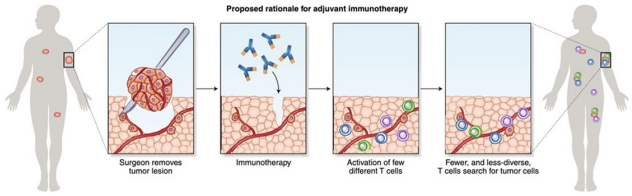
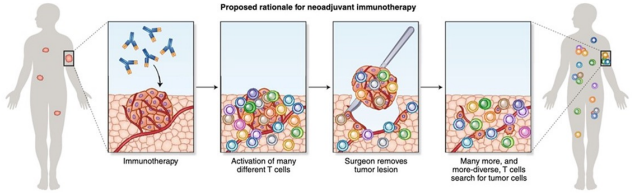
Neoadjuvant checkpoint inhibition is thought to be superior to adjuvant due to induction of a larger and broader immune repertoire









Blank et al, Nature Medicine 2018 | Versluis et al, Nature Medicine 2020

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: Christian U Blank

- It can induce a **stronger and broader** tumor-specific T cell response
- It can **reduce tumor burden** and facilitate easier surgical excision of the tumor
- Pathologic response as **fast efficacy readout** and **surrogate outcome marker** for survival
- Pathologic response can **guide further treatment decisions** regarding extent of surgery and adjuvant therapy
- It is a platform for baseline **biomarker identification** and testing of new neoadjuvant treatment combinations

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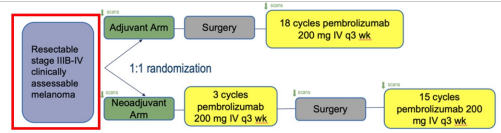

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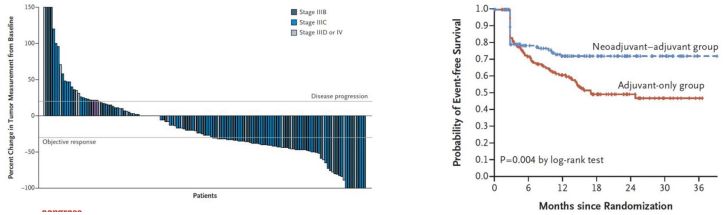
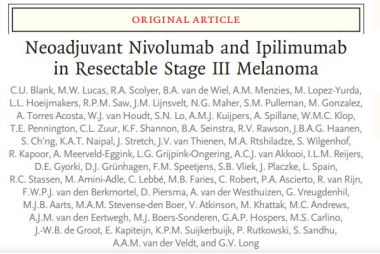
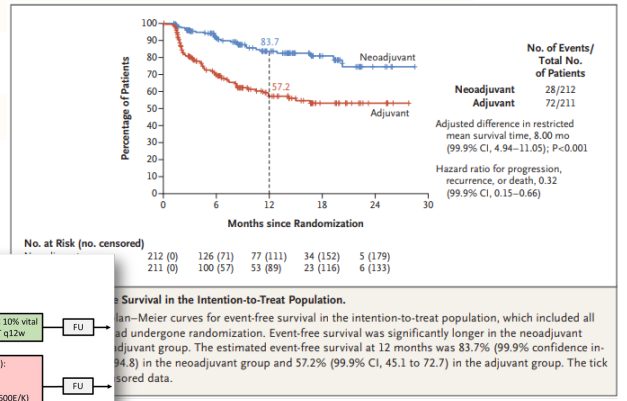
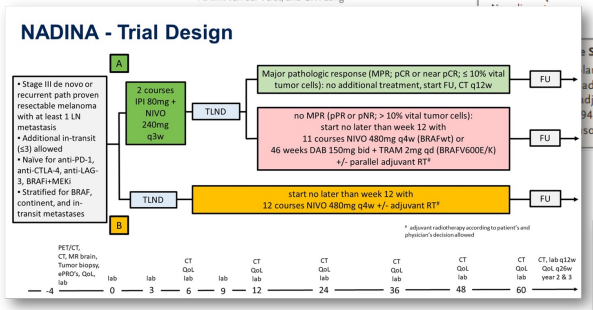


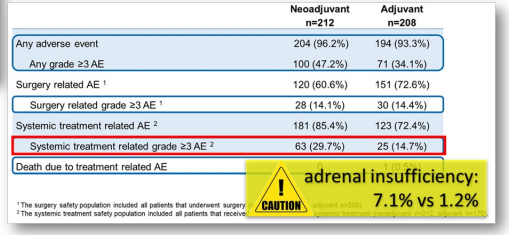
2025

RELATIVITY-098,
REGN3767-ONC-201112
KEYNOTE V940-001







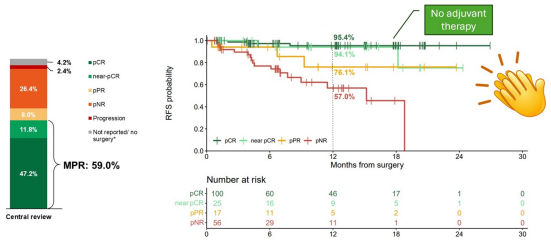


	Neoadjuvant n=212	Adjuvant n=208
Any adverse event	204 (96.2%)	194 (93.3%)
Any grade ≥3 AE	100 (47.2%)	71 (34.1%)
Surgery related AE [1]	120 (60.6%)	151 (72.6%)
Surgery related grade ≥3 AE [1]	28 (14.1%)	30 (14.4%)
Systemic treatment related AE [2]	181 (85.4%)	123 (72.4%)
Systemic treatment related grade ≥3 AE [2]	63 (29.7%)	25 (14.7%)
Death due to treatment related AE		

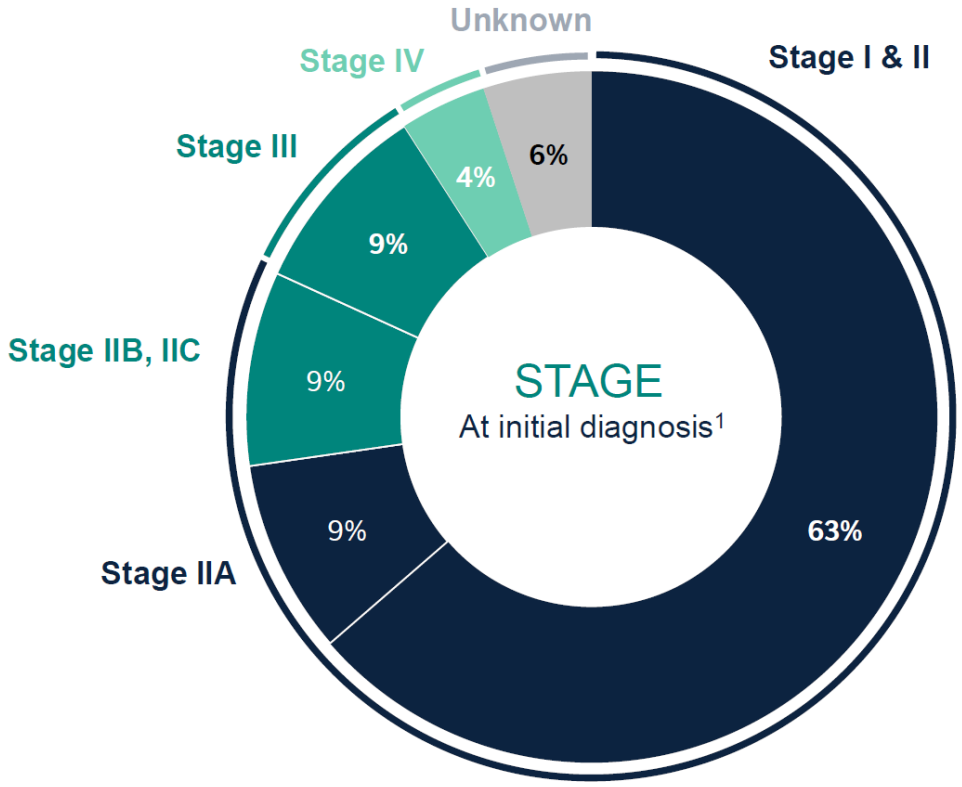
[1] The surgery safety population included all patients that underwent surgery
[2] The systemic treatment safety population included all patients that received

CAUTION adrenal insufficiency: 7.1% vs 1.2%

NADINA – RFS According to Pathologic Response



The majority of melanoma's are diagnosed at an "early stage" However, more patients die from "thin" (pT1-T2) as opposed to "thick" melanomas (pT3-T4)



		Queensland		USA	
Thickness category	5 year survival	Cases n=13,006	Deaths n=1,021	Cases n=49,319	Deaths n=3,660
0.01-1.00mm	97%	72%	29%	72%	29%
1.01-2.00mm	88%	14%	27%	16%	27%
2.01-4.00mm	74%	9%	26%	8%	27%
>4.00mm	56%	5%	18%	4%	17%

1 Gershenwald et al. AJCC 8th Edition 2017; 2 Shaikh et al, JNCI 2016; 3 Whiteman DC, et al. J Invest Dermatol 2015; 4 Landow et al. J Am Acad Dermatol. 2016

1. https://seer.cancer.gov/statfacts/html/melan.html.
2. Poklepovic AS, Luke JJ. Considering adjuvant therapy for stage II melanoma. *Cancer*. 2020;126:1166–1174.

Gene expression profiling (GEP) for early-stage primary melanoma

- GEPs detect messenger RNA's in the primary melanoma
- Clinical utility
  - Predict sentinel positivity (Merlin test, SkylineDx)
  - Determine prognosis (RFS/DMFS/OS)
- Development/validation of following GEPs has been most advanced
  - 8-GEP-CP assay (Merlin Test, Skyline Diagnostics, NL)
  - 31-GEP assay (DecisionDx, Caste Bioscience, USA)
  - 11-GEP assay (MelaGenix, NeraCare, DE)
- Additional GEP's under development, inl. RNAseq based profiles

Table 4 Prognostic end-points for original studies of commercially available gene-expression profile tests

GEP test	Study	Design	CM AJCC8 stage (n)	GEP Risk	3-Year RFS (%)	*p* value	3-Year DMFS (%)	*p* value	3-Year MSS (%)	*p* value
31-GEP	Keller et al. 2019 [44]	Prospective	Stage I-III	Class 1	96	< 0.0001	99	< 0.0001	-[e]	-[e]
			(159)	Class 2	47		64			
	Hsueh et al. 2021 [43]	Prospective	Stage I-III	Class 1	95	0.02	97	0.4	97[d]	0.02
		(clinical trial)	(323)	Class 2	66		79		81[d]	
			Stage I-IIA	Class 1	97	< 0.0001	99	< 0.0001	98[d]	0.01
			(256)[a]	Class 2	83		87		90[d]	
			CM AJCC8 stage	GEP risk	5-Year RFS (%)	*p* value	5-Year DMFS (%)	*p* value	5-Year MSS (%)	*p* value
31-GEP	Ferris et al. 2017 [41]	Retrospective	Stage I-IIA	Class 1	95	< 0.05	96	< 0.05	96[d]	< 0.05
			(135)	Class 2	62		76		71[d]	
			Stage IIB-IIC	Class 1	75	< 0.05	92	< 0.05	83[d]	< 0.05
			(70)	Class 2	17		39		44[d]	
	Gastman et al. 2019 [42]	Retrospective	Stage I-III	Class 1A	80	< 0.0001	83	< 0.0001	98	< 0.0001
			(157)	Class 1B	74		74		90	
				Class 2A	46		50		84	
				Class 2B	25		33		61	
	Zager, et al. 2018 [39]	Retrospective	Stage I	Class 1	96	0.01[d]	97	0.085[d]	99	0.37[d]
			(264)	Class 2	85		90		97	
				Class 1A	98	< 0.001[d]	98	0.05[d]	100	< 0.01[d]
				Class 2B	73		87		93	
			Stage II	Class 1	74	0.043[d]	90	0.004[d]	100	0.022[d]
			(93)	Class 2	55		63		87	
				Class 1A	77	0.13[d]	95	< 0.001[d]	100	0.13[d]
				Class 2B	50		57		82	
			Stage IIIA	Class 1	72	0.015[d]	80	0.019[d]	100	0.009[d]
			(69)	Class 2	51		54		67	
	Groenhaw et al. 2018 [40]	Retrospective	Stage IIcII	Class 1	93[b]	< 0.00001	-[e]	-[e]	99	0.00003
			(256)	Class 2	69[b]				79	
11-GEP	Gambichler et al. 2020 [36]	Retrospective	Stage I-III	≤ 0	96[c]	< 0.0001	-[e]	-[e]	99	0.001
			(291)	> 0	78[c]				88	
	Almaral et al. 2019 [50]	Prospective	Stage II (245)	≤ 0	76[c]	0.009	89	0.005	92	0.018
				> 0	58[c]		70		82	
8-GEP + CP	Eggermont et al. 2020 [51]	Retrospective	Stage I-III	Low	87	< 0.001	92	0.001	96	0.064
			(837)	High	62		72		88	
			Stage I-III, SLNBx(-)	Low	89	< 0.001	94	0.002	96	0.152
			(637)[a]	High	70		78		89	
			Stage I-IIA	Low	89	0.006	94	0.025	97	0.123
			(580)[a]	High	74		80		91	

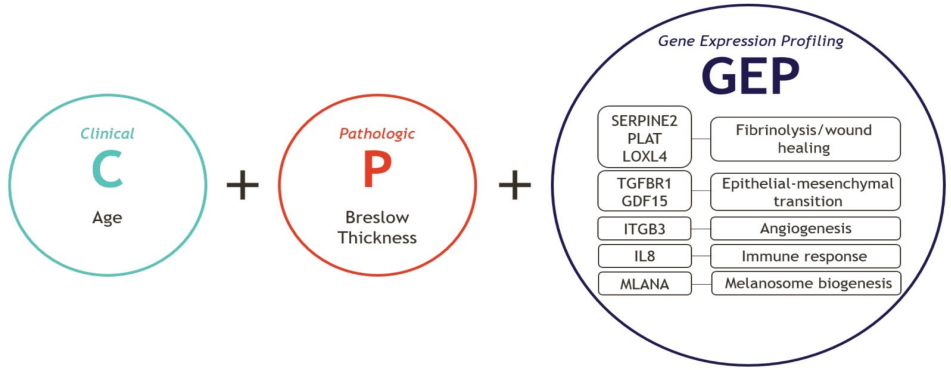
Farberg et al. Dermatol Ther (Heidelb). 2022

SkylineDx CASTLE BIOSCIENCES NERACARE

GEP: the Merlin™ test

SkylineDx announces commercial launch Merlin Assay as CE-IVD kit in Europe

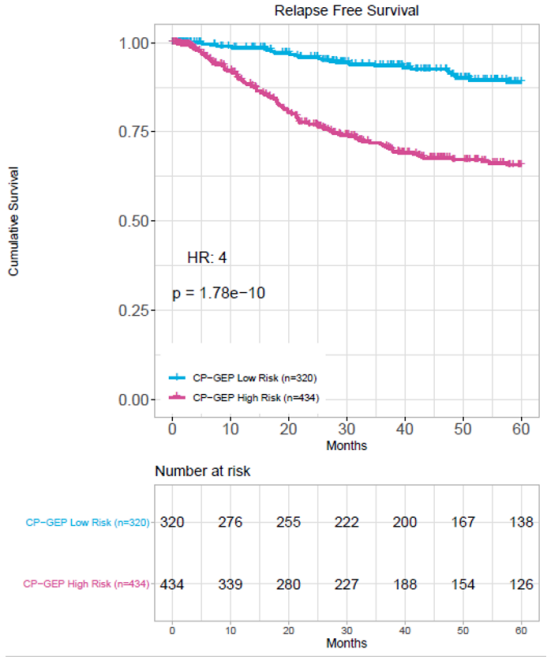
ROTTERDAM (the Netherlands), SAN DIEGO (CA, USA), September 1, 2022: Today, SkylineDx,



Discovery cohort (Mayo): Bellomo et al., Merlin Performance per T-stage

T-stage	N	SLNB pos rate	PPV	NPV	SLNB_RR	LRisk	HRisk	SLNB pos rate HRisk	SLNB pos rate LRisk
T1a	8	0	0	100	87.5	7	1	0,0%	0,0%
T1b	184	3.3	9.1	98	82.1	151	33	9.1%	2,0%
T2a	290	13.1	20.6	95.6	46.6	135	155	20.6%	4,4%
T2b	66	16.7	21.6	100	22.7	15	51	21.6%	0,0%
T3a	124	31.5	32.8	87.5	6.5	8	116	32.8%	12,5%
T3b	79	43	44.7	100	3.8	3	76	44.7%	0,0%
T4a	1	0	NA	100	100	1	0	0,0%	0,0%
T4b	0					0			
T1	192	3.1	8.8	98.1	82.3	158	34	8.8%	1,9%
T2	357	13.7	20.8	96	42	150	207	20.8%	4,0%
T3	204	35.8	37.3	90.9	5.4	11	193	37.3%	9,1%
T4	1	0	NA	100	100	1	0	0,0%	0,0%

Complete cohort RFS 5 years (Mayo)



Total cohort size: 754

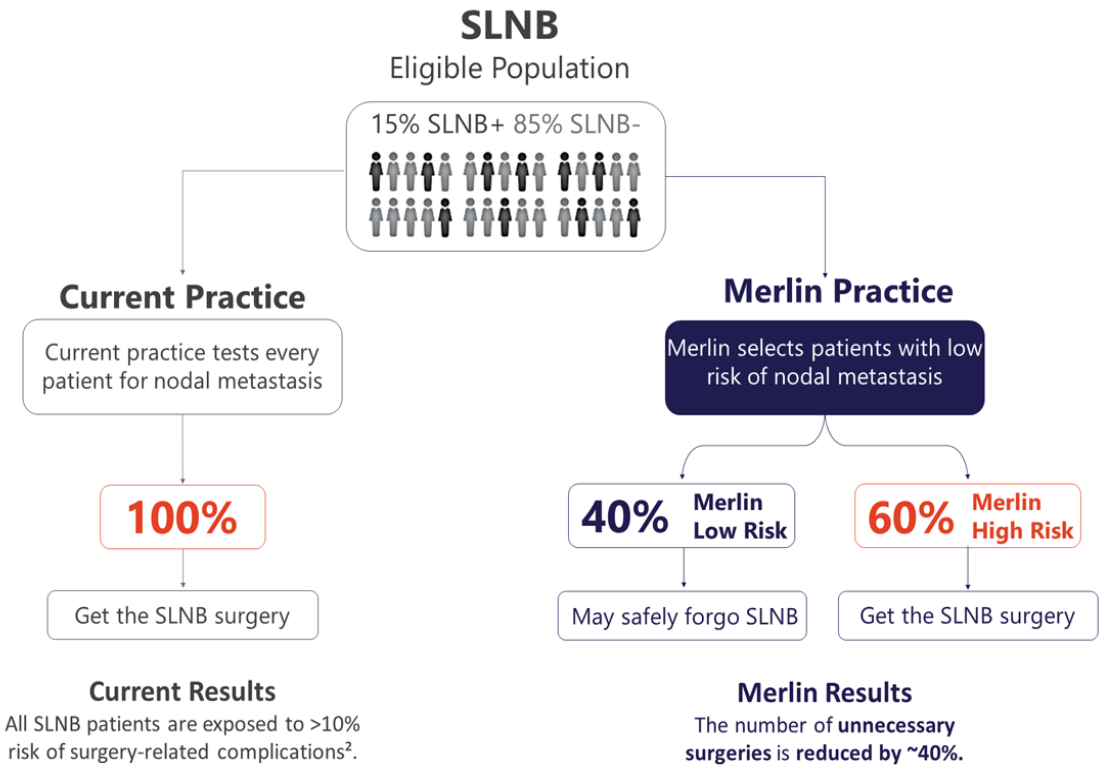
5-year follow-up data

Very significant difference between low- vs high-risk patient group in terms of RFS

Group	N	# events RFS	5-years RFS	95% CI RFS
Complete Cohort	754	141	75,7	[71.9-79.1]
CP-GEP Low Risk	320	26	**88,8**	[83.8-92.3]
CP-GEP High Risk	434	115	**65,8**	[60.2-70.7]

GEP: the Merlin™ test

- Initially developed to identify a low-risk group for nodal dissemination, allowing about 40% of patients to forego sentinel lymph node biopsy



- Prognostic value, complemenary to SLNB

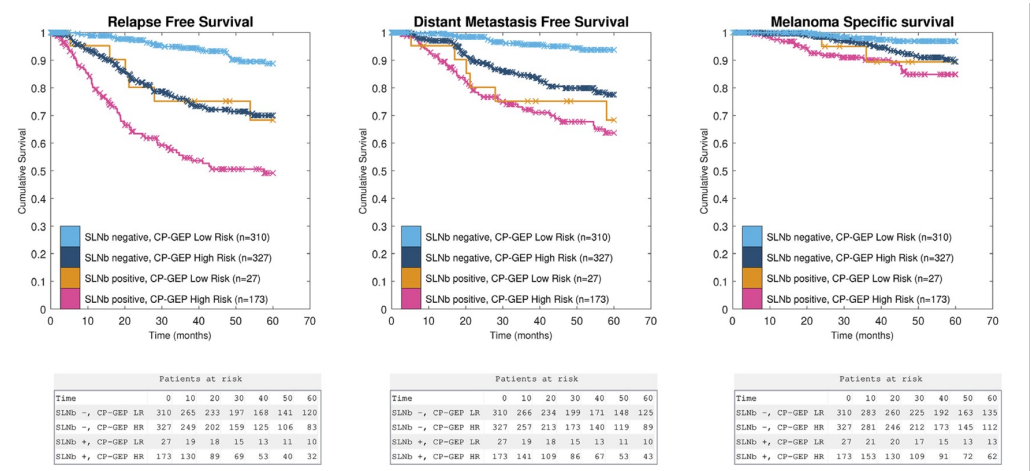


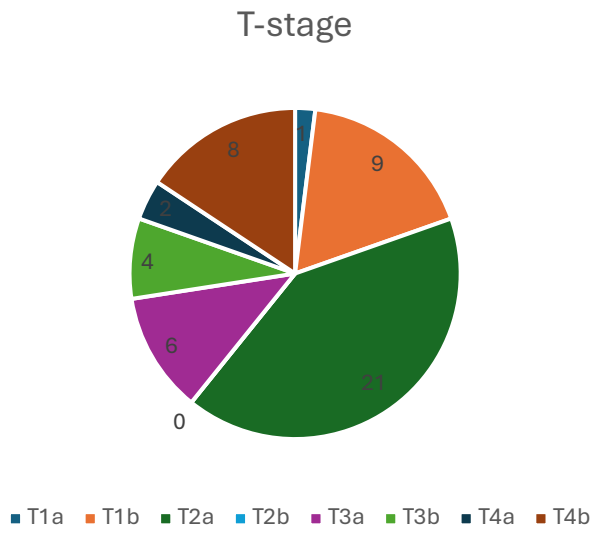
Fig. 1. **Kaplan–Meier analysis of the entire 837 cohort, stratification by SLNb status and CP-GEP classification.** Survival end-points were relapse-free survival (RFS), distant metastasis–free survival (DMFS) and melanoma-specific survival (MSS) at five-years of follow-up. SLNb negative, CP-GEP Low Risk (light blue curve); SLNb negative, CP-GEP High Risk (dark blue curve); SLNb positive, CP-GEP Low Risk (orange curve); SLNb positive, CP-GEP High Risk (magenta curve). CP-GEP, a model that combines clinicopathologic and gene expression variables; HR, High Risk; LR, Low Risk; SLNb, sentinel lymph node biopsy.

Eggermont et al. European Journal of Cancer 2020

Bellomo D, Arias-Mejias S, Ramana C, et al. A model combining tumor molecular and clinicopathologic risk factors predicts sentinel lymph node metastasis in primary cutaneous melanoma. JCO Precis Oncol. 2020:DOI 10.1200/PO.19.00206.

RetroSenti results (CP-GEP/Idylla)

- N = 51; retrospectively identified
  - Primary melanoma and SLN available at UZ Brussel
- 53% male, 47% female
- Average Breslow index: 2,49 mm
- Mean age at diagnosis: 65 yo
- **Informative test result for all samples**



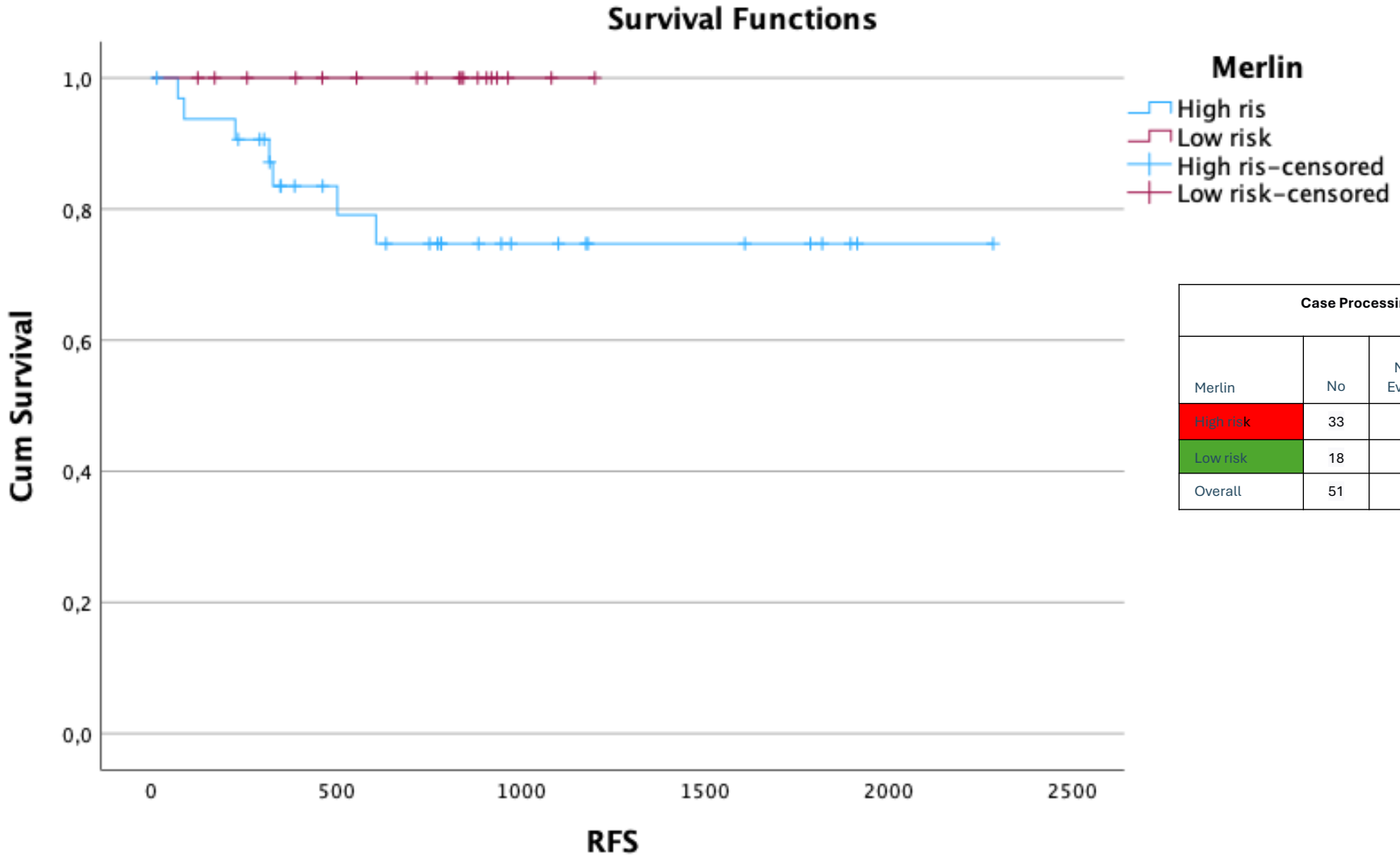
T-stage distribution

Sentinel positivity

	T1a		T1b		T2a		T2b		T3a		T3b		T4a		T4b	
	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR	LR	HR
Sn neg	1	0	5	3	10	10	0	0	0	6	1	2	0	1	0	4
Sn pos	0	0	1	0	0	1	0	0	0	0	0	1	0	1	0	4

RFS +16 months

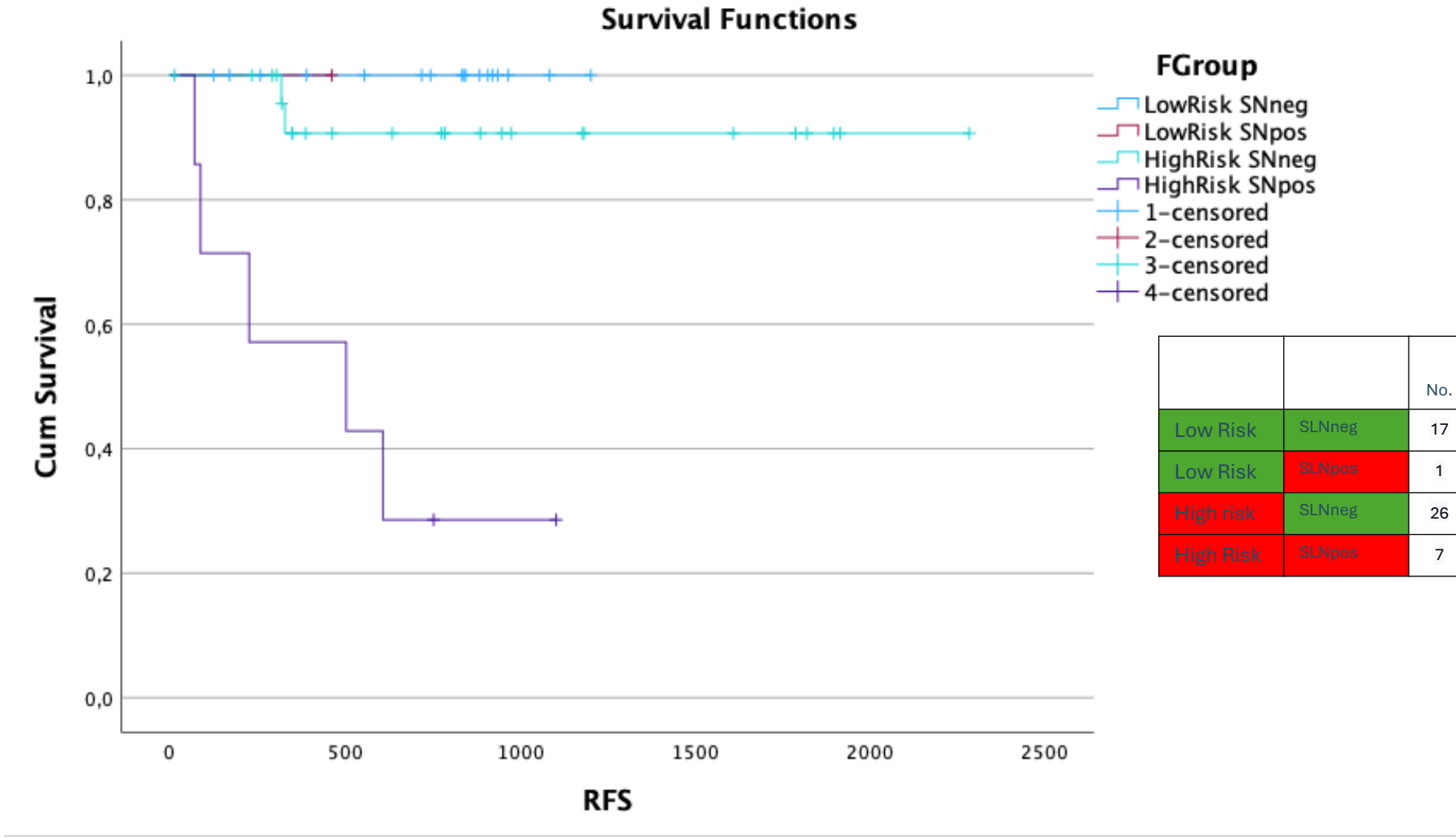
RetroSenti results (Idylla)



Case Processing Summary

Merlin	No	N of Events	Censored	
			N	%
High risk	33	7	26	79
Low risk	18	0	18	100
Overall	51	7	44	86

RetroSenti results (Idylla)



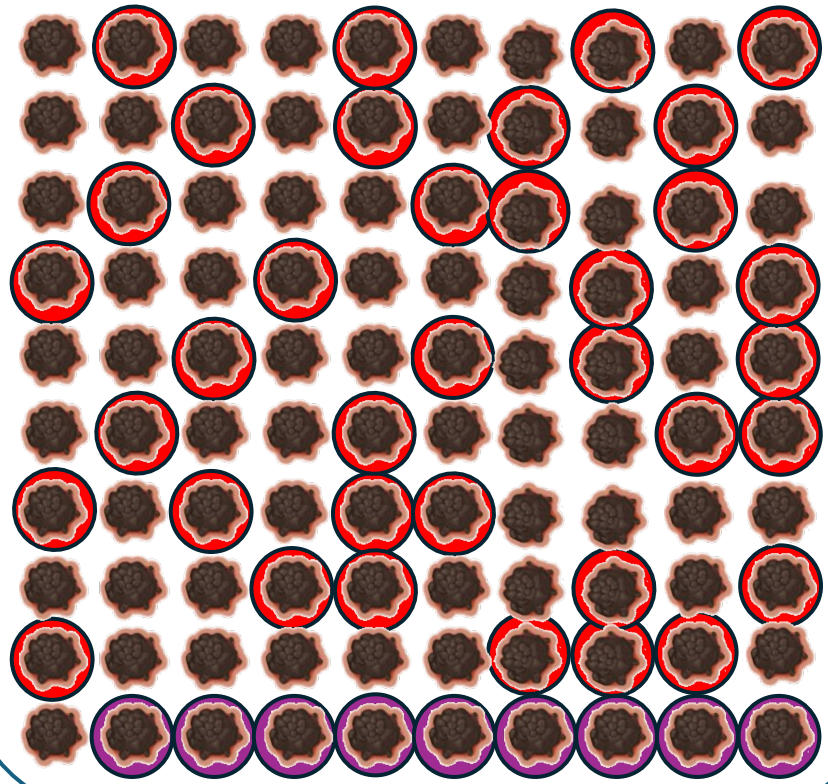
		No.	N of Events	Censored	
				N	%
Low Risk	SLNneg	17	0	17	100
Low Risk	SLNpos	1	0	1	100
High risk	SLNneg	26	2	24	92
High Risk	SLNpos	7	5	2	29

Diagnosis

pT1b-4b
cN0M0

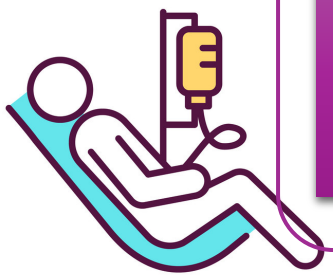
Merlin™ GEP

pT3b-4b pT1b-3a Merlin™ high risk



Pembrolizumab 400 mg iv

pT3b-4b *OR*
pT1b-3a with poor prognosis
Merlin™ GEP

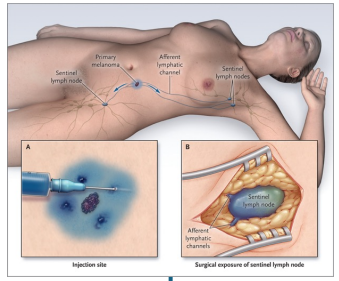


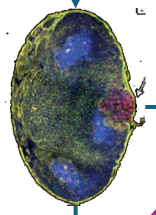
N = 49

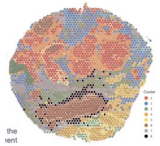
6 Weeks

Expected = 30%
Positive trial = ≤15%

Sentinel Lymph Node Procedure







Spatial Biology

Adjuvant Therapy

Observation

pT1b-3a
N(sn)0cM0

pT3b-4b
N(sn)0cM0

BRAF V600

WT

MUT

Acknowledgements

ACKNOWLEDGMENTS

Patients, their families & caregivers

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Kom op tegen Kanker

Stichting tegen Kanker

fwo

#LIVE FOR BETTER DAYS VZW

Thank you for your attention!