UNIVERSITÀ CATTOLICA del Sacro Cuore

Dermatology and Venereology
Catholic University
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, *Rome Italy*

Melanoma in adiuvante e metastatico

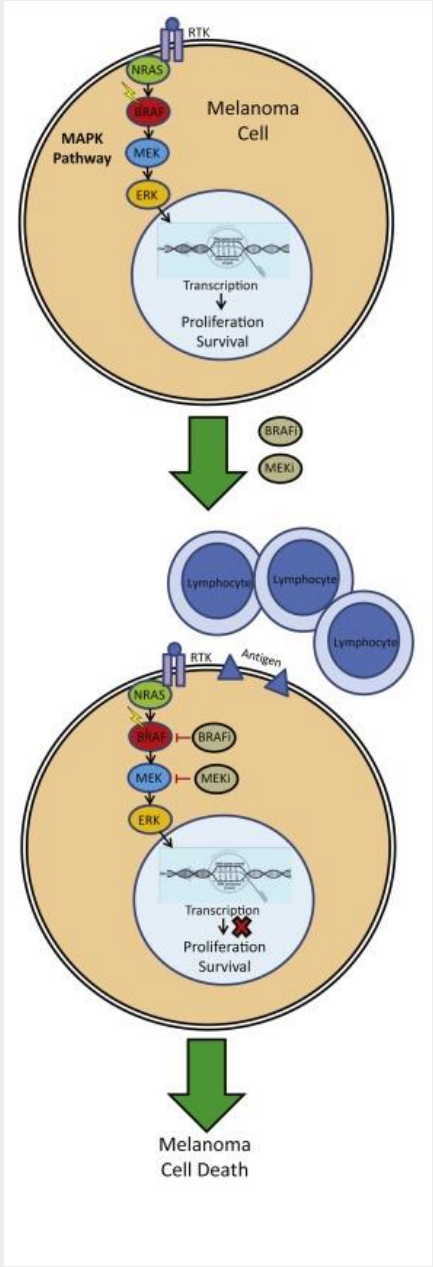
Ketty Peris

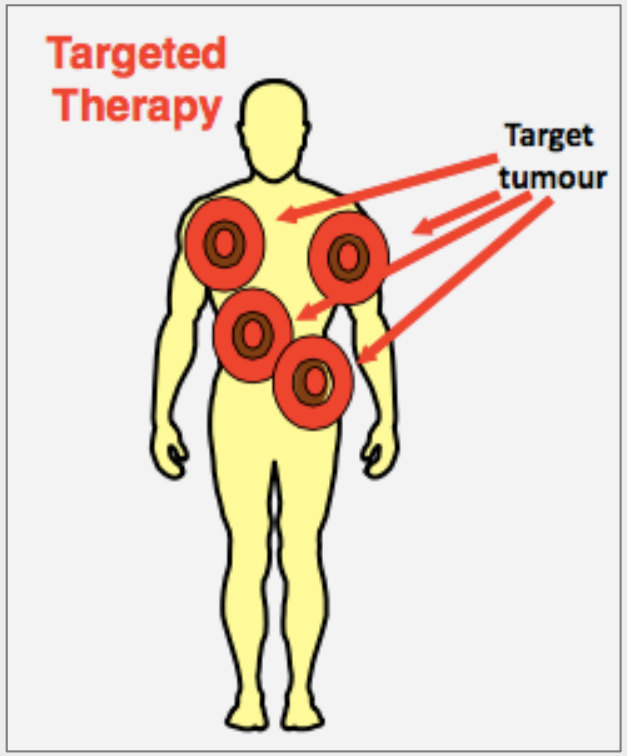
ketty.peris@unicatt.it

Conflict of interest

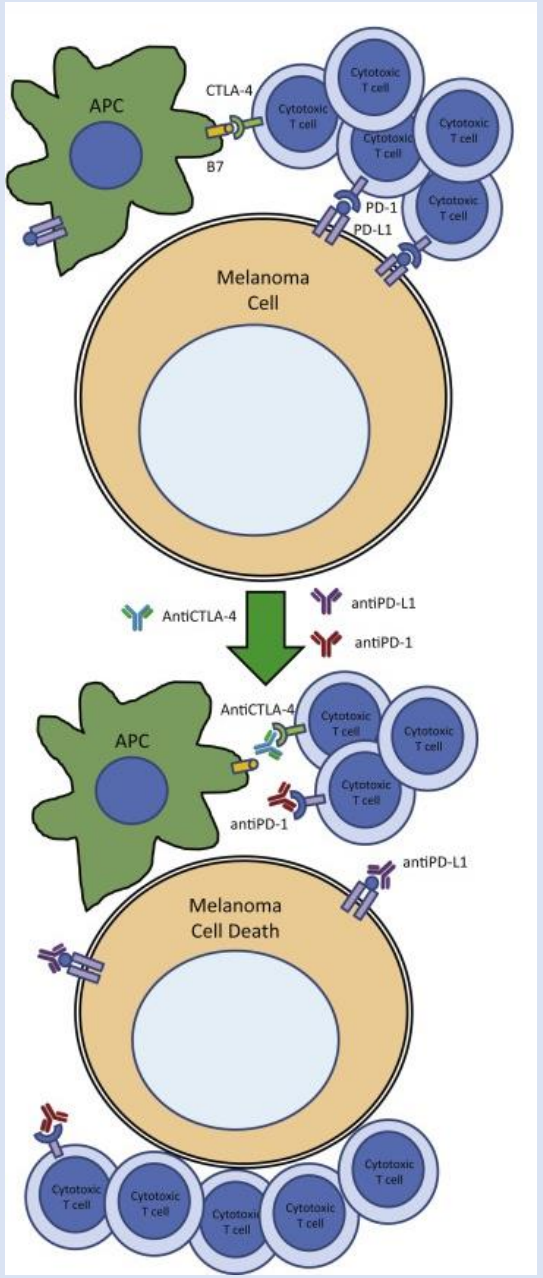
- ABBVIE
- ALLMIRAL
- GALDERMA
- LEO PHARMA
- LILLY
- PIERRE FABRE
- NOVARTIS
- SANOFI
- SUN PHARMA
- JANSSEN

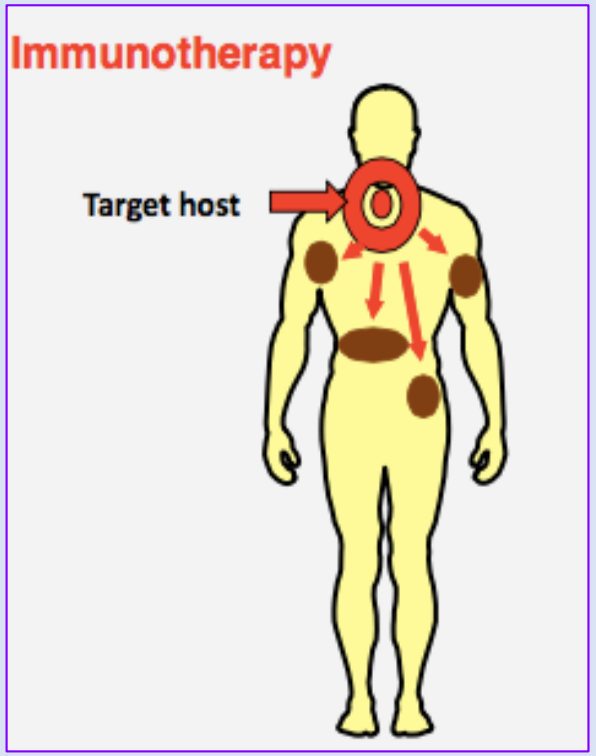
TARGET THERAPY TARGETS THE TUMOR



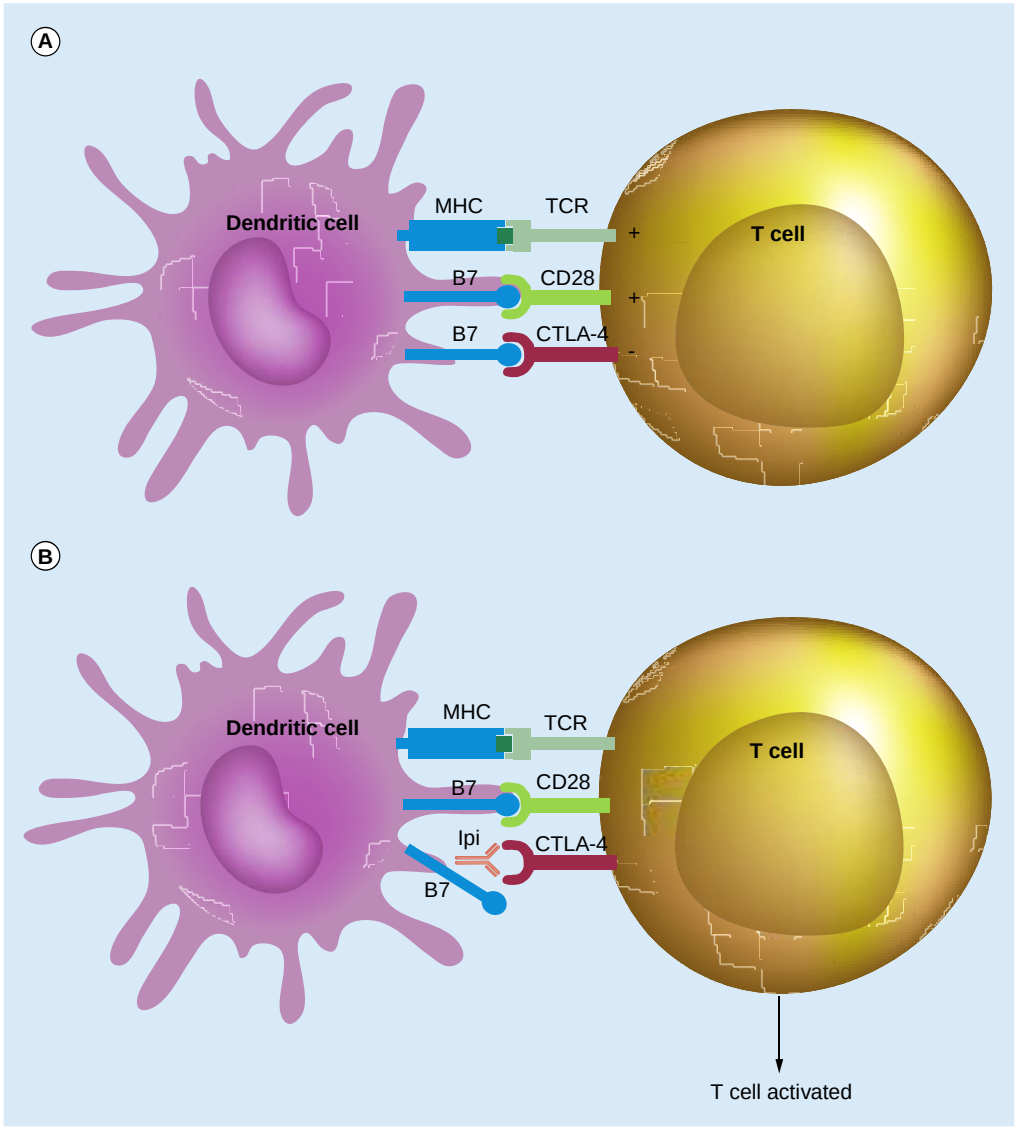


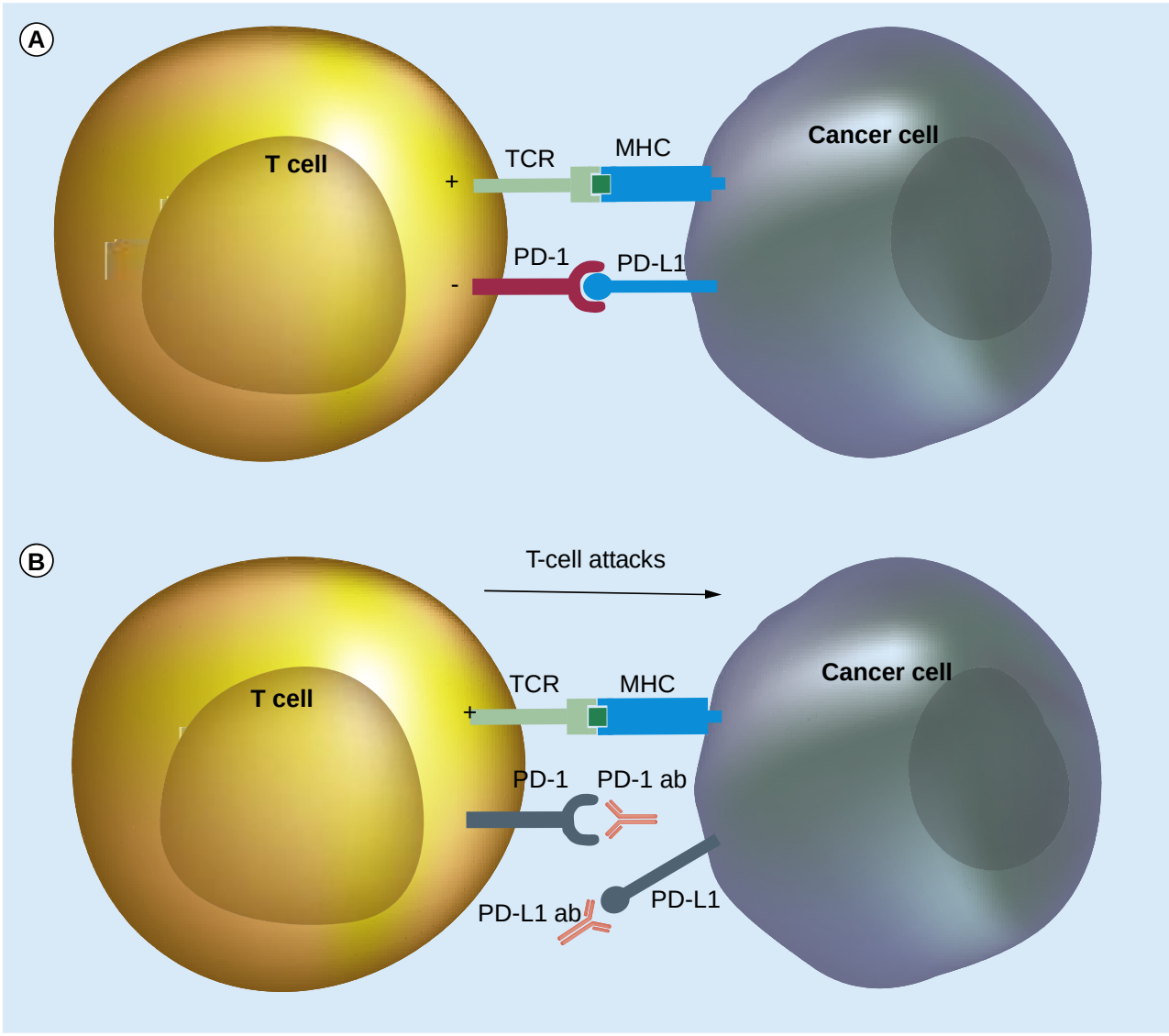
IMMUNOTHERAPY TARGETS THE HOST



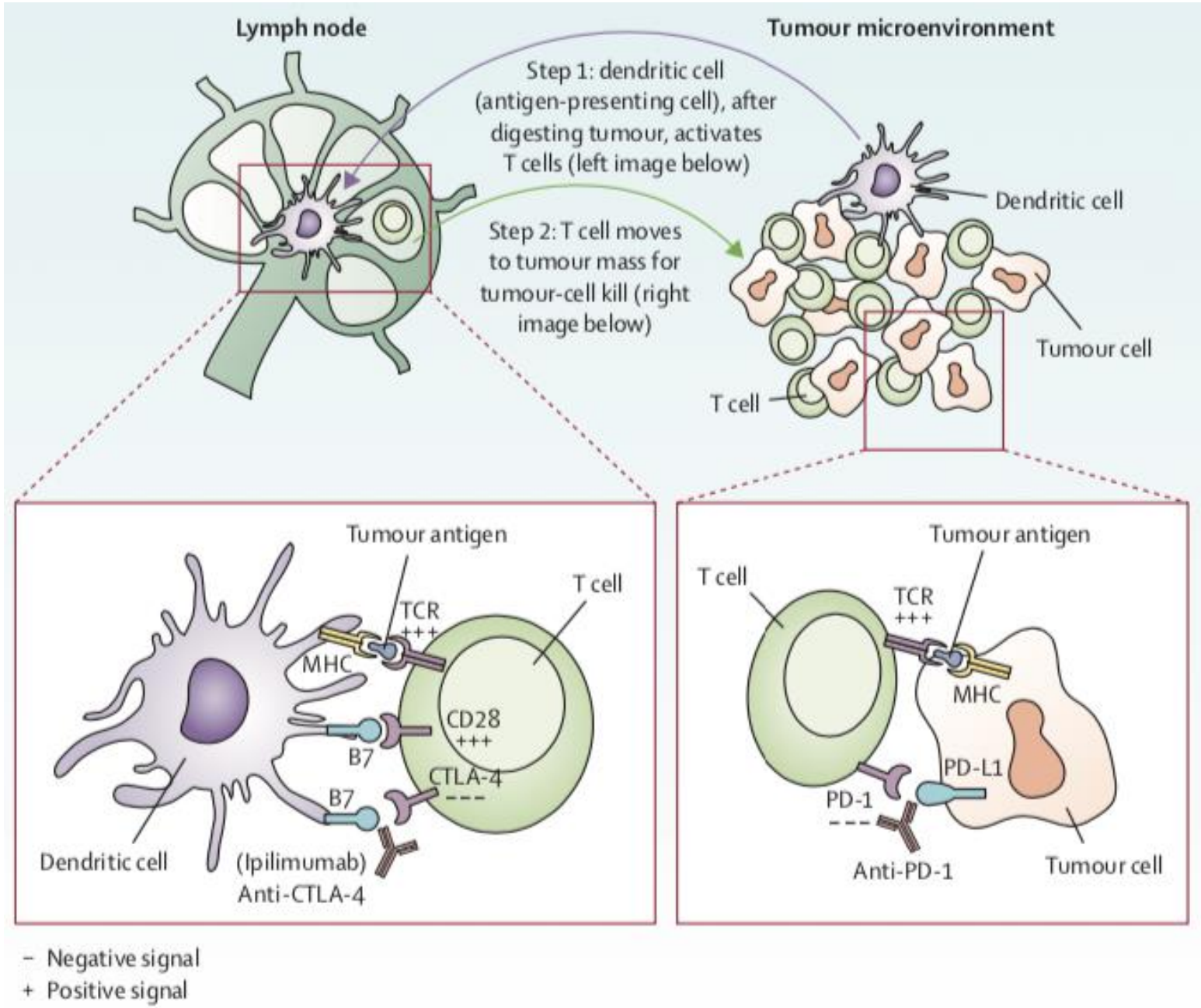


Anti-CTLA4 (ipilimumab) and anti-PD1 (nivolumab, pembrolizumab) antibodies target distinct immune checkpoint pathways

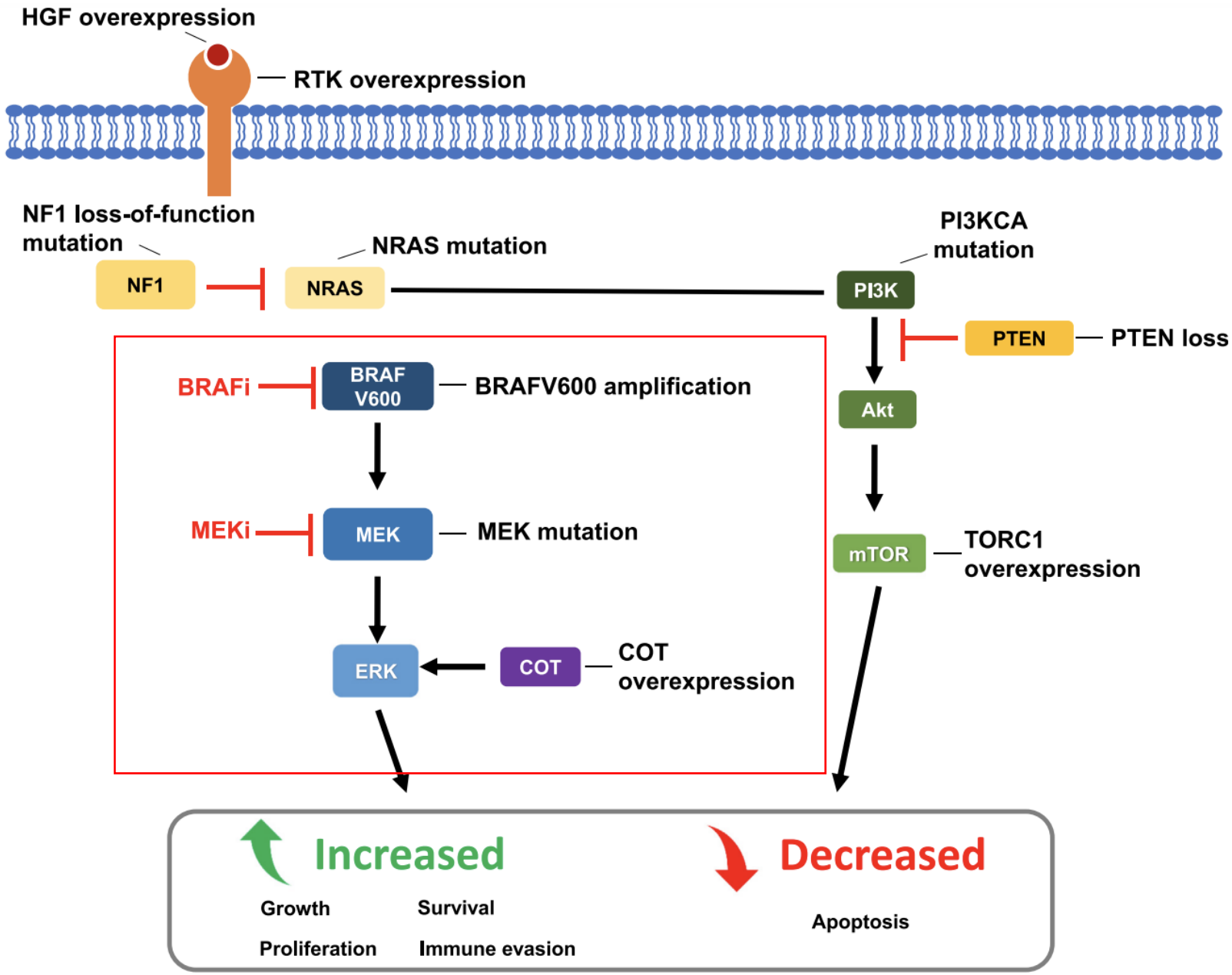




T-cell activation by anti-CTLA4 and anti-PD1



Oncogenic BFRA signalling pathway ans alternative pathways with downstream activity



Subbiah V, 2023

Immunotherapy

Anti-CTLA4

IPILIMUMAB

- Approved by FDA for patients stage IIIA (with LN metastasis > 1mm); stage IIIB and IIIC
- 10 mg/kg given every 3 weeks for the first 12 weeks followed by an infusion every 12 weeks in patients with stage III

Anti-PD1

NIVOLUMAB

- Approved by FDA and EMA for resected stage IIB-C, III and IV (<12y)
- 240 mg flat dose i.v. every 2 weeks for 1 year

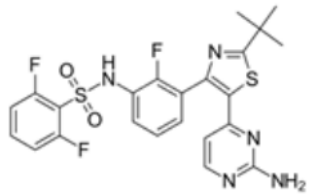
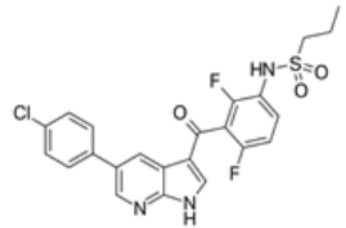
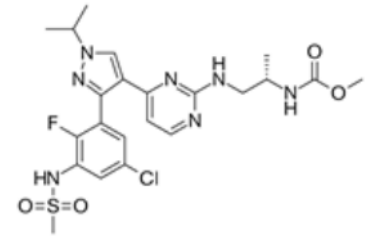
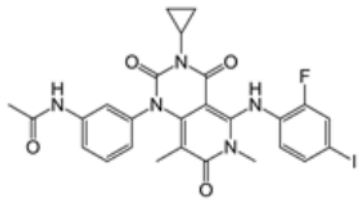
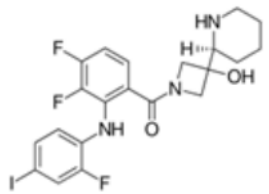
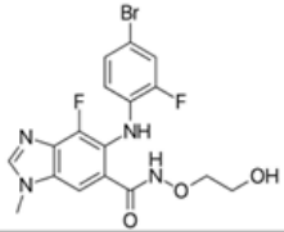
  or
- 480 mg i.v. every 4 weeks for 1 year

PEMBROLIZUMAB

- Approved by FDA and EMA for stage IIB-C/III (>12y)
- 200 mg i.v. every 3 weeks for 1 year

  or
- 400 mg i.v. every 6 weeks

Structural and pharmacokinetic properties of BRAF and MEK inhibitors

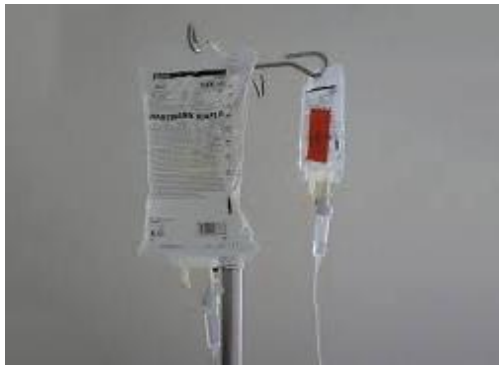
	Dabrafenib / Trametinib	Vemurafenib / Cobimetinib	Encorafenib / Binimetinib
BRAF Inhibitors **Dab.** (GSK2118436) / **Vem.** (PLX4032,RG7204) / **Enc.** (LGX818)			
	RP2D: **150 mg td** (MTD not reached) * BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.9 h** Time to steady-state ($t_{max,ss}$): **14 d** $AUC_{0-24,ss}$: **4.3 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **1478 ng/mL** (37 %CV_b) Clearance (CL/F): **17.3 L/h** (nc) Elimination half-life (t½): **8.4 h** (nc)	RP2D: **960 mg td** (=MTD) BCS class: IV (low permeability, low solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): ~**4 h** Time to steady-state ($t_{max,ss}$): **15-22 d** $AUC_{0-8,ss}$: **380.2 h*µg/mL** (38 %CV_b) $C_{max,ss}$: **56,700 ng/mL** (38 %CV_b) Clearance (CL/F): **1.2 L/h** (32 CV_b%) Elimin. half-life (t½): **56 h** [30-120]	RP2D: **300 mg od** (MTD: 450 mg od) BCS class: *nr* Food effect: None (Intake with/without food) Absorption (t_{max}): **2.0 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-24,ss}$: **12.3 h*µg/mL** (med.) $C_{max,ss}$: **3100 ng/mL** (med.) Clearance (CL/F): **24.4 L/h** (med.) Elimination half-life (t½):**6.3 h** [3.7-8.1]
MEK Inhibitors **Tra.** (GSK1210212) / **Cob.** (RG7420) / **Bin.** (MEK162)			
	RP2D: **2 mg od** (MTD: 3 mg od) BCS class: II (high permeability, low solubility) Food effect: Intake 1h prior or 2 h after meal Absorption (t_{max}): **1.5 h** Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-24,ss}$: **0.4 h*µg/mL** (22 %CV_b) $C_{max,ss}$: **22 ng/mL** (28 %CV_b) Clearance (CL/F): **5.4 L/h** (nc) Elimination half-life (t½): **90 h** [58-183]	RP2D: **60 mg od** (d1-21 q4w) (=MTD) BCS class I: (high permeability, high solubility) Food effect: none (Intake with/without food) Absorption (t_{max}): **2.4 h** Time to steady-state ($t_{max,ss}$): **10 d** $AUC_{0-24,ss}$: **4.3 h*µg/mL** (61 %CV_b) $C_{max,ss}$: **273 ng/mL** (60 CV_b%) Clearance (CL/F): **13.8 L/h** (61% CV) Elimination half-life (t½): **44 h** [23-69]	RP2D: **45 mg td** (MTD: 60 mg td) BCS class: *nr* Food effect: none (Intake with/without food) Absorption (t_{max}): **2.0 h** (1.5 h at 60 mg td) Time to steady-state ($t_{max,ss}$): **15 d** $AUC_{0-8,ss}$: **1.5 h*µg/mL** (nc) $C_{max,ss}$: **273 ng/mL** (65 %CV_b) Clearance (CL/F): *nr* Elimination half-life (t½): **8.7 h** (nc)

* no-dose-limiting toxicity recorded at 300 mg td

AR, accumulatiomn rate; AUC 0-24, area under the curve for 0-24h (AUC 0-8; 0-8h); BCS biopharmaceutics classification system; Cmax, maximum concentration; C 24, concentration after 24 h; d, days; h, hours; MTD, maximun tolerated dose; od, once daily; RP2D, recommended phase 2 dose; t ½ eff, effective hal-life calculated as -0.693*tau/(ln[1-(1/AR)]; td, twice daily; t max, time taken to reach maximum concentration reported as median. In brackets: (%CVb), between-subject coefficient of variation; (nc), not calculated; (nr), not reported; […], range. All reported values are means, if not indicated otherwise (i.e., median).

Adjuvant Therapy

Surgery → Adjuvant Therapy



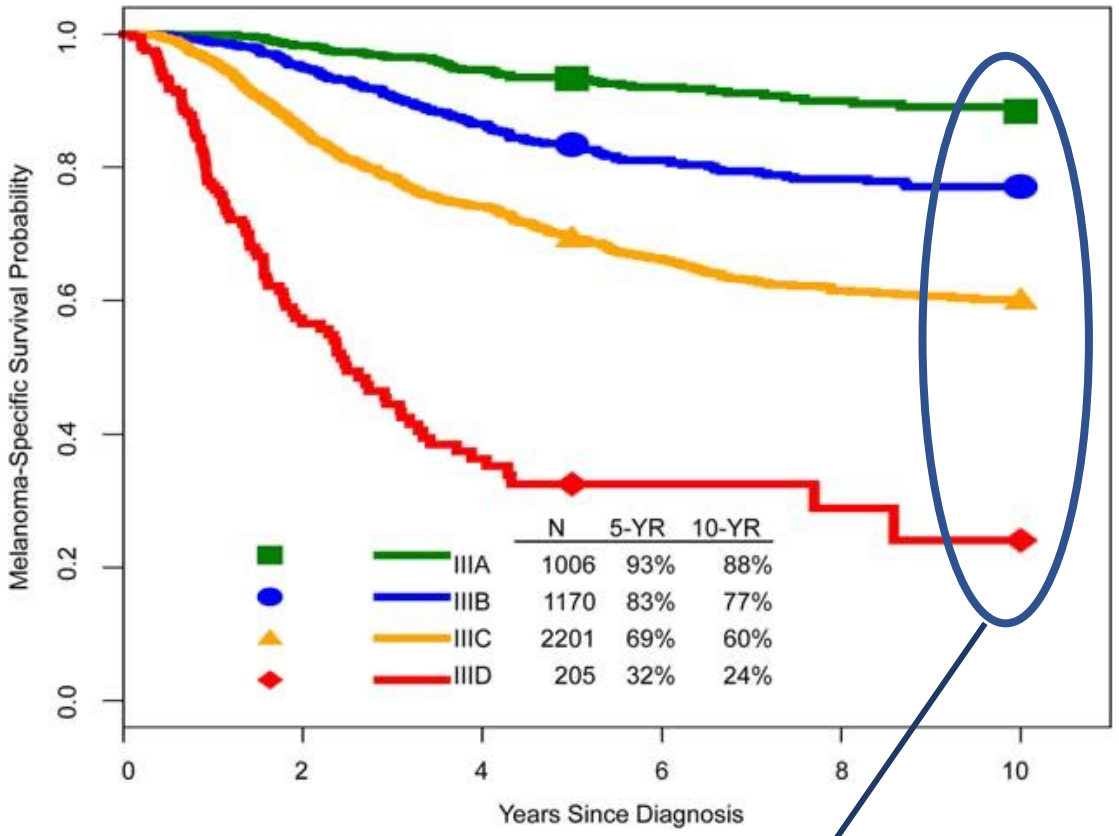
- The aims are: to target the residual micro-metastatic disease, reduce the risk of melanoma relapse, reduce the risk of death from melanoma
- Adjuvant therapy should be offered to patients with **high risk of recurrence but no evidence of macroscopic metastases**
- Adjuvant therapy improves the effect of the primary treatment
- Balance efficacy with safety in the effort to avoid exposing patients to an unnecessary risk of toxicity

Garbe C et al. EJC 2022; https://www.cancer.gov/publications/dictionaries/cancer-terms

AJCC v8

WHEN T IS...	AND N IS...	AND M IS...	THEN THE PATHOLOGICAL STAGE GROUP IS...
Tis	N0[b]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Melanoma-Specific Survival Curves According to ***Stage III*** Subgroups (AJCC v8)



Patients with resected stage III-IV have a high risk of recurrence and relatively poor survival

Gershenwald JE et al. CA CANCER J CLIN 2017

Adjuvant therapy

European Journal of Cancer 170 (2022) 256–284

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022

Claus Garbe [a,*], Teresa Amaral [a], Ketty Peris [b,c], Axel Hauschild [d], Petr Arenberger [e], Nicole Basset-Seguin [f], Lars Bastholt [g], Veronique Bataille [h], Veronique del Marmol [i], Brigitte Dréno [j], Maria C. Fargnoli [k], Ana-Maria Forsea [l], Jean-Jacques Grob [m], Christoph Hoeller [n], Roland Kaufmann [o], Nicole Kelleners-Smeets [p], Aimilios Lallas [q], Celeste Lebbé [f], Bodhan Lytvynenko [r], Josep Malvehy [s], David Moreno-Ramirez [t], Paul Nathan [u], Giovanni Pellacani [v], Philippe Saiag [w], Alexander J. Stratigos [x], Alexander C.J. Van Akkooi [y], Ricardo Vieira [z], Iris Zalaudek [aa], Paul Lorigan [ab] On behalf of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC)

Recommendation 21

Adjuvant therapy in stage III/IV	Evidence-based recommendation
Level of recommendation A	Adjuvant therapy (anti-PD-1 or targeted therapy) shall be offered to all patients in resected stages IIIA – IIID. * Adjuvant anti-PD-1 therapy shall be offered to patients in resected stages IIIA - IIID irrespective of the mutational status. * Adjuvant BRAF/MEK inhibitor therapy shall be offered to patients with BRAFV600 E/K mutation in resected stages IIIA – IIID. * For fully resected stage IV melanoma patients, nivolumab can be offered regardless of mutation status.
Level of evidence: 1 b	De novo literature research [76,77,98] Consensus rate: 100%

Recommendation 22

Adjuvant therapy in stage III/IV	Evidence-based recommendation
Level of recommendation B	* For stage IIIA with nodal metastasis of less than 1 mm in diameter, the uncertainty of the individual risk/benefit ratio should be carefully discussed with the patients.
Level of evidence: 1 b	De novo literature research [76,77,98] Consensus rate: 100%

European Journal of Cancer 119 (2019) 1–10

Available online at www.sciencedirect.com

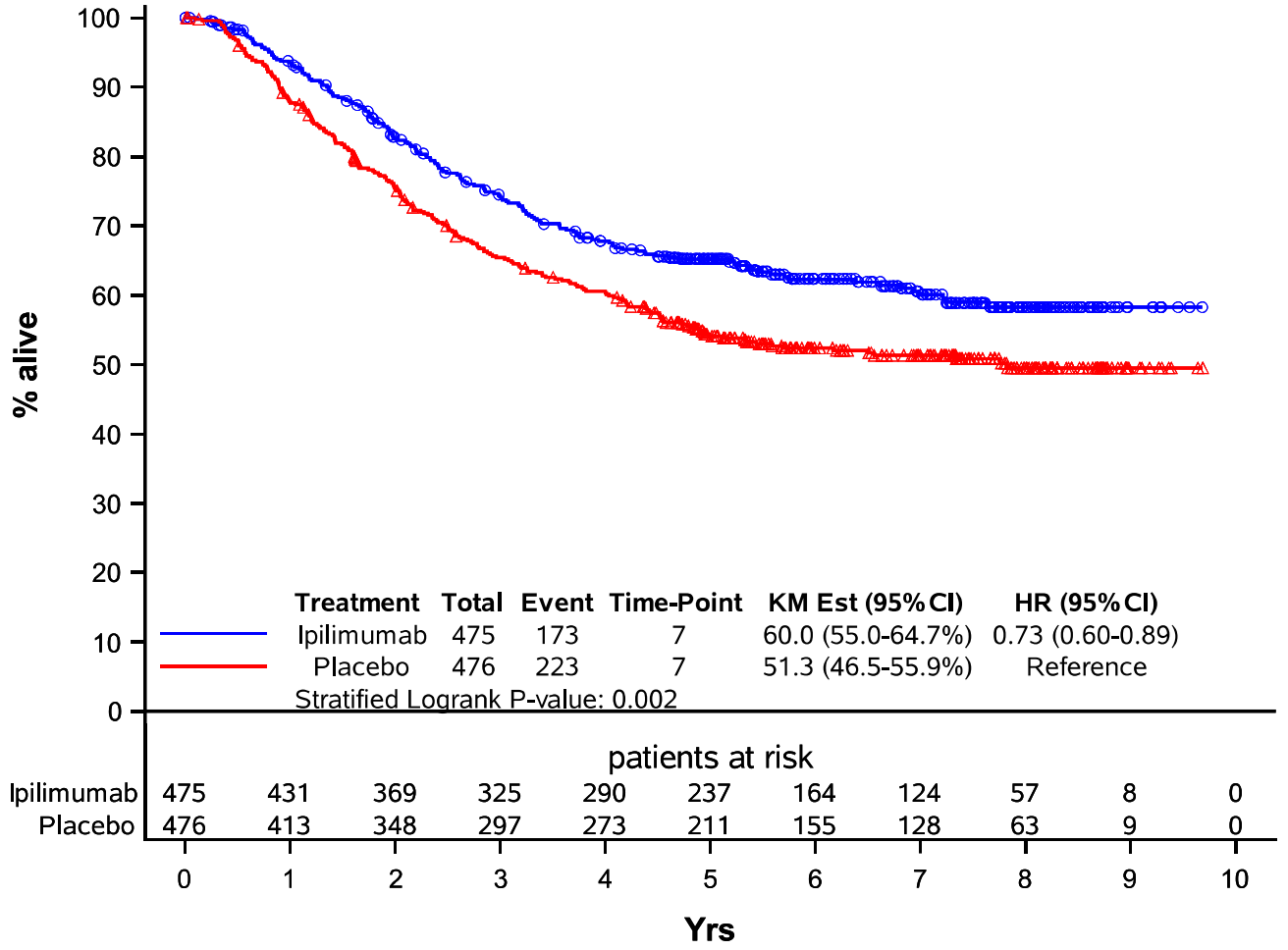
ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial

Alexander M.M. Eggermont [a,*], Vanna Chiarion-Sileni [b], Jean-Jacques Grob [c], Reinhard Dummer [d], Jedd D. Wolchok [e], Henrik Schmidt [f], Omid Hamid [g], Caroline Robert [h], Paolo Antonio Ascierto [i], Jon M. Richards [j], Celeste Lebbe [k], Virginia Ferraresi [l], Michael Smylie [m], Jeffrey S. Weber [n], Michele Maio [o], Fareeda Hosein [p], Veerle de Pril [q], Michal Kicinski [r], Stefan Suciu [r,1], Alessandro Testori [s,1]



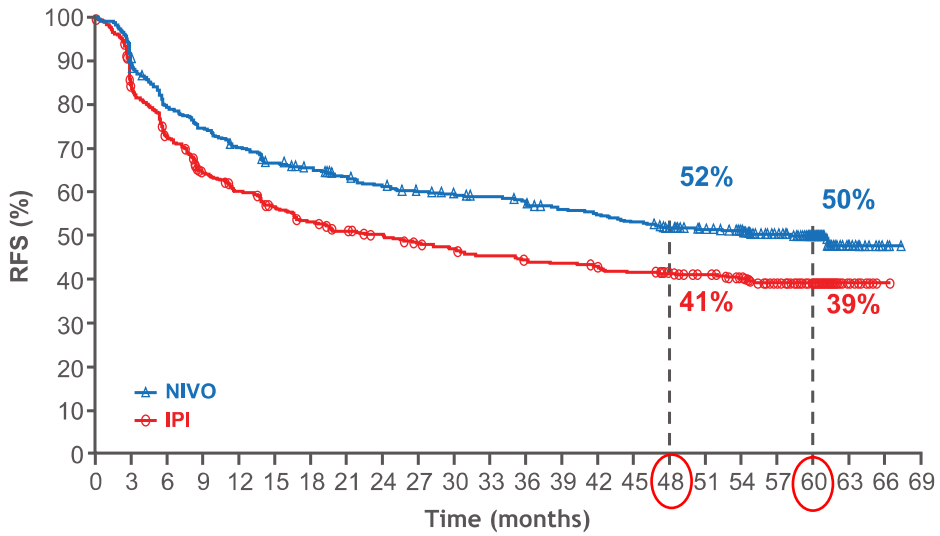
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III/IV Melanoma: 5-Year Efficacy and Biomarker Results from CheckMate 238

James Larkin[1], Michele Del Vecchio[2], Mario Mandalá[3], Helen Gogas[4], Ana M. Arance Fernandez[5], Stéphane Dalle[6], Charles Lance Cowey[7], Michael Schenker[8], Jean-Jacques Grob[9], Vanna Chiarion-Sileni[10], Ivan Marquez-Rodas[11], Marcus O. Butler[12], Anna Maria Di Giacomo[13], Mark R. Middleton[14], Jose Lutzky[15], Luis de la Cruz-Merino[16], Petr Arenberger[17], Victoria Atkinson[18], Andrew G. Hill[19], Leslie A. Fecher[20], Michael Millward[21], Paul D. Nathan[22], Nikhil I. Khushalani[23], Paola Queirolo[24], Corey Ritchings[25], Maurice Lobo[25], Margarita Askelson[25], Hao Tang[25], Sonia Dolfi[25], Paolo A. Ascierto[26], and Jeffrey Weber[27]

Clin Cancer Res; 29(17) September 1, 2023

At **5 years' follow-up**, nivolumab demonstrated sustained ***recurrence-free survival*** benefit versus IPI

	NIVO (*n* = 453)	IPI (*n* = 453)
Events, *n*	218	257
Median, mo (95% CI)	61.0 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)	0.72 (0.60–0.86)	

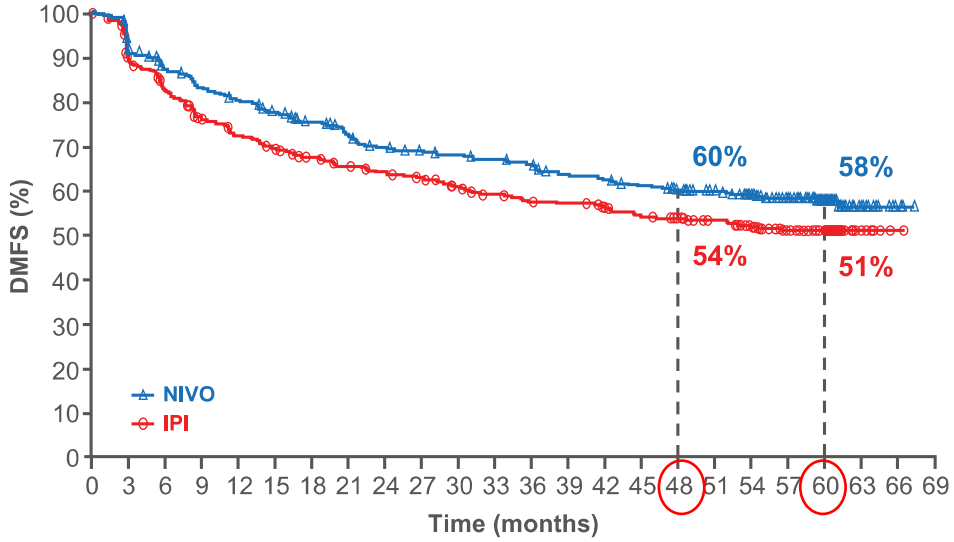


No. at risk

NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	234	225	220	213	202	191	176	147	94	17	4	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	178	173	170	165	159	152	145	134	114	78	18	1	0

Distant metastasis-free survival

	NIVO (*n* = 370)	IPI (*n* = 366)
Events, *n*	146	164
Median, mo (95% CI)	NR	NR (42.4–NR)
HR (95% CI)	0.79 (0.63–0.99)	



No. at risk

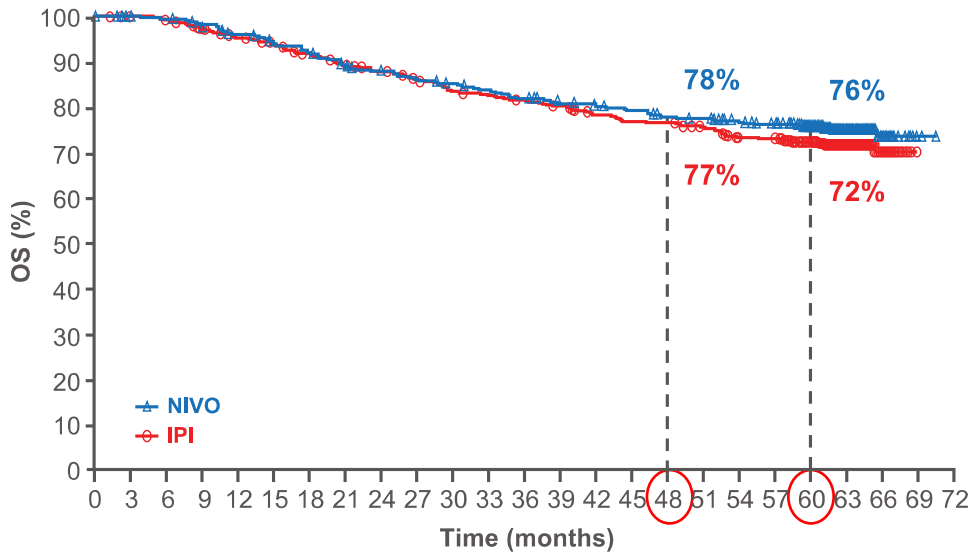
NIVO 3 mg/kg	370	334	312	295	284	272	256	243	232	223	220	216	210	200	197	191	182	172	156	130	87	20	4	0
IPI 10 mg/kg	366	314	287	257	244	233	222	213	206	200	188	180	173	171	163	156	150	139	130	111	76	17	2	0

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III/IV Melanoma: 5-Year Efficacy and Biomarker Results from CheckMate 238

James Larkin[1], Michele Del Vecchio[2], Mario Mandalá[3], Helen Gogas[4], Ana M. Arance Fernandez[5], Stéphane Dalle[6], Charles Lance Cowey[7], Michael Schenker[8], Jean-Jacques Grob[9], Vanna Chiarion-Sileni[10], Ivan Marquez-Rodas[11], Marcus O. Butler[12], Anna Maria Di Giacomo[13], Mark R. Middleton[14], Jose Lutzky[15], Luis de la Cruz-Merino[16], Petr Arenberger[17], Victoria Atkinson[18], Andrew G. Hill[19], Leslie A. Fecher[20], Michael Millward[21], Paul D. Nathan[22], Nikhil I. Khushalani[23], Paola Queirolo[24], Corey Ritchings[25], Maurice Lobo[25], Margarita Askelson[25], Hao Tang[25], Sonia Dolfi[25], Paolo A. Ascierto[26], and Jeffrey Weber[27]

Clin Cancer Res; 29(17) September 1, 2023

Overall survival	NIVO (*n* = 453)	IPI (*n* = 453)
Events, *n*	108	120
Median, mo (95% CI)	NR	NR
HR (95% CI)	0.86 (0.66–1.12)	



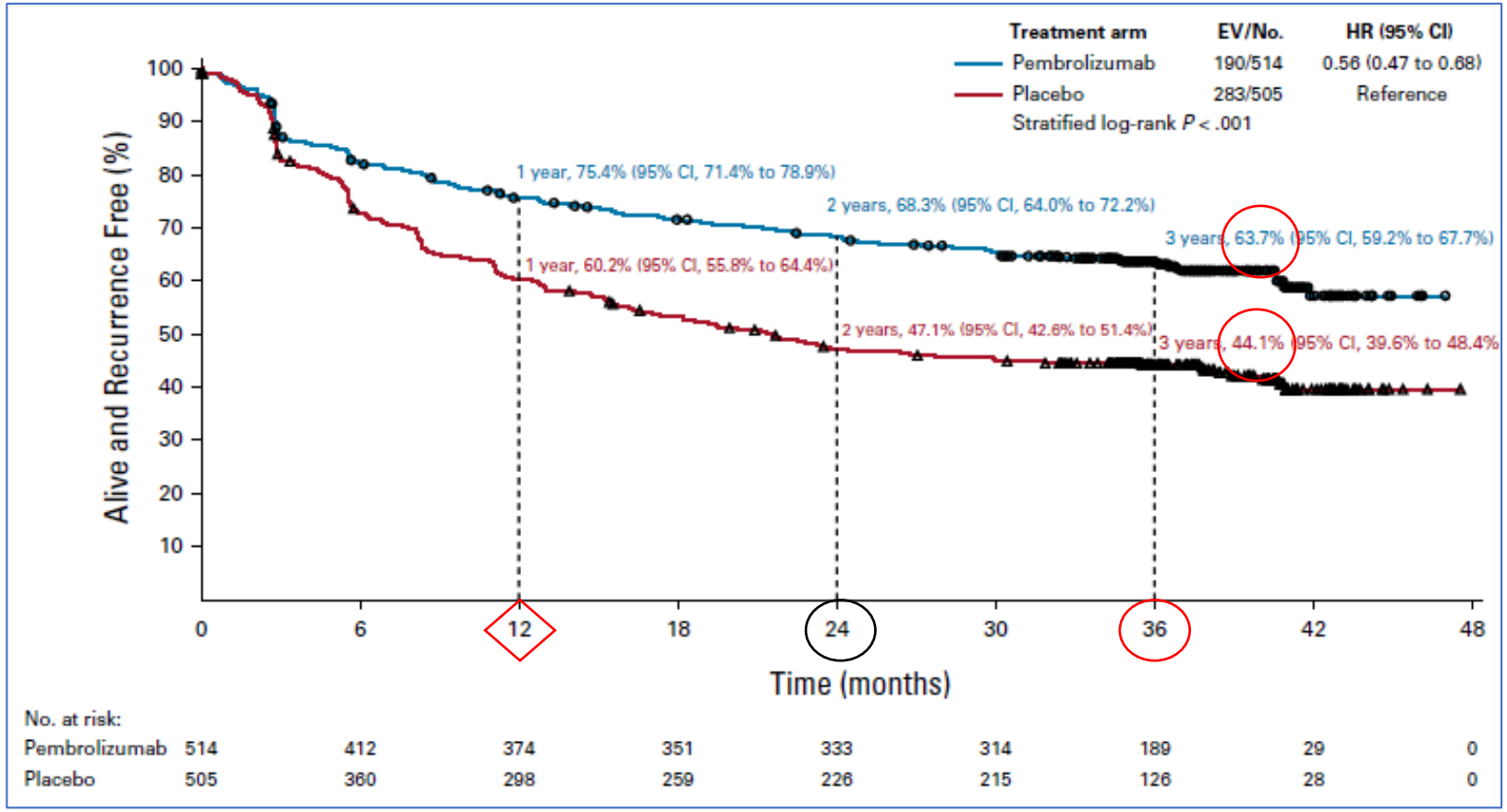
No. at risk

NIVO 3 mg/kg	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	321	312	305	280	178	42	3	0
IPI 10 mg/kg	453	447	442	430	416	407	395	382	373	362	350	345	340	333	322	316	315	306	294	292	261	155	36	0	0

Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial

Alexander M. M. Eggermont, MD, PhD[1]; Christian U. Blank, MD, PhD[2]; Mario Mandala, MD[3]; Georgina V. Long, BSc, MBBS[4]; Victoria G. Atkinson, MBBS[5]; Stéphane Dalle, MD, PhD[6]; Andrew M. Haydon, MBBS, PhD[7]; Andrey Meshcheryakov, MD, PhD[8]; Adnan Khattak, MD[9]; Matteo S. Carlino, BMedSc, MBBS[10]; Shahneen Sandhu, MD[11]; James Larkin, PhD[12]; Susana Puig, MD, PhD[13]; Paolo A. Ascierto, MD[14]; Piotr Rutkowski, MD, PhD[15]; Dirk Schadendorf, MD, PhD[16,17]; Rutger Koornstra, MD, PhD[18]; Leonel Hernandez-Aya, MD[19]; Anna Maria Di Giacomo, MD[20]; Alfonsus J. M. van den Eertwegh, MD, PhD[21]; Jean-Jacques Grob, MD[22]; Ralf Gutzmer, MD[23]; Rahima Jamal, MD, BSc[24]; Paul C. Lorigan, MD[25]; Alexander C. J. van Akkooi, MD, PhD[2]; Clemens Krepler, MD[26]; Nageatte Ibrahim, MD[26]; Sandrine Marreaud, MD[27]; Michal Kicinski, PhD[27]; Stefan Suciu, PhD[27]; and Caroline Robert, MD, PhD[28]

J Clin Oncol 2020



- 1091 pts
- Pembro 200mg Q3 vs Pbo for approximately 1 year or until disease recurrence or unacceptable toxicity
- Primary endpoint: RFS

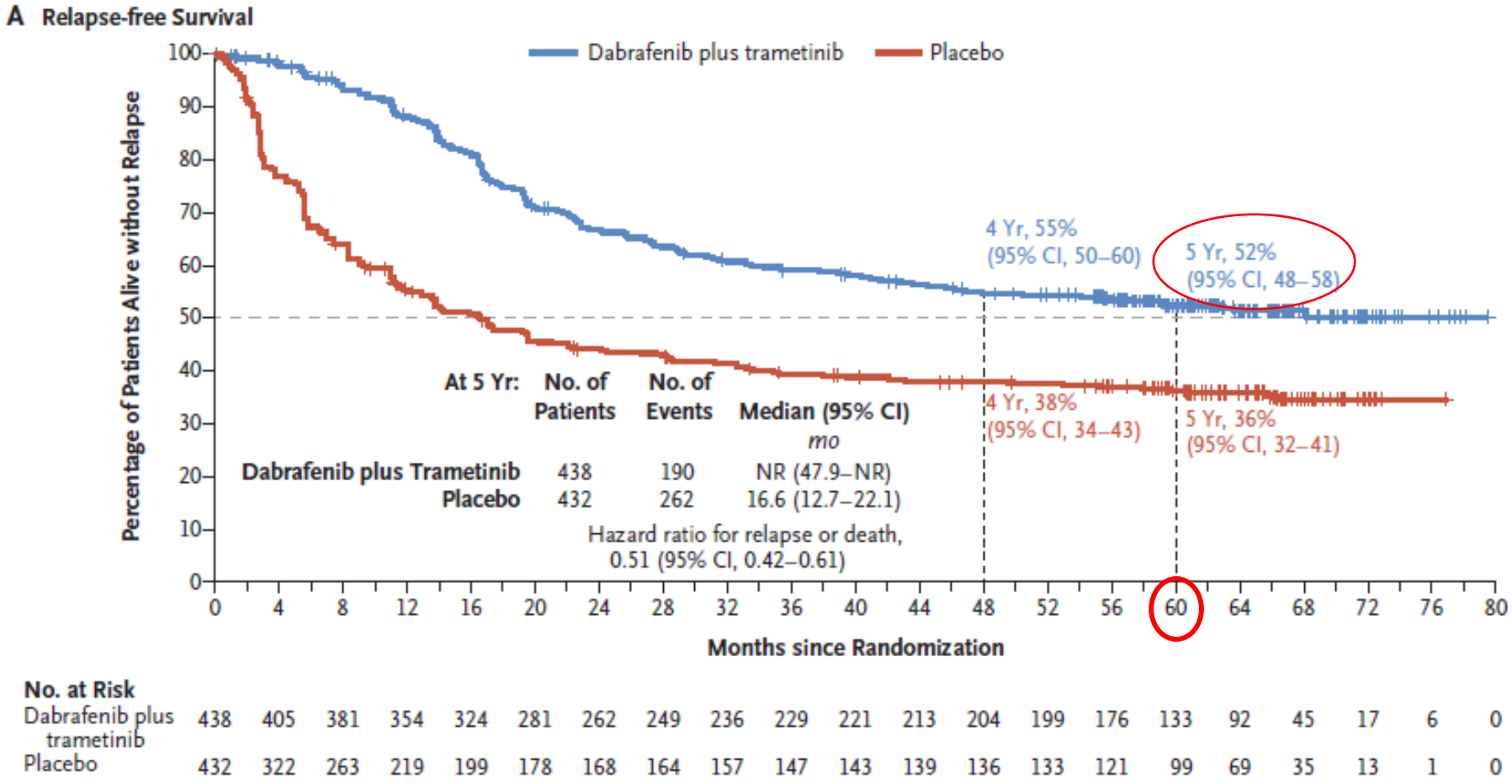
In resected high-risk stage III melanoma, pembrolizumab adjuvant therapy provided a sustained and clinically meaningful improvement in RFS at **3-year median follow-up**

Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma

R. Dummer, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, J.M. Kirkwood, V. Chiarion Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, T. Lesimple, R. Plummer, K. Dasgupta, E. Gasal, M. Tan, G.V. Long, and D. Schadendorf

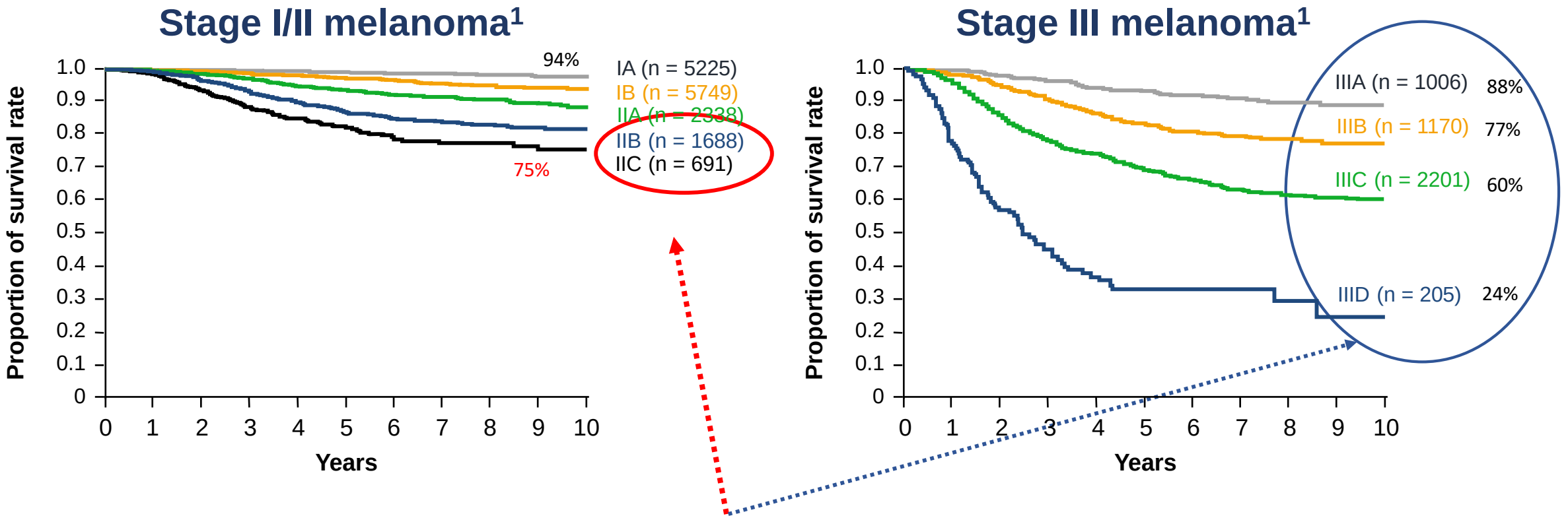
NEJM 2020

COMBI AD (5-year)



durable, long-term RFS benefit

Survival by Disease Stage per AJCC 8th Edition[a]



High-risk patients: Higher recurrence rate and relatively poor survival[1,2]

[a]Based on AJCC 8th Edition International Melanoma Database.

1. Adapted from Gershenwald JE, et al. *CA Cancer J Clin.* 2017;67:472-492. 2. Davar D, Kirkwood JM. *Cancer Treat Res.* 2016;167:181-208.

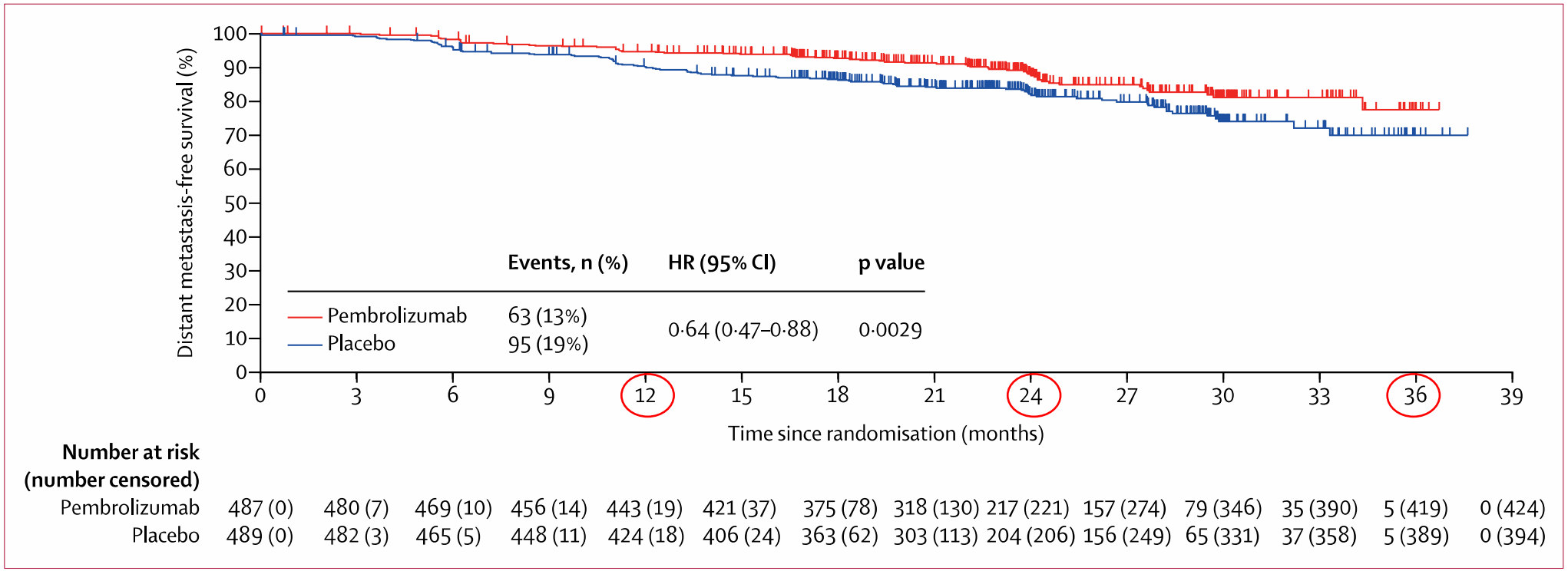
Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial

Georgina V Long, Jason J Luke*, Muhammad A Khattak, Luis de la Cruz Merino, Michele Del Vecchio, Piotr Rutkowski, Francesco Spagnolo, Jacek Mackiewicz, Vanna Chiarion-Sileni, John M Kirkwood, Caroline Robert, Jean-Jacques Grob, Federica de Galitiis, Dirk Schadendorf, Matteo S Carlino, Peter Mohr, Reinhard Dummer, Jeffrey E Gershenwald, Charles H Yoon, Xi Lawrence Wu, Mizuho Fukunaga-Kalabis, Clemens Krepler, Alexander M M Eggermont, Paolo A Ascierto, on behalf of the KEYNOTE-716 Investigators†*

Lancet Oncology 2022

Sulla base di questi risultati FDA ed EMA hanno approvato l'utilizzo della terapia adiuvante con PEMBROLIZUMAB 200 mg i.v. ogni 3 settimane per 1 anno per pazienti in stadio IIB e IIC

Distant metastasis-free survival

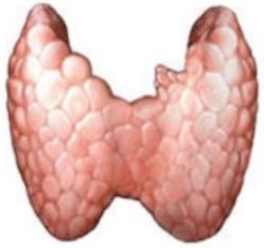


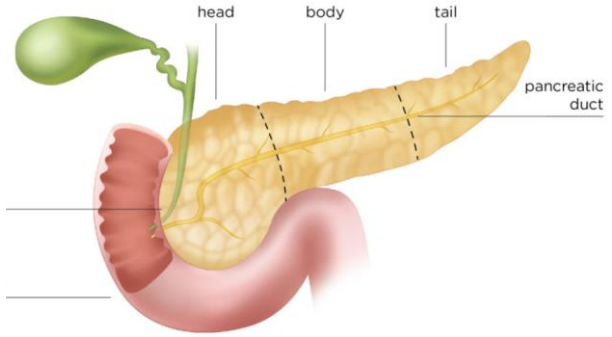
13% dei pazienti nel gruppo pembrolizumab versus 19% nel gruppo placebo hanno sviluppato metastasi

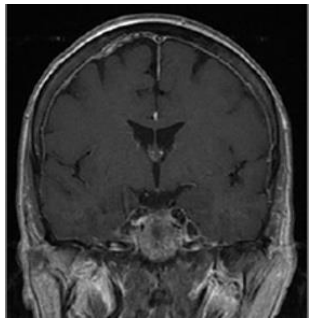
Long GV et al. Lancet Oncology 2022

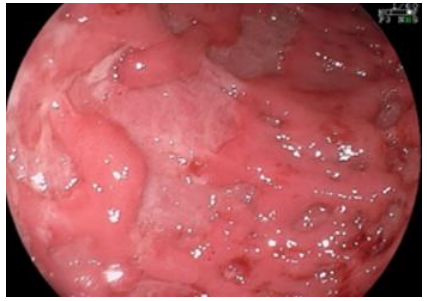
Immunotherapy: Adverse Events

- **IPI:** AEs occurred in 80-94% of patients (5 deaths)
- Grade 3-4 AE with nivolumab (14%) and pembrolizumab (15%)
- Endocrine toxicities (hypothyroidism, hyperthyroidism): 10% Nivo, 14% Pembro
- Type 1 diabetes (1%)
- Adrenal insufficiency (1.5% Nivo; 1% Pembro)
- Colitis (2.0%)
- Hypophysitis/hypopituitarism (0-6%)







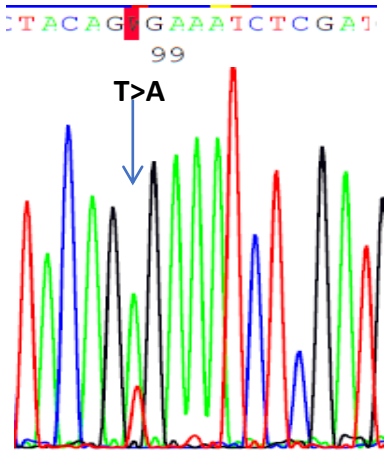


Garbe C at al; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019. Eur J Cancer. 2020 Feb;126:159-177. doi: 10.1016/j.ejca.2019.11.015. Epub 2019 Dec 19. PMID: 31866016.

Therapy with BRAF/MEK inhibitors: Adverse Events

- Grade 3-4 AE: 31%
- Pyrexia grade I-II in 97% (grade III-IV in 5%)
- Hypertension: 6%; Fatigue: 4%; Hepatitis: 4%
- Drug discontinuation: 26% of patients

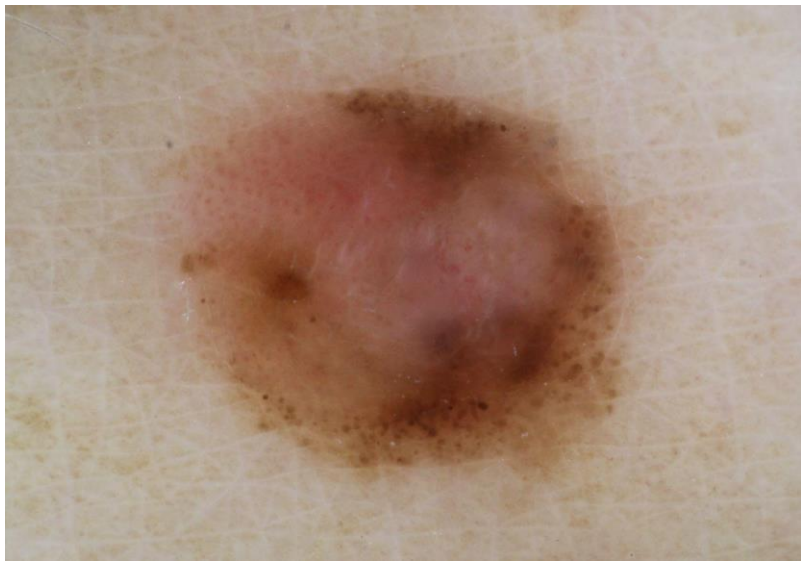
***BRAF* V600E +**



Garbe C at al; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2019. Eur J Cancer. 2020 Feb;126:159-177. doi: 10.1016/j.ejca.2019.11.015. Epub 2019 Dec 19. PMID: 31866016.

F; 45 anni
Fumatrice
Fototipo III
Nessuna comorbidità

Aprile 2022



Asportazione chirurgica di melanoma localizzato alla gamba sinistra (spessore di Breslow 1.1 mm, non ulcerato, presenza di infiltrato intratumorale)

Maggio 2022

Ampliamento della cicatrice chirurgica e SLNB inguinale sx: «10 micrometastasi sottocapsulari di melanoma (la maggiore del diametro 0.8 mm) del linfonodo localizzato in regione inguinale sx e negatività di un secondo linfonodo sentinella localizzato sempre in regione inguinale sx».

Esami di imaging negativi

B-RAF: wild type

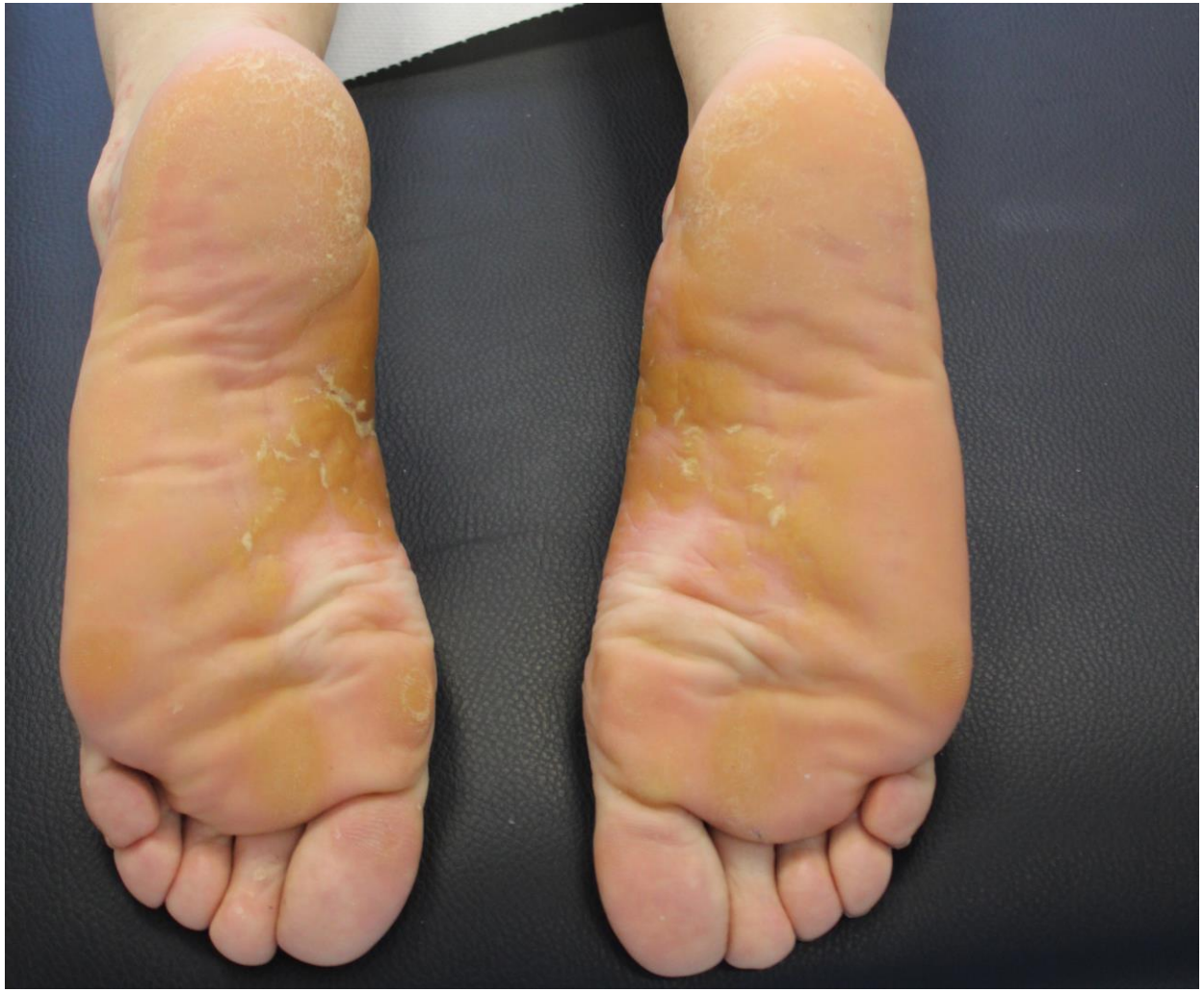
T2aN1M0 – Stadio IIIA

Luglio 2022

Inizio terapia con PEMBROLIZUMAB 400 mg ogni 6 w

Ottobre 2022 (3ª infusione)

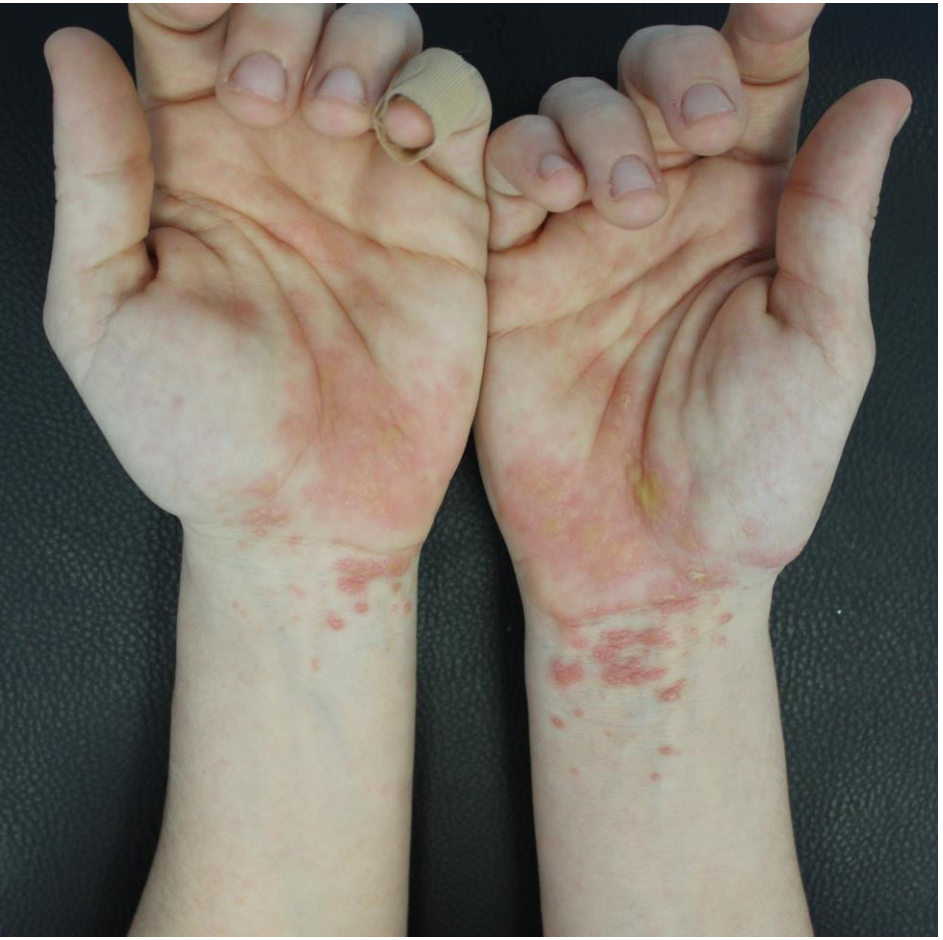
Cheratodermia palmo-plantare diffusa

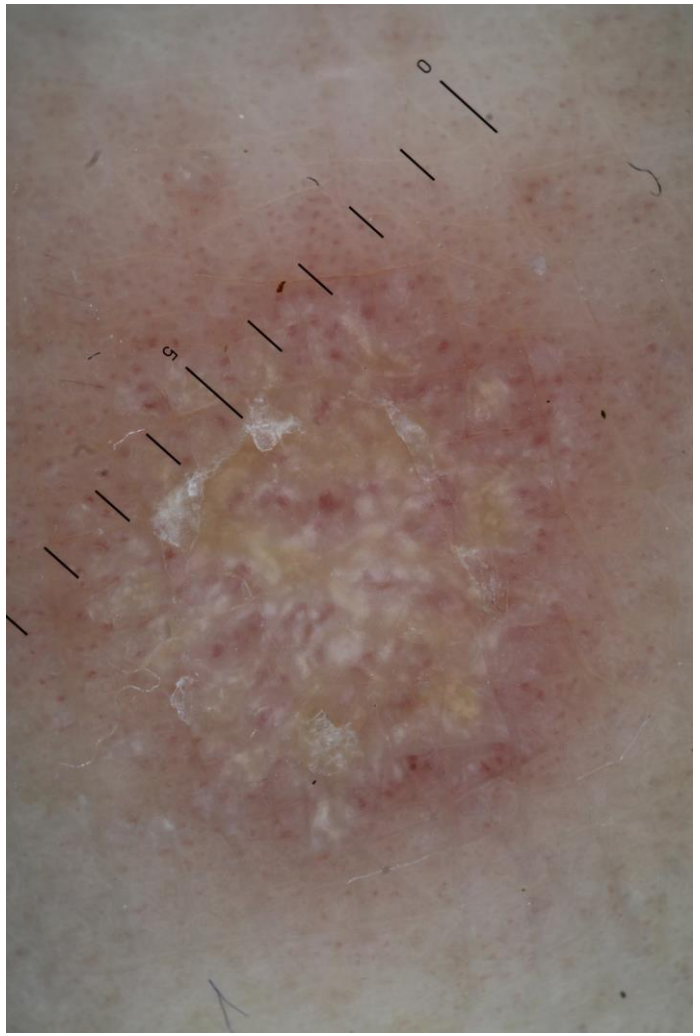


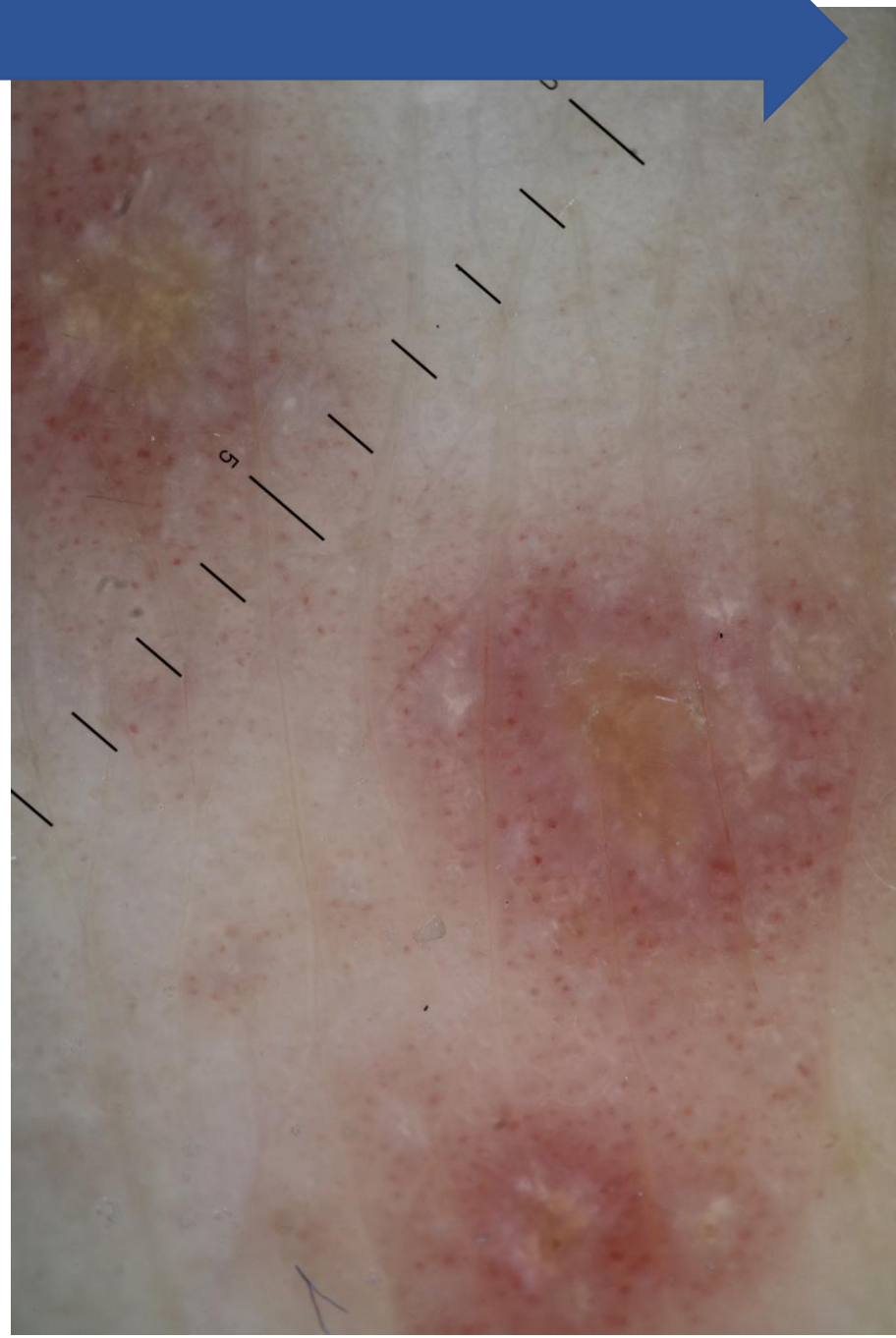
Esame istologico di una biopsia cutanea

"Le sezioni mostrano un infiltrato infiammatorio dermico superficiale con danno dello strato basale dell'interfaccia, come da reazione a farmaci."

Ottobre 2022 (3ª infusione)

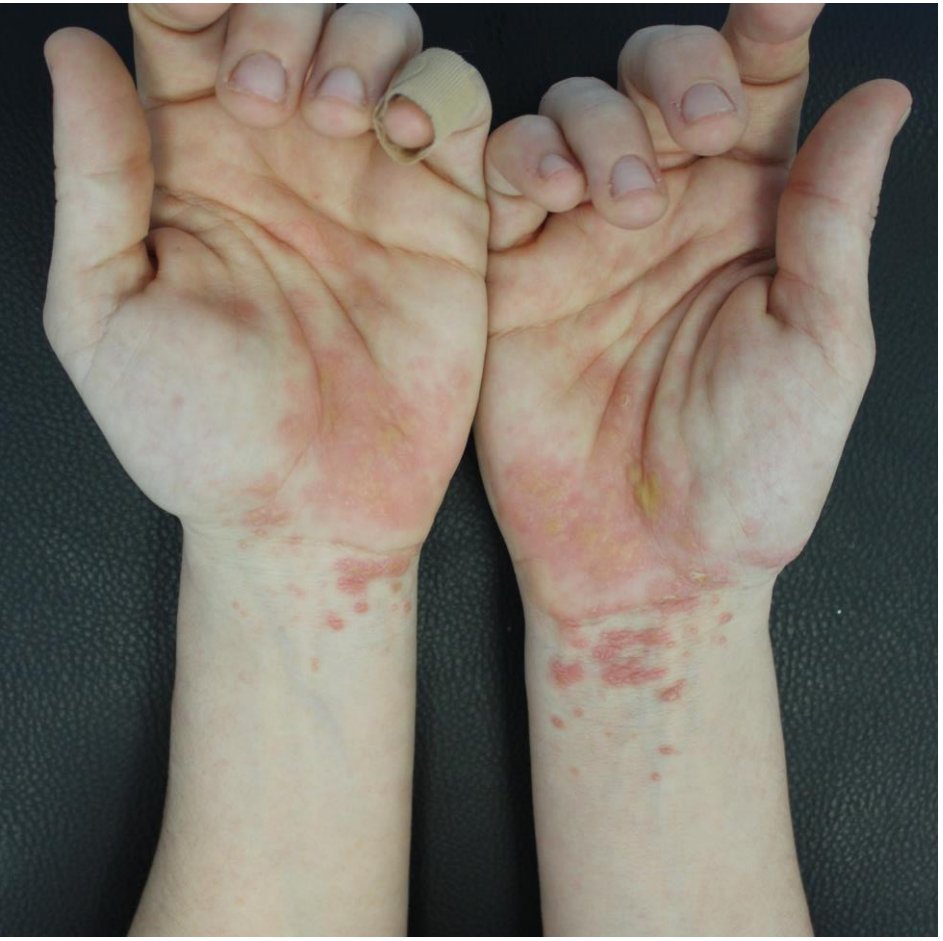


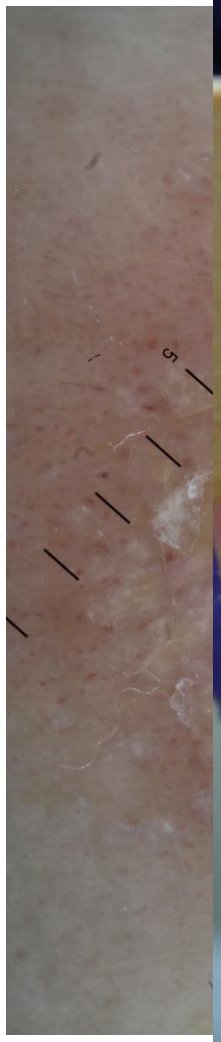


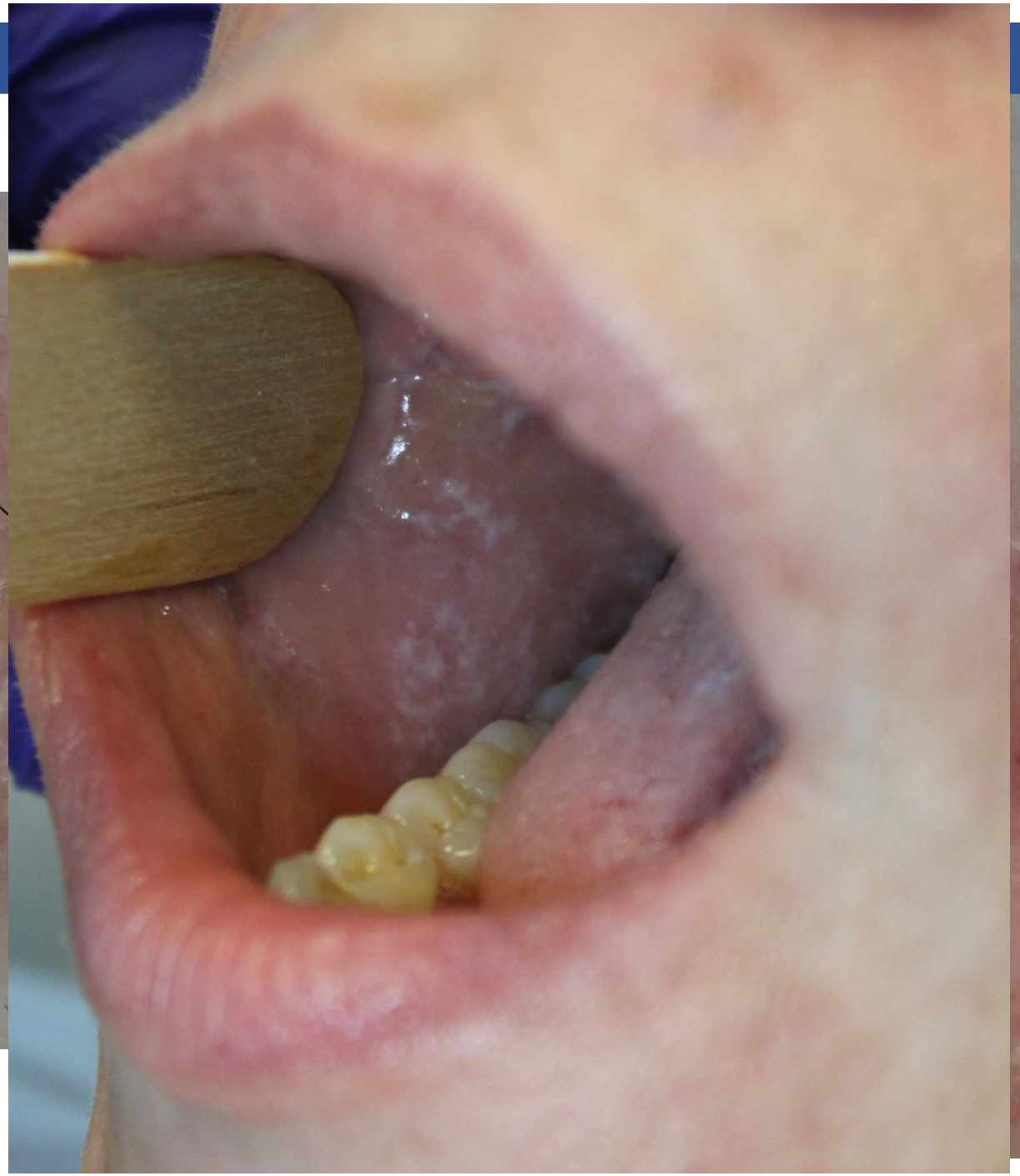


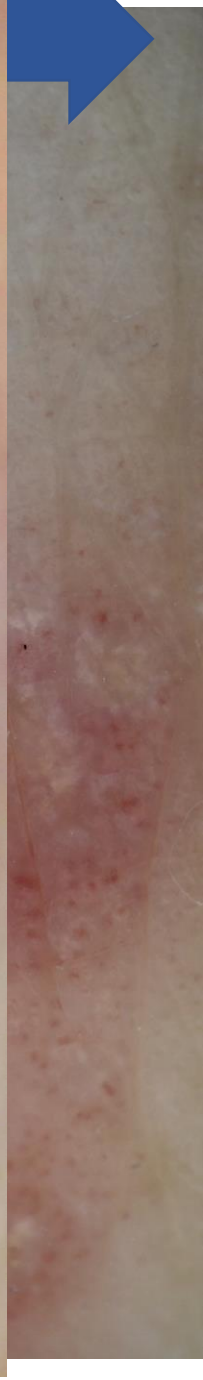
Papule e placche ai polsi e eminenza ipotenar

Ottobre 2022 (3ª infusione)



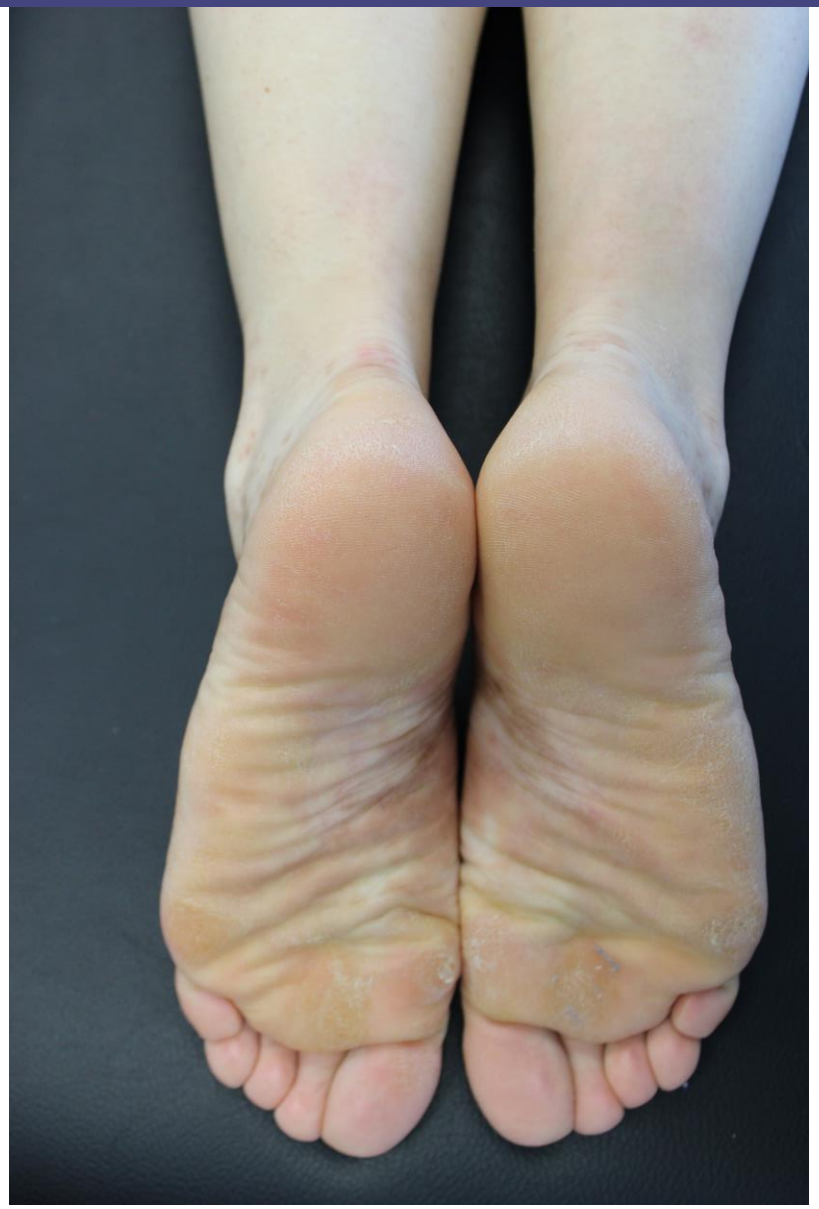


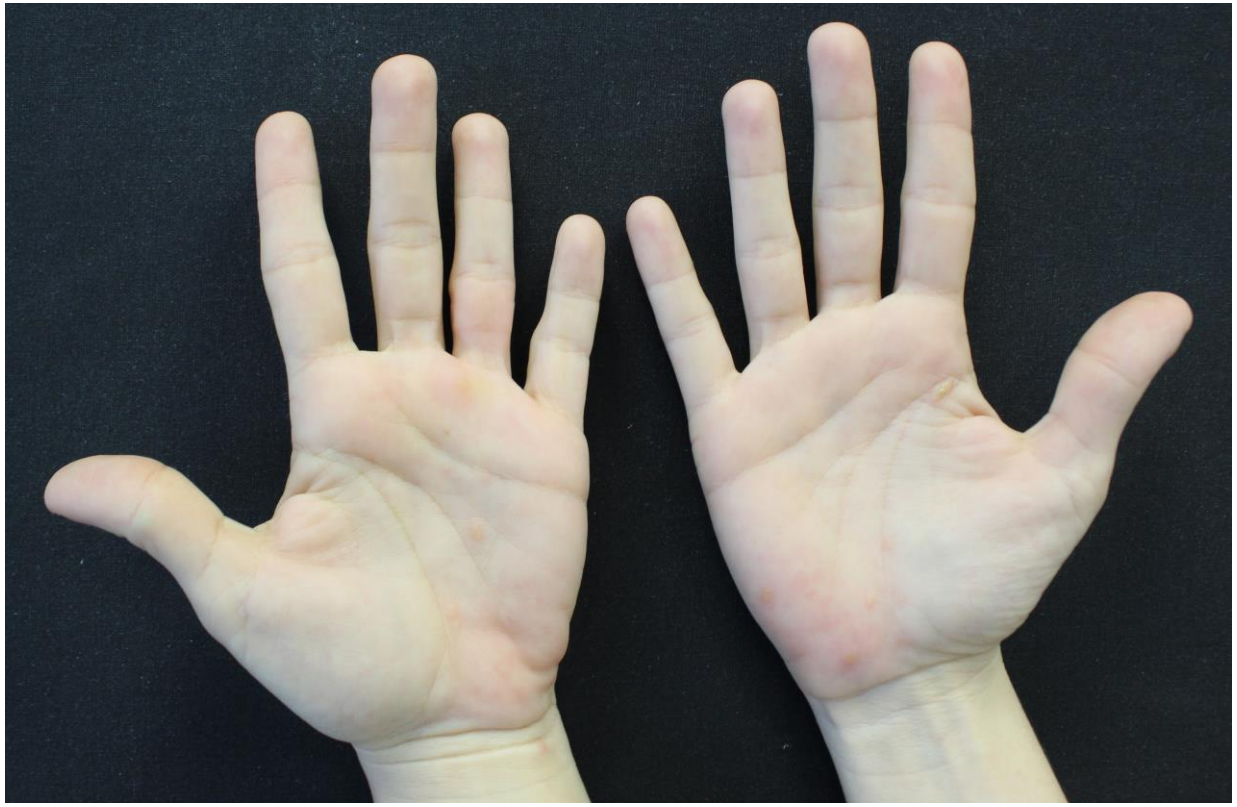




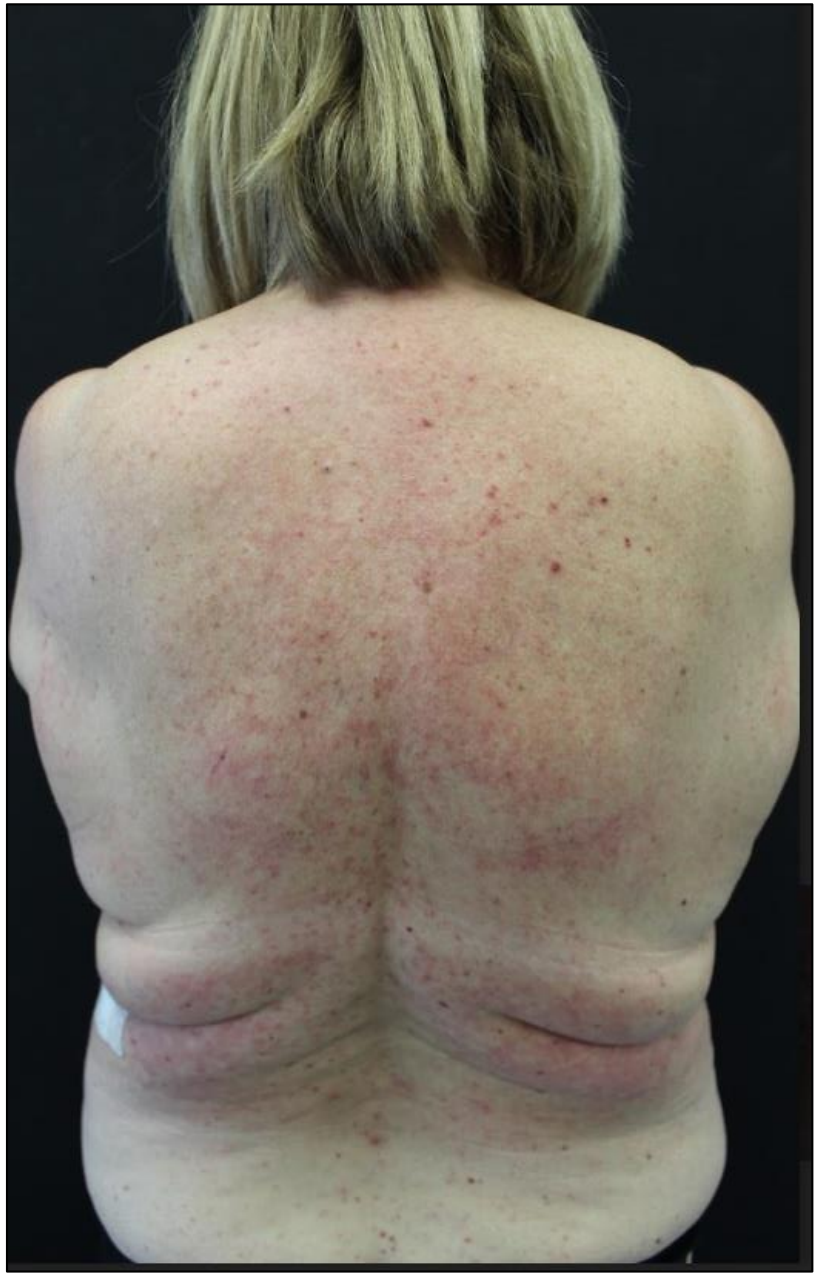
lesioni bianche reticolari sulla parte vestibolare del cavo orale

Efficacia della terapia con corticosteroidi topici

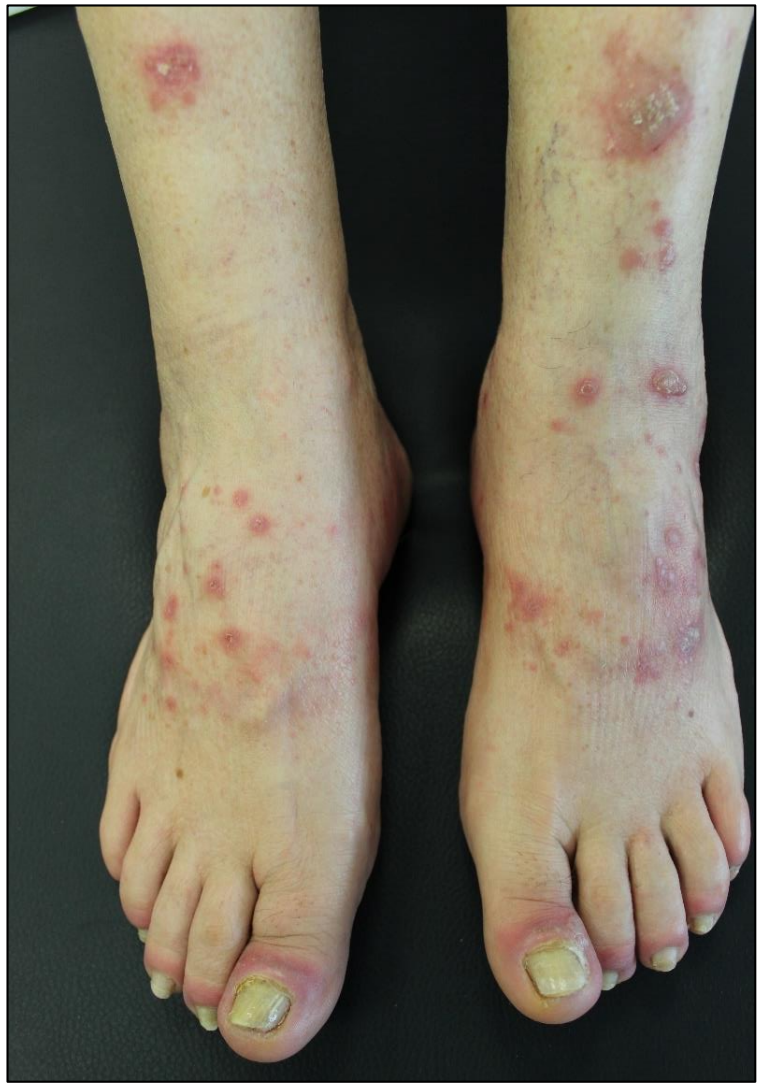


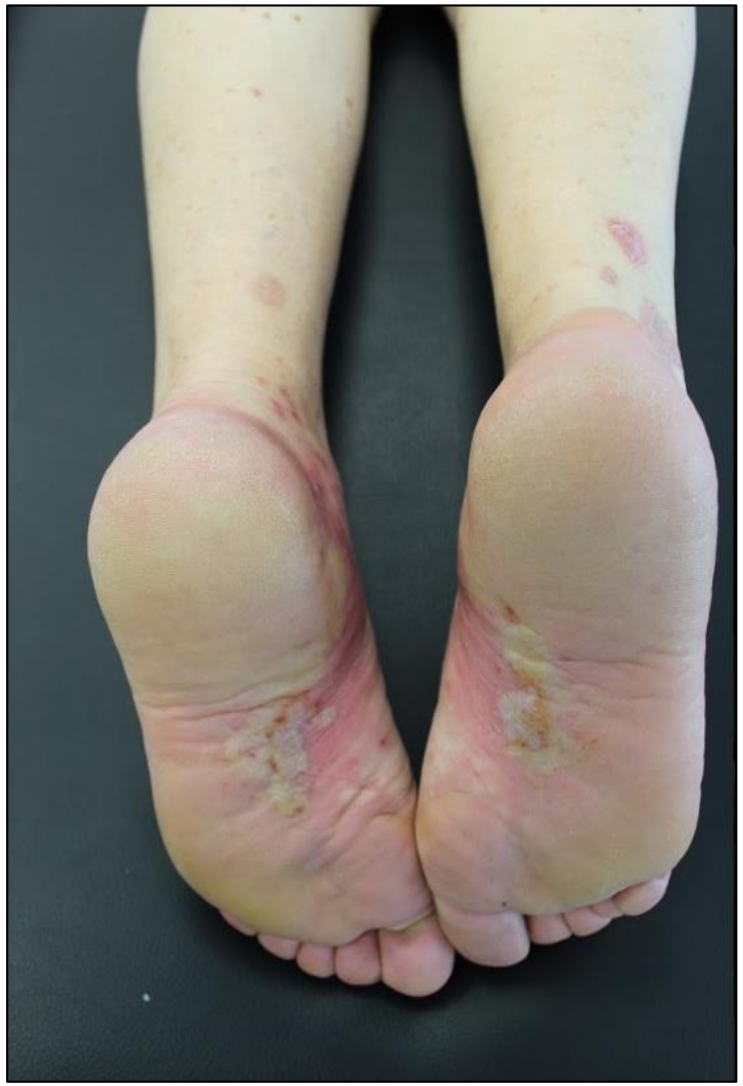


Luglio 2023: TERMINE DELLA TERAPIA ADIUVANTE IN ASSENZA DI ULTERIORI EFFETTI AVVERSI E DI RECIDIVA DI MALATTIA



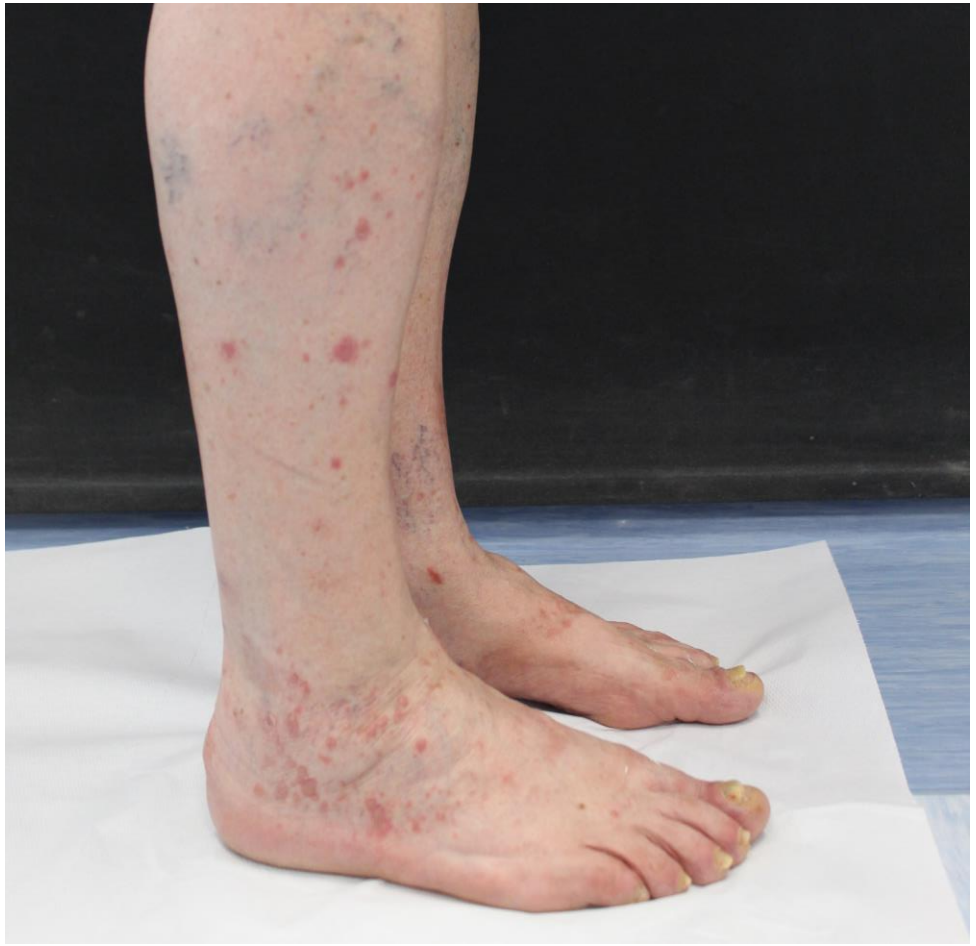
F, 65y

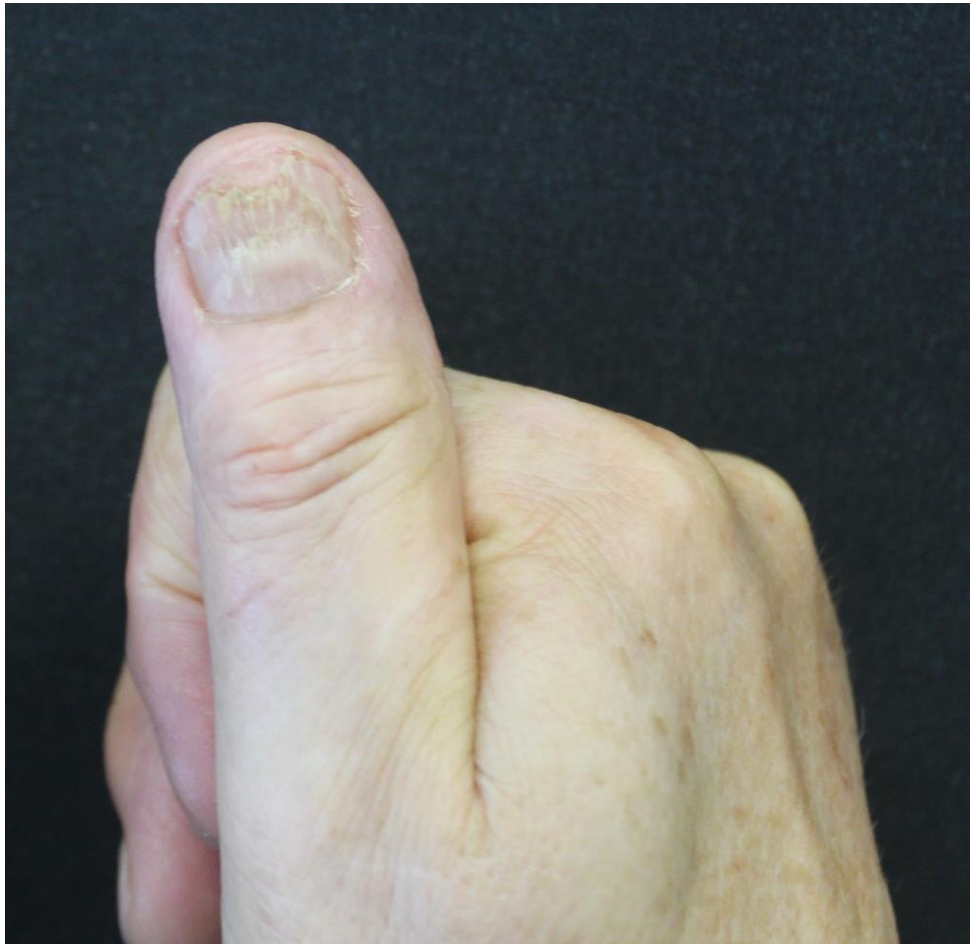




Confluent erythemato-papular lesions on the back and décolleté associated with erythematous-desquamative plaques on the legs and feet occurring at the 7th infusion of nivolumab

Prescritta terapia steroidea topica e sistemica con parziale risoluzione del quadro.





La paziente presentava tuttavia recidive alla sospensione della terapia steroidea, prurito intenso, dolore alla deambulazione.
Si decideva, in accordo con la paziente, sospensione della terapia con NIVOLUMAB

La paziente è attualmente in FUP, libera da malattia

Quali terapie sistemiche, in monoterapia o in combinazione, hanno dimostrato benefici clinici nei pazienti con **melanoma cutaneo non resecabile e/o metastatico**?

- **Raccomandazione 3.1***

  Per i pazienti con melanoma ***BRAF* wild-type**, dovrebbero essere offerte le seguenti opzioni:

  - Nivolumab + ipilimumab seguito da nivolumab
  - Nivolumab + relatlimab
  - Nivolumab
  - Pembrolizumab

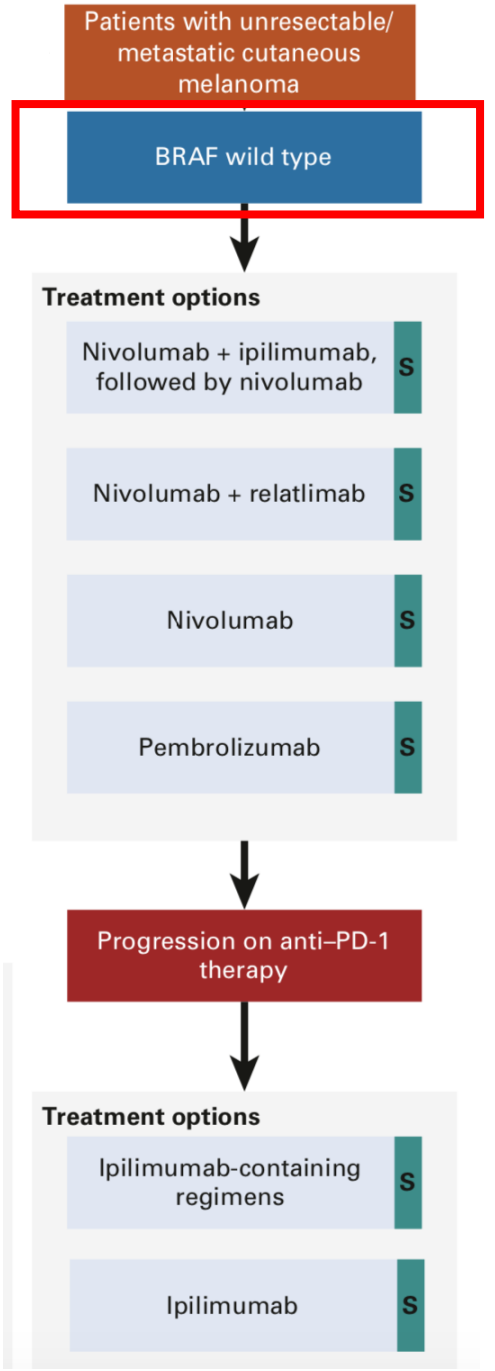
- **Raccomandazione 3.3 ****

  In caso di progressione durante terapia con anti–PD-1, possono essere proposti **l'ipilimumab in monoterapia o schemi contenenti ipilimumab**.

- *Qualità dell'evidenza: Alta; Forza della raccomandazione: Forte)*

*** Qualità delle prove: Bassa; Forza della raccomandazione: Debole*

I pazienti dovrebbero essere incoraggiati a partecipare a trial clinici quando possibile



Quali terapie sistemiche, in monoterapia o in combinazione, hanno dimostrato benefici clinici nei pazienti con **melanoma cutaneo non resecabile e/o metastatico**?

- **Raccomandazione 3.1***

  Per i pazienti con melanoma ***BRAF* wild-type,** dovrebbero essere offerte le seguenti opzioni:

  - Nivolumab + ipilimumab seguito da nivolumab
  - Nivolumab + relatlimab
  - Nivo…

La decisione sulla scelta della terapia dovrebbe essere presa **congiuntamente con il paziente**, dopo aver considerato i rischi e i benefici; i pazienti che preferiscono una terapia più aggressiva potrebbero desiderare di ricevere una terapia di combinazione

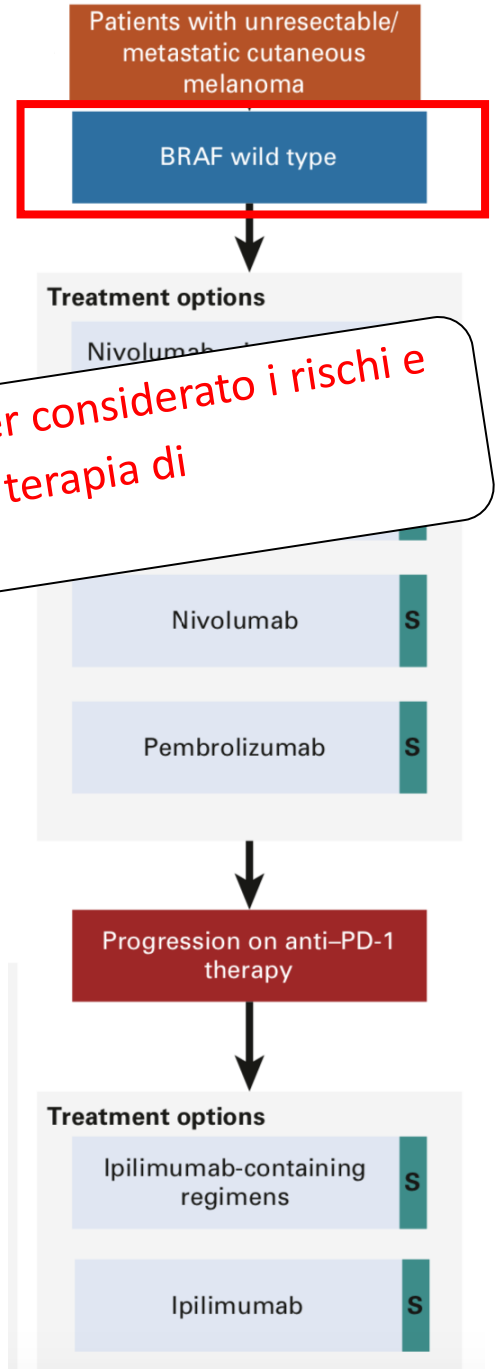
- **…mandazione 3.3 ****

  In caso di progressione durante terapia con anti–PD-1, possono essere proposti **l'ipilimumab in monoterapia o schemi contenenti ipilimumab**.

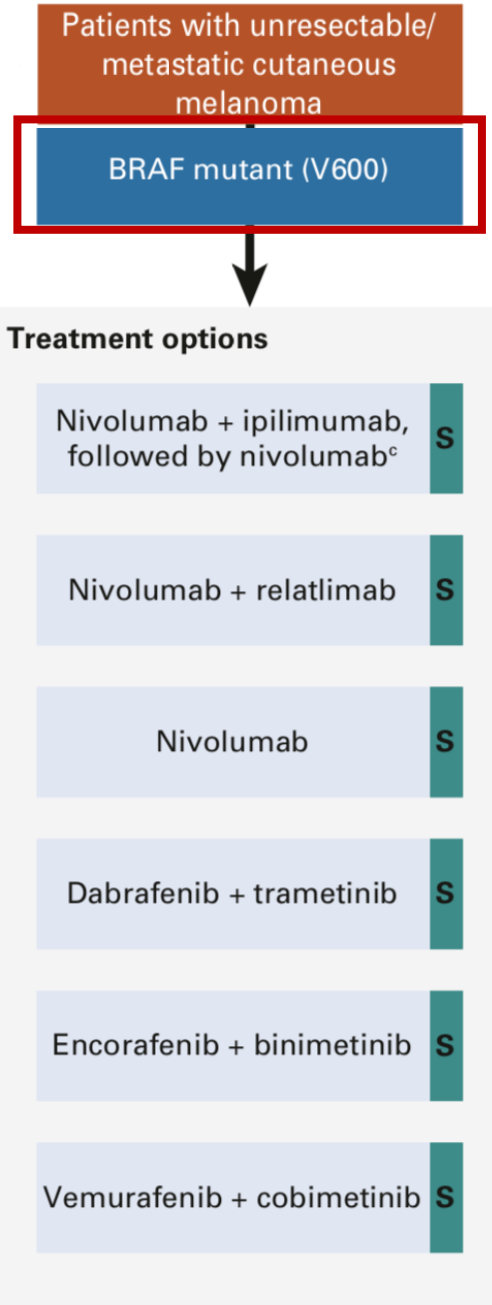
- *Qualità dell'evidenza: Alta; Forza della raccomandazione: Forte)*

*** Qualità delle prove: Bassa; Forza della raccomandazione: Debole*

I pazienti dovrebbero essere incoraggiati a partecipare a trial clinici quando possibile



Quali terapie sistemiche, in monoterapia o in combinazione, hanno dimostrato benefici clinici nei pazienti con **melanoma cutaneo non resecabile e/o metastatico**?



- **Raccomandazione 3.2.1***

  Ai pazienti con melanoma ***BRAF* mutato (V600)** dovrebbe essere offerta una delle seguenti terapie:

  - Nivolumab + ipilimumab seguito da nivolumab
  - Nivolumab + relatlimab
  - Nivolumab
  - Pembrolizumab
  - Dabrafenib + trametinib o encorafenib + binimetinib o vemurafenib + cobimetinib

- **Raccomandazione 3.2.2****

  La terapia di combinazione con nivolumab + ipilimumab è raccomandata come terapia di prima linea rispetto alla terapia di combinazione con inibitori BRAF/MEK.

- *Qualità dell'evidenza: Alta; Forza della raccomandazione: Forte)*

** *Qualità delle prove: Qualità delle prove: Alta per dabrafenib più trametinib, Bassa per altri inibitori BRAF/MEK; Forza della raccomandazione: Forte*

Checkpoint blockade therapies for advanced cutaneous melanoma described in prospective randomized trials.

Substance	Dose	Response rate	Overall survival
Ipilimumab [111,120,123]	3 mg/kg i.v. every three weeks for four cycles	12–19%	3 y OS 22%
Nivolumab [124,137]	3 mg/kg i.v. every two weeks until tumor progression	40%–44%	
Nivolumab [127]	480 mg i.v. every four weeks (flat dose) until tumor progression		
Pembrolizumab [138] + update KEYNOTE 006 SMR 21 (ref)	2 mg/kg i.v. every three weeks until tumor progression	33%	7 y OS 37.8%
Pembrolizumab [128–130]	400 mg i.v. every six weeks (flat dose) until tumor progression 200 mg i.v. every three weeks (flat dose) until tumor progression		
Nivolumab + Ipilimumab [125,139]	Ipilimumab 3 mg/kg i.v. plus nivolumab 1 mg/kg i.v. every three weeks for four cycles, continuation with 3 mg/kg nivolumab every two weeks until tumor progression	49%	6.5 y OS 49%
Nivolumab + Ipilimumab [133,135]	Ipilimumab 1 mg/kg i.v. plus nivolumab 3 mg/kg i.v. every three weeks for four cycles, continuation with 3 mg/kg nivolumab every two weeks until tumor progression	59%	3 y OS 59%
Pembrolizumab + ipilimumab (KEYNOTE 029) (ref)	Pembrolizumab 2 mg/kg every three weeks for 24 months plus four doses ipilimumab 1 mg/kg every three weeks (part 1 B)	65.8%	5 y OS 68.3%
	Pembrolizumab 200 mg every three weeks for 24 months plus four doses ipilimumab 50 mg every six weeks (part 1C arm A)	69.9%	3 y OS74.3%
	Pembrolizumab 200 mg every three weeks for 24 months plus four doses ipilimumab 100 mg every 12 weeks (part 1C arm B)	76.7%	3 y OS 70.4%

Garbe C et al. EJC 2022

Caso clinico

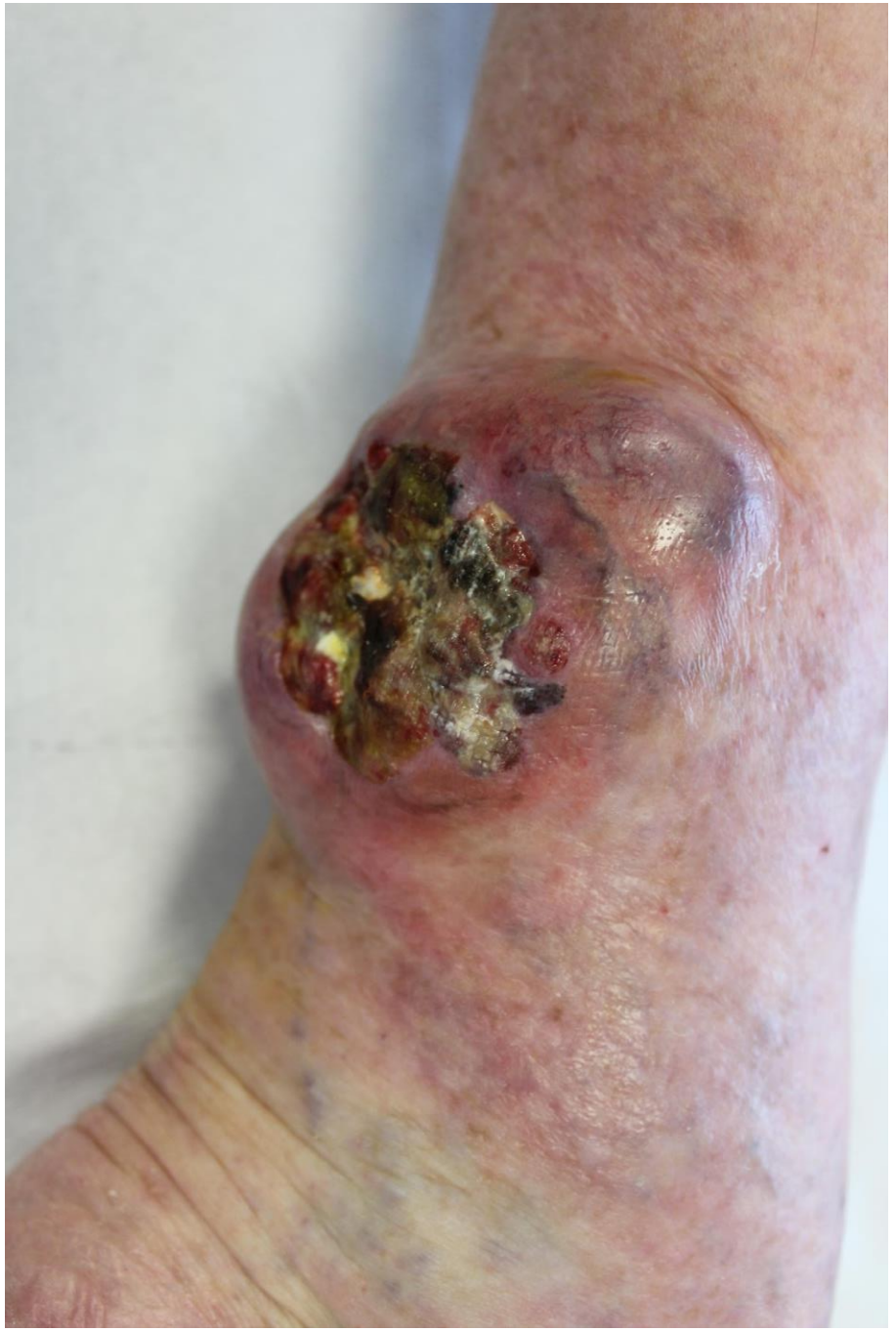
F, 75 aa
Comorbidità: Dislipidemia, Sindrome delle gambe senza riposo

Luglio 2021. Lesione nodulare, ulcerata, 8 x 6 x 3 cm, aderente ai piani sottostanti, localizzata alla gamba sx, caratterizzata da una crescita progressiva per «diversi anni»

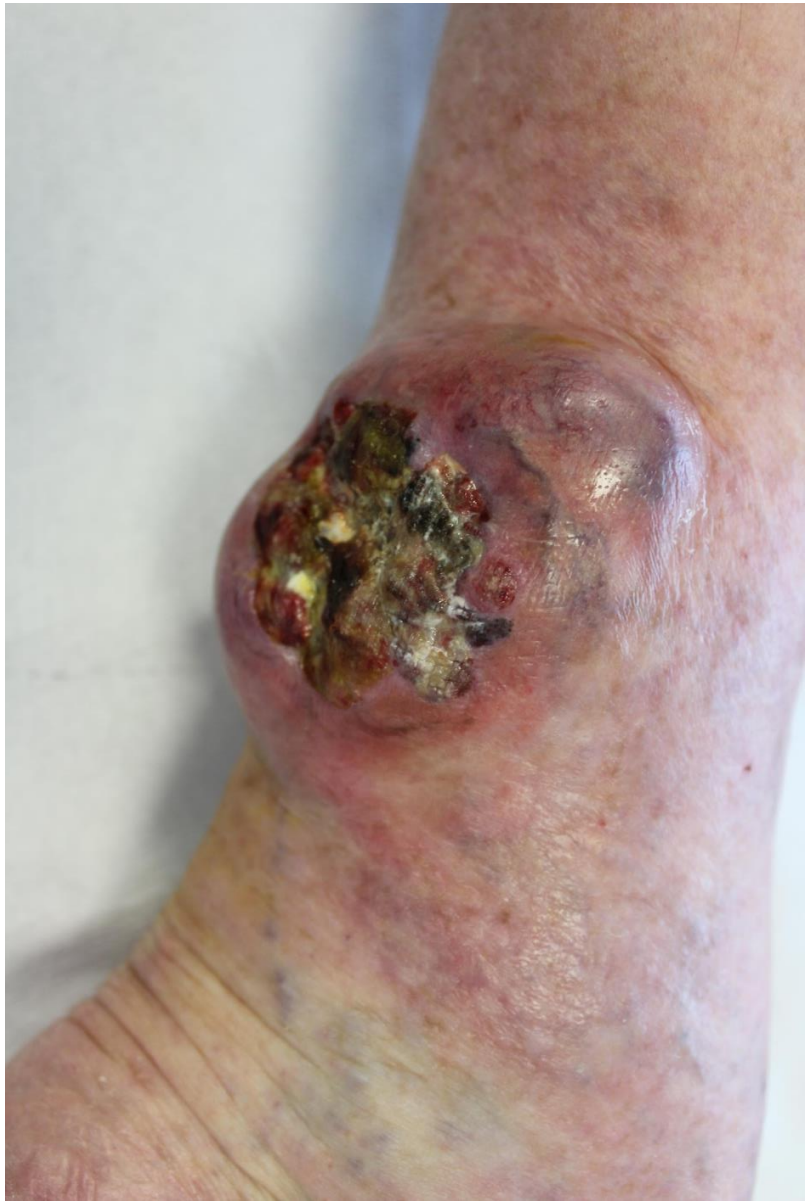
Melanoma BRAF wild-type

PET-TC: **patologia neoplastica ad elevata attività metabolica** (linfonodi in sede inguinale sinistra, addominale para-aortica sinistra e iliaca interna e lungo l'asse iliaco-otturatorio di sinistra, quelli maggiormente attivi in sede iliaca comune). **Stadio IV: pT4bN3bM1a**

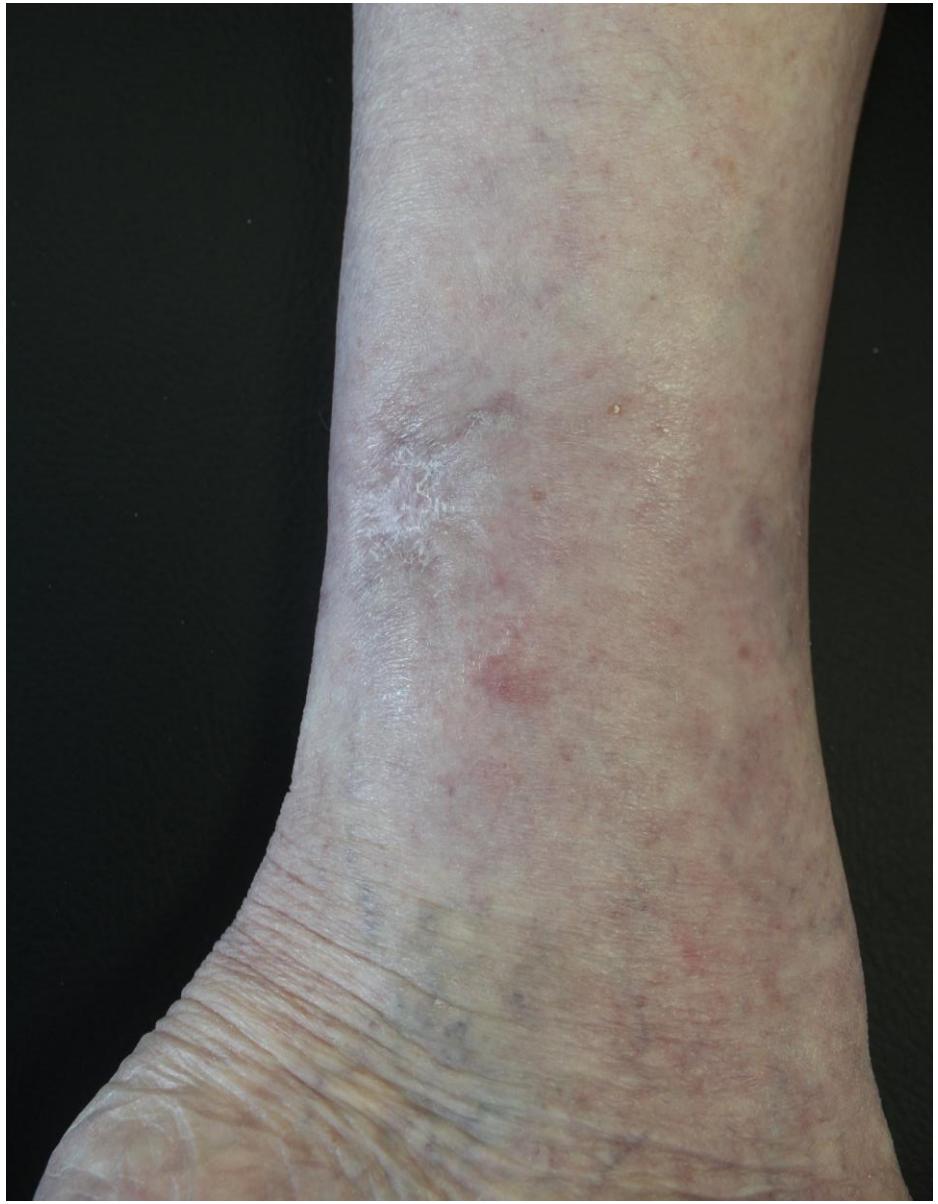
Settembre 2021. Inizio terapia con ***Nivolumab*** 480 mg ogni 4 settimane
Da Dicembre 2021 risposta clinica e alla PET-TC fino ad ottobre 2022



Settembre 2021
Inizio terapia con Nivolumab 480 mg ogni 4 w



Ottobre 2022 - 16 infusioni di nivolumab
RISPOSTA CLINICA COMPLETA



Caso clinico

F, 76 aa
Comorbidità: Ipertensione arteriosa
Pregressa asportazione di *multipli BCC a livello frontale*

Gennaio 2021: Melanoma ulcerato, (spessore di Breslow: 1.7 mm.; mitosi > 1 mm2; margini di exeresi profondi sede di neoplasia)

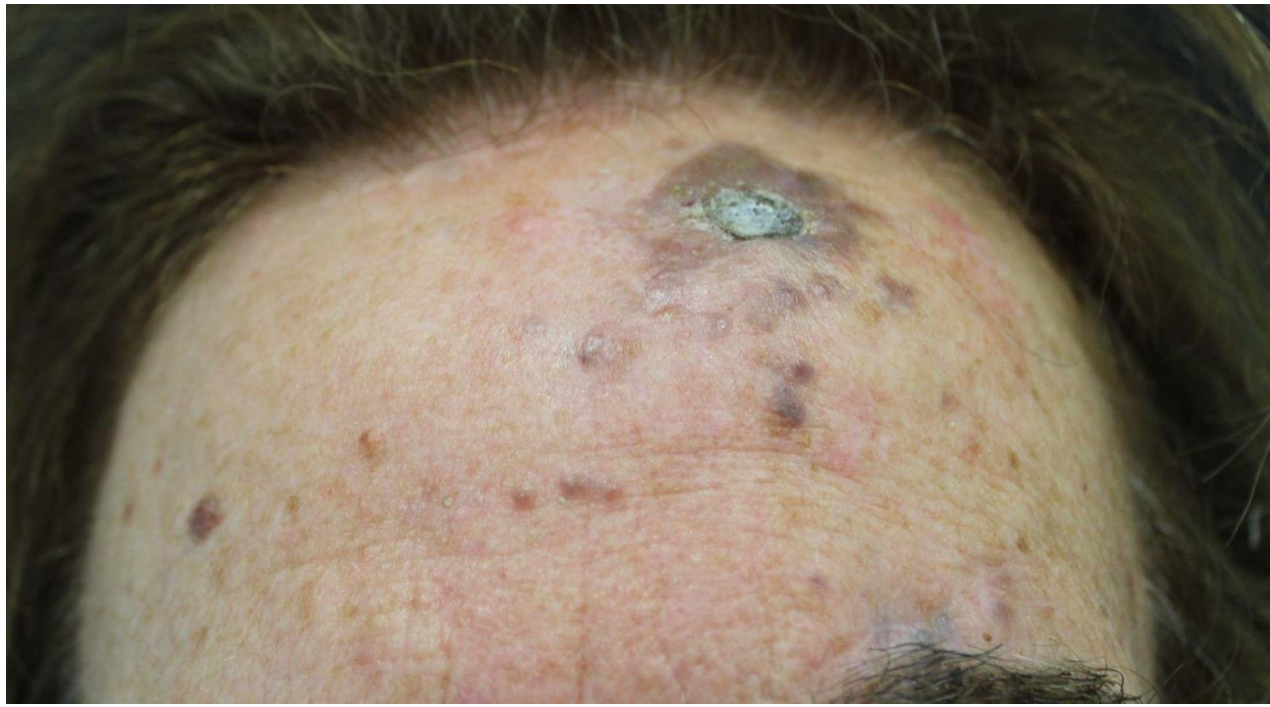
- BRAF wild-type

TC total body: addensamento nodulare a margini irregolari (0.6 cm) a livello del lobo superiore del polmone destro in sede subpleurica laterale. Altro piccola lesione di analoga natura nel segmento apicale del LID.

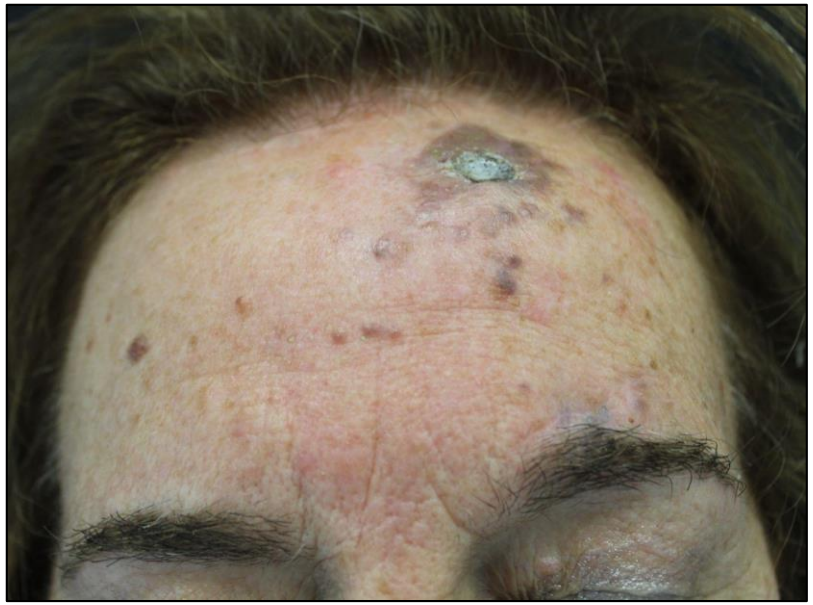
Stadio IIIB T2bN1cM0

Stadio III non resecabile con lesione polmonare aspecifica

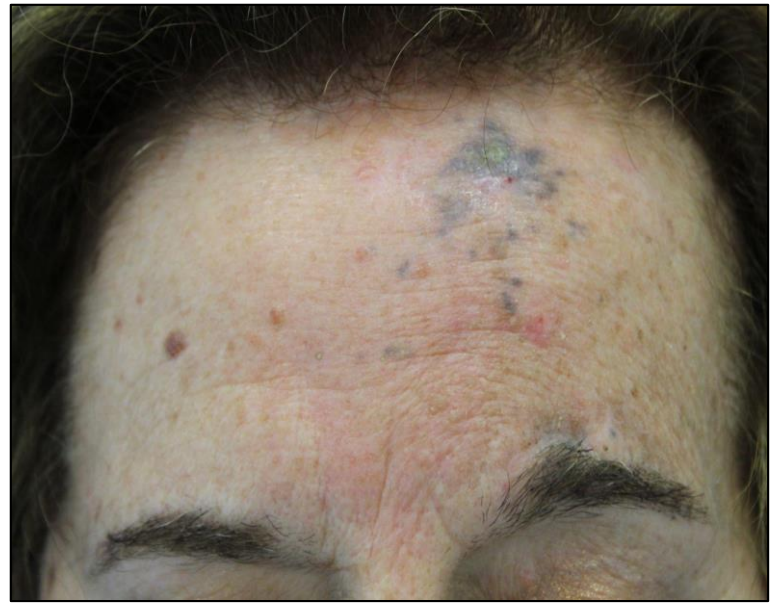
Febbraio 2021 - Inizio immunoterapia con **nivolumab** 480 mg (ogni 4 settimane)



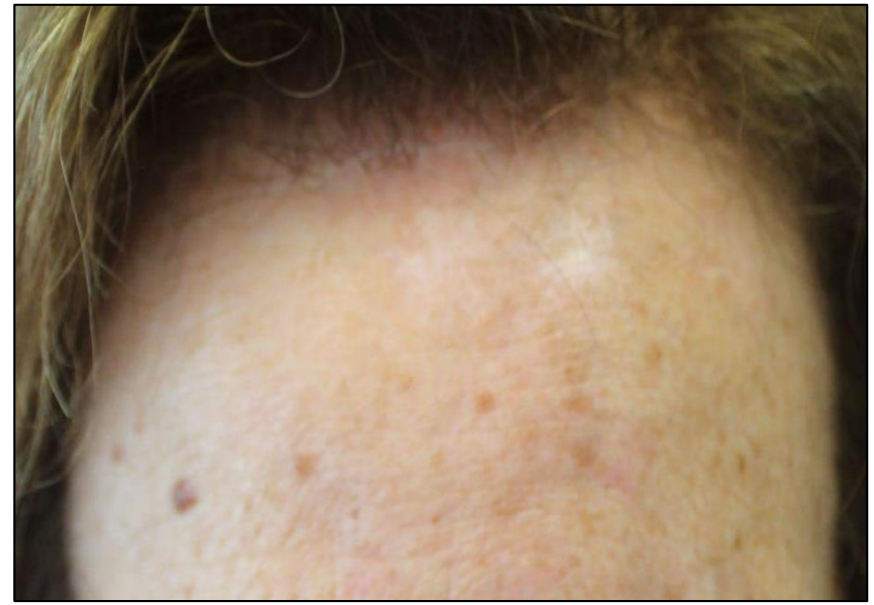
Febbraio 2021



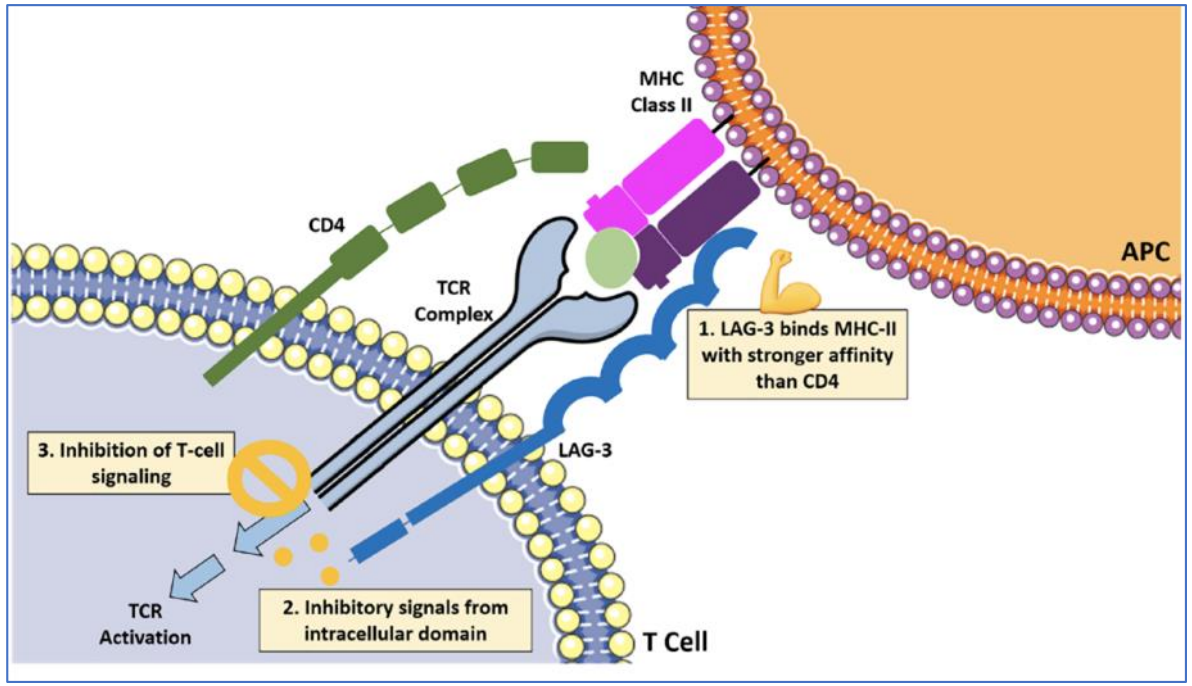
Aprile 2021
(3 infusioni di nivolumab)



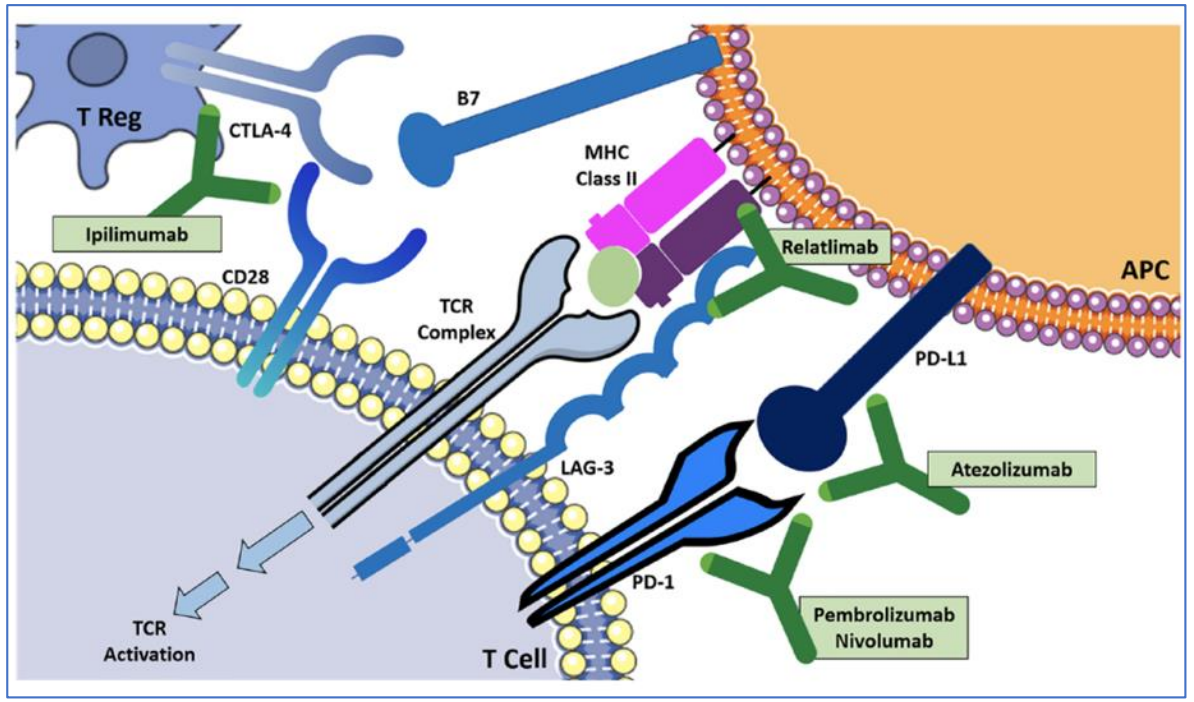
Gennaio 2022
(13 infusioni di nivolumab)



LAG-3 signalling pathway



Different checkpoints as immunotherapy targets



- Lymphocyte-activation gene 3 (LAG-3) is a cell-surface molecule that is expressed on immune cells, including T cells, and negatively regulates T-cell proliferation and effector T-cell function
- LAG-3 is upregulated in many tumor types, including melanoma
- LAG-3 and PD-1 are distinct inhibitory immune checkpoints that are often co-expressed on tumor-infiltrating lymphocytes, thus contributing to tumor-mediated T-cell exhaustion
- Relatlimab is a first-in-class human IgG4 LAG-3–blocking antibody that binds to LAG-3 and restores the effector function of exhausted T cells

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

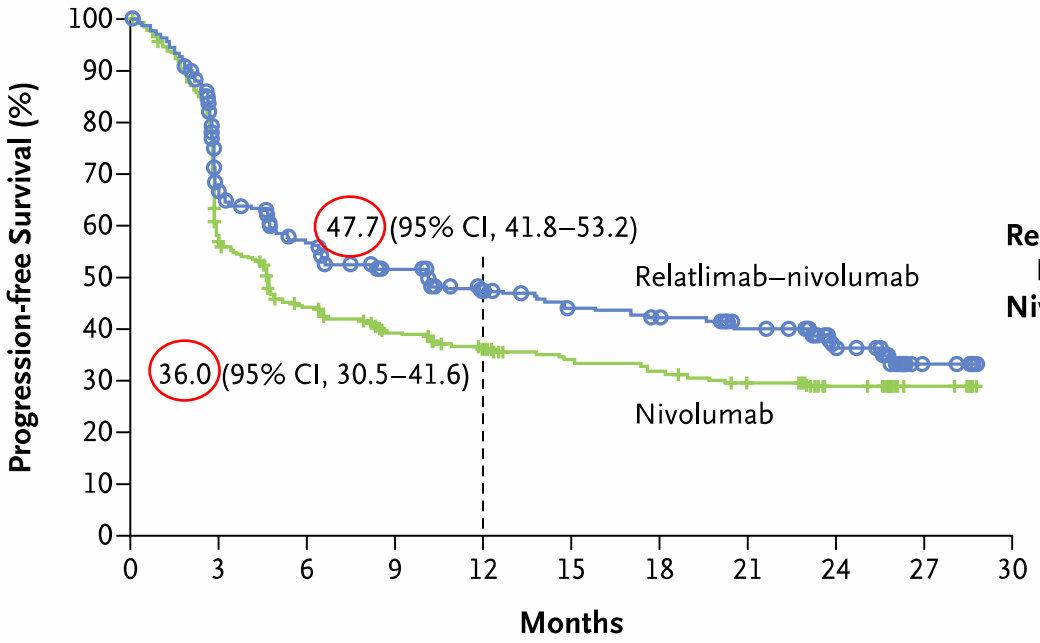
Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Hussein A. Tawbi, M.D., Ph.D., Dirk Schadendorf, M.D., Evan J. Lipson, M.D., Paolo A. Ascierto, M.D., Luis Matamala, M.D., Erika Castillo Gutiérrez, M.D., Piotr Rutkowski, M.D., Ph.D., Helen J. Gogas, M.D., Christopher D. Lao, M.D., M.P.H., Juliana Janoski De Menezes, M.D., Stéphane Dalle, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean-Jacques Grob, M.D., Shivani Srivastava, M.D., Mena Abaskharoun, Pharm.D., Melissa Hamilton, M.P.H., Sarah Keidel, M.B., Ch.B., Katy L. Simonsen, Ph.D., Anne Marie Sobiesk, Ph.D., Bin Li, Ph.D., F. Stephen Hodi, M.D., and Georgina V. Long, M.D., Ph.D., for the RELATIVITY-047 Investigators*

2002

The inhibition of two immune checkpoints, LAG-3 and PD-1, provide a greater benefit with regard to progression-free survival than inhibition of PD-1 alone in patients with previously untreated metastatic or unresectable melanoma

Fixed dose combination of **relatlimab 160 mg and nivolumab 480 mg**
or
nivolumab 480 mg



No. at Risk											
Relatlimab–nivolumab	355	201	163	132	99	81	75	67	30	6	0
Nivolumab	359	174	124	94	72	61	57	49	27	6	0

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Relatlimab–Nivolumab	355	10.12 (6.37–15.74)
Nivolumab	359	4.63 (3.38–5.62)

Hazard ratio for progression or death, 0.75 (95% CI, 0.62–0.92)
P=0.006

Grade 3 or 4 treatment- related adverse events occurred in 18.9% of patients in the relatlimab–nivolumab group and in 9.7% of patients in the nivolumab group

Talimogene laherparepvec (T-VEC)

Talimogene laherparepvec (T-VEC) è un **virus herpes simplex di tipo I geneticamente modificato** ed è il primo virus oncolitico a dimostrare un beneficio clinico nei pazienti affetti da melanoma.

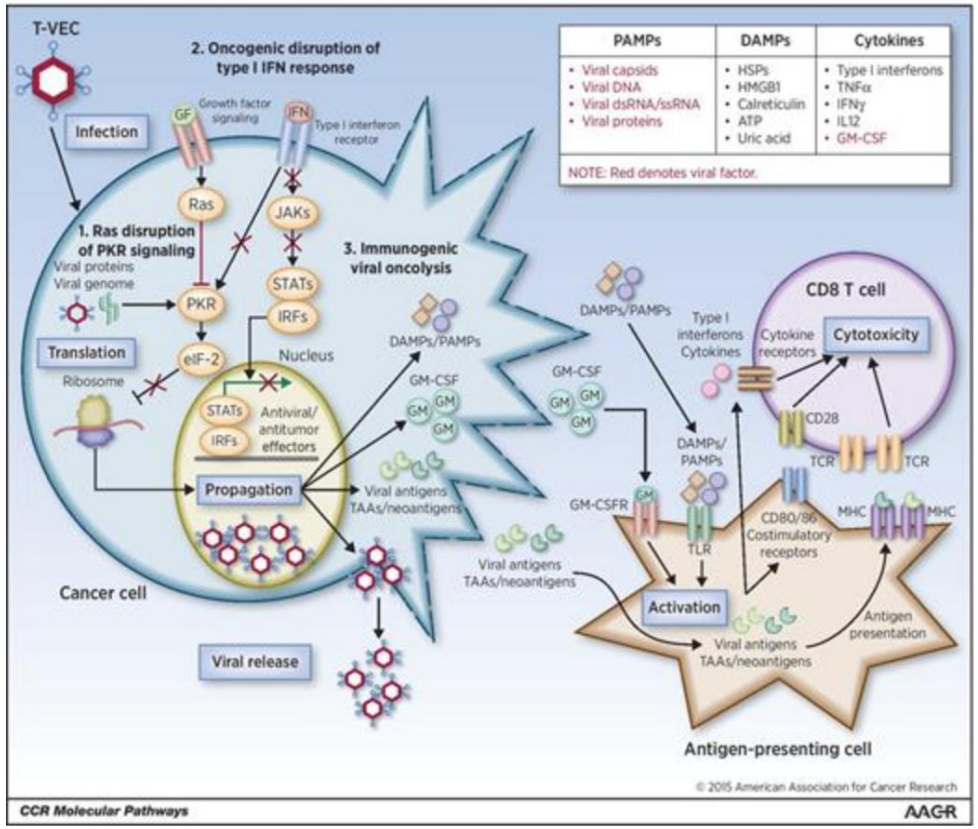
T-VEC è ottenuto mediante delezione funzionale di 2 geni dell'HSV-1 e l'inserimento della sequenza codificante per il fattore umano stimolante le colonie di granuloci e macrofagi (GM-CSF).

MECCANISMO D'AZIONE

T-VEC si **replica selettivamente a livello delle cellule neoplastiche** a causa della ridotta funzionalità in queste cellule della **PKR** (a causa di un segnale Ras iperattivo) e del segnale di **IFN di tipo I**.
Dopo la replicazione virale e la propagazione nel nucleo, i virioni maturi completano l'assemblaggio nel citoplasma e producendo GM-CSF inducono la lisi cellulare, rilasciando nuovi virioni progenitori che possono infettare altre cellule tumorali e vari fattori pro immunogenici e citochine.
Questi fattori orchestrano il reclutamento e la maturazione delle APC, come le cellule dendritiche, che possono presentare antigeni associati al tumore ai linfociti T citotossici CD8+.

MODALITÀ' DI SOMMINISTRAZIONE

Iniezione intralesionale di lesioni cutanee, sottocutanee, linfonodali o anche viscerali localizzabili ecograficamente.



I virus oncolitici sono virus nativi o ingegnerizzati che **replicano preferenzialmente e distruggono le cellule cancerogene**.
Si ritiene che la replicazione selettiva nelle cellule tumorali dipenda dall'infezione delle cellule neoplastiche, che ospitano bassi livelli di proteina chinasi R (PKR) e elementi disfunzionali del segnale di interferone di tipo I (IFN).

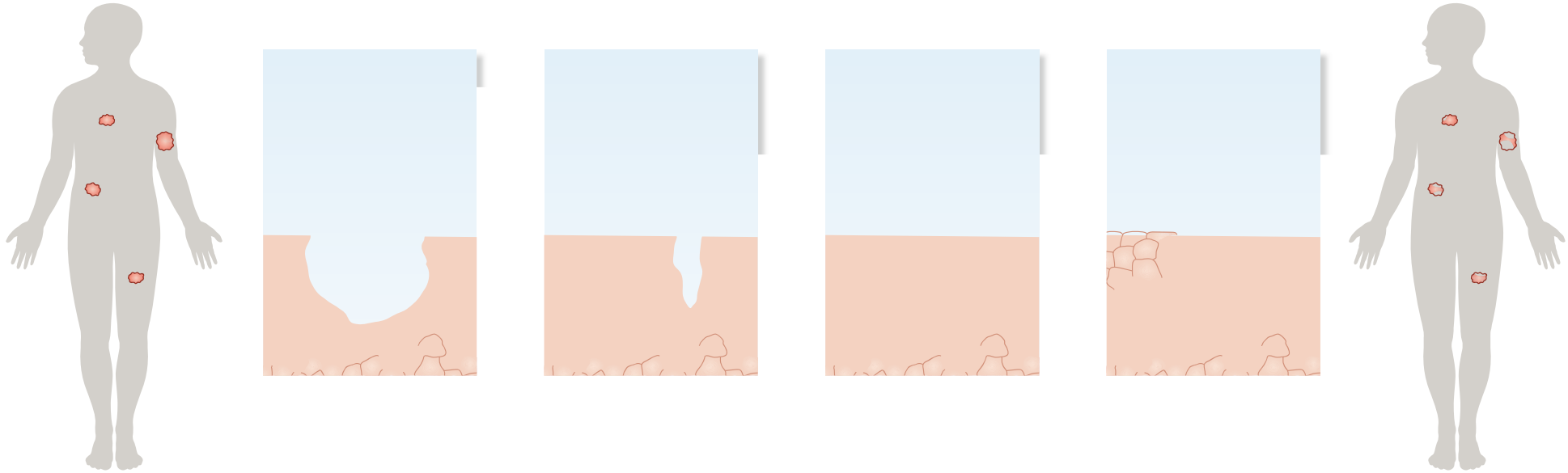
Questi cambiamenti consentono una replicazione virale più efficiente e, con la delezione selettiva di geni virali specifici, potrebbe non essere possibile la replicazione nelle normali cellule con attivazione di PKR.

Si ritiene che la lisi diretta delle cellule tumorali, il rilascio di antigeni tumorali solubili contribuiscano a favorire l'immunità specifica contro il tumore.

Kohlapp FJ, Kaufman HL, 2016

Adjuvant and neoadjuvant Immunotherapy

ADJUVANT



NEOADJUVANT

Versluis JM et al
Nat Med 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

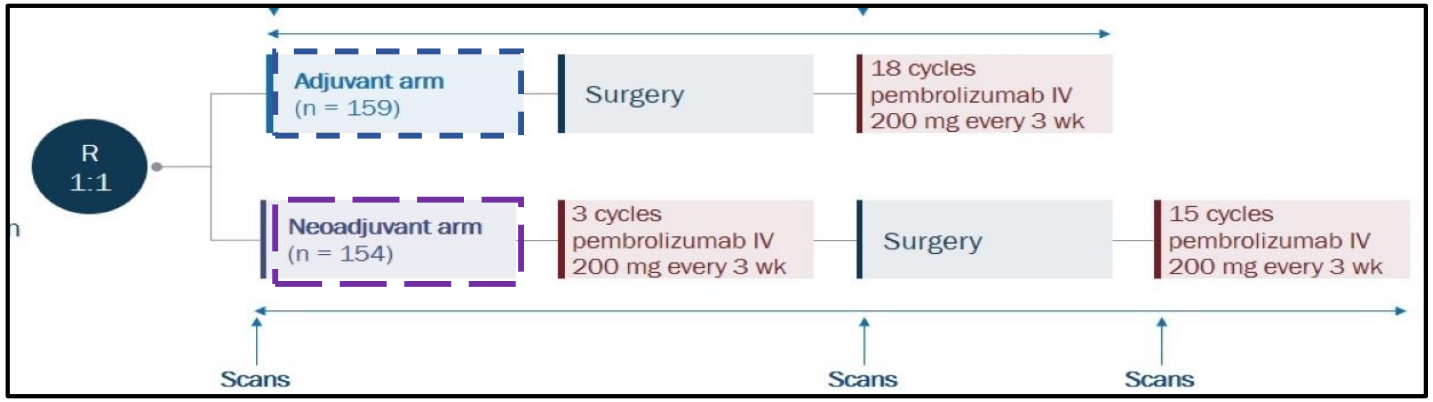
Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

2023;388;813-23

SWOG S1801 phase 2 trial

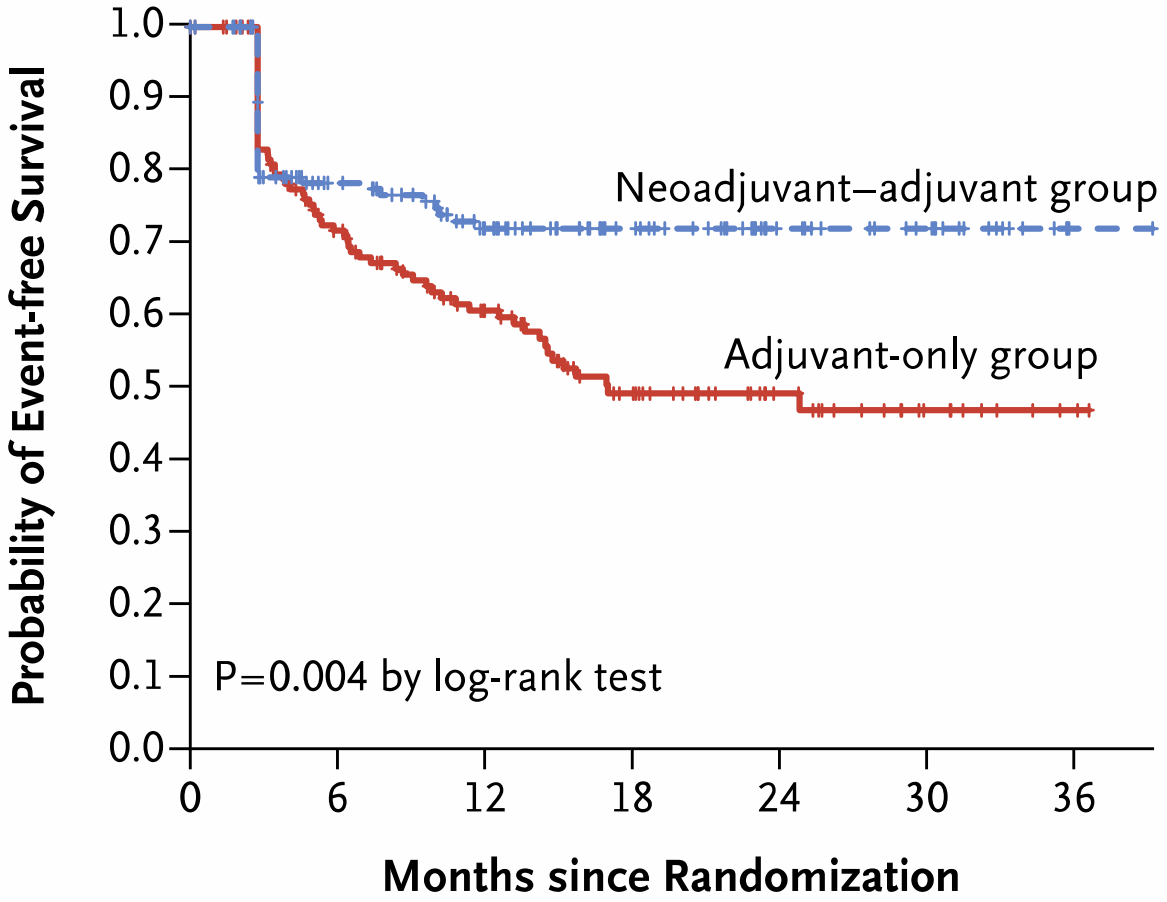
Resectable stage IIIB-IV (no brain mets)



for 1 y or until disease recurrence or unacceptable toxic effects

Primary end point: event-free survival

Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause.



No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

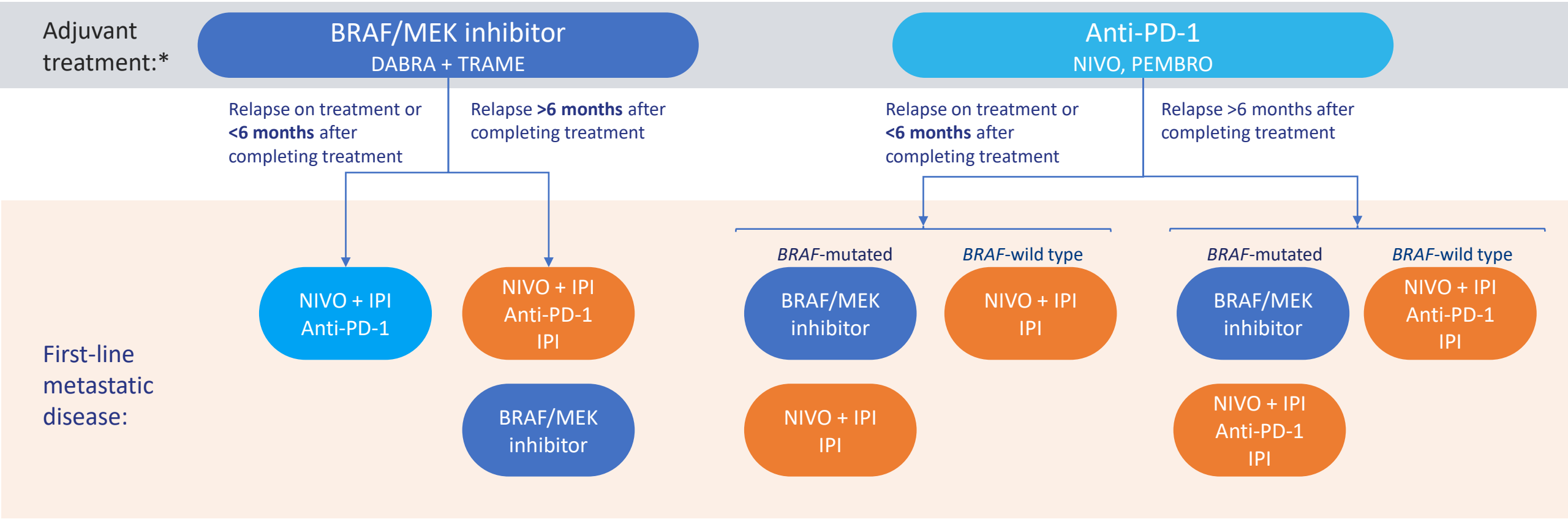
At a median follow-up of 14.7 months, the neoadjuvant–adjuvant group (154 patients) had significantly longer event-free survival than the adjuvant-only group (159 patients)

Patel et al. NEJM 2023

CONCLUSIONS

- Adjuvant therapy (nivolumab, pembrolizumab and dabrafenib/trametinib) administered for 1 year should be offered to patients in stage IIB-C and stage III-IV melanoma, with high risk of recurrence and death
- Schedules, delivery and toxicity are key factors to select a specific adjuvant treatment
- Long-term data are required to determine which therapy has the greatest impact on overall survival
- Different successfult treatment options are available for unresectable and/or metastatic melanoma
- Neoadjuvant therapy represents a promising approach

Melanoma treatment algorithm[1]



*Only DABRA + TRAME are approved in the adjuvant setting. BRAFTOVI + MEKTOVI are not approved in the adjuvant setting.
BRAFTOVI, encorafenib; MEKTOVI, binimetinib.
DABRA, dabrafenib; IPI, ipilimumab; IPI, ipilimumab; MEK, mitogen-activated protein kinase (MAPK) kinase; NIVO, nivolumab; PD-1, programmed cell death protein 1; PEMBRO, pembrolizumab; TRAME, trametinib.
1. Keilholz U, et al. *Ann Oncol*. 2020;31(11):1435-1448.

No definitive evidence that adjuvant therapy improves OS in stage III melanoma

Risk reduction

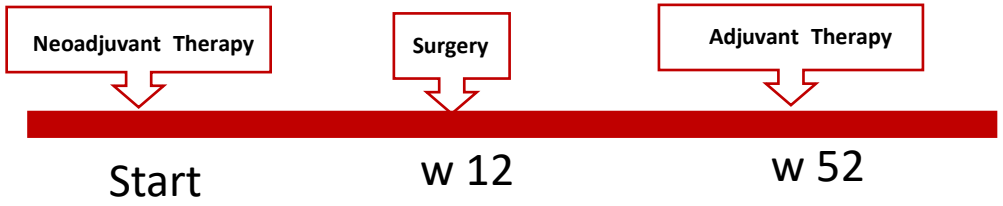
Toxicity

Salvage

NEO-Combi - phase 2 trial

NEOADJUVANT DABRAFENIB COMBINED WITH TRAMETINIB

35 patients with resectable stage IIIB-C, $BRAF^{V600+}$ melanoma received 150 mg Dabrafenib orally, twice daily, plus 2 mg Tramentinib orally, once daily for 52 weeks



At resection

	Study population (n=35)
Pathological response	
Complete	17 (49%; 95% CI 31–66)
Non-complete	18 (51%; 95% CI 34–69)
RECIST response	
Complete response	16 (46%; 95% CI 29–63)
Partial response	14 (40%; 95% CI 24–58)
Stable disease	5 (14%; 95% CI 5–30)
Metabolic response	
Complete	18 (51%; 95% CI 34–69)
Non-complete	17 (49% 95% CI 31–61)

Data are n (%; 95% CI). RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: **Patients with pathological, RECIST, and metabolic responses at 12 weeks**

- No evidence of clinical or radiological progression during 12w of neoadjuvant treatment
- 40% recurred after resection within the 1st year
- First site of recurrence: locoregional (55%) or distant (45%)
- Median OS: not reached

Side effects	Grade 1–2	Grade 3	Grade 4
Any	35 (100%)	9 (26%)	1 (3%)
Pyrexia	24 (69%)	3 (9%)	1 (3%)
Fatigue	27 (77%)	..	..
Chills	24 (69%)	..	..
Nausea	21 (60%)	..	..
Vomiting	14 (40%)	..	..
Diarrhoea	12 (34%)	..	..
Stomach pain	7 (20%)	..	..
Dry mouth	6 (17%)	..	..
Abdominal pain	4 (11%)	..	..
Oral mucositis	4 (11%)	..	..
Headache	26 (74%)	1 (3%)	..

Long GV et al. Lancet Oncol 2019

Clinical Trials of neoadjuvant Therapies for Advanced Melanoma

Efficacy and Toxicity

Trial	Regimen	Patients, n	pCR Rate, %	ORR, %	Grade ≥ 3 Toxicity, %
NCT02519322[a]	Ipi 3 mg/kg + nivo 1 mg/kg **Nivo 3 mg/kg**	11 **12**	45 **25**	73 **25**	73 **8**
NCT02437279[b]	Ipi 3 mg/kg + nivo 1 mg/kg	10	33	50	90
NCT02977052[c]	Ipi 3 mg/kg + nivo 1 mg/kg **Ipi 1 mg/kg + nivo 3 mg/kg** **Ipi 3 mg/kg + nivo 3 mg/kg**	30 **30** **26**	47 **57** **23**	63 **57** **35**	4
NCT02434354[d]	Pembrolizumab 200 mg	29	19	n/a	0
NCT02519322[e]	Nivo 480 mg + rela 160 mg	30	59	57	Neoadjuvant: 0 **Adjuvant: 26**

Ipi, ipilimumab; n/a, not available; nivo, nivolimumab; ORR, objective response rate; pCR, pathologic complete response; rela, relatlimab.

a. Amaria R, et al. Nat Med. 2018;24:1649-54; b. Blank CU, et al Nat Med 2018;24:1655-1661; c. Rozeman EA, et al. Lancet Oncol. 2019;20:948-960; d. Huang A, et al. Nat Med. 2019;25:454-461; e. Lipson E, et al. J Clin Oncol. 2021;39:15_suppl:9503-9503.