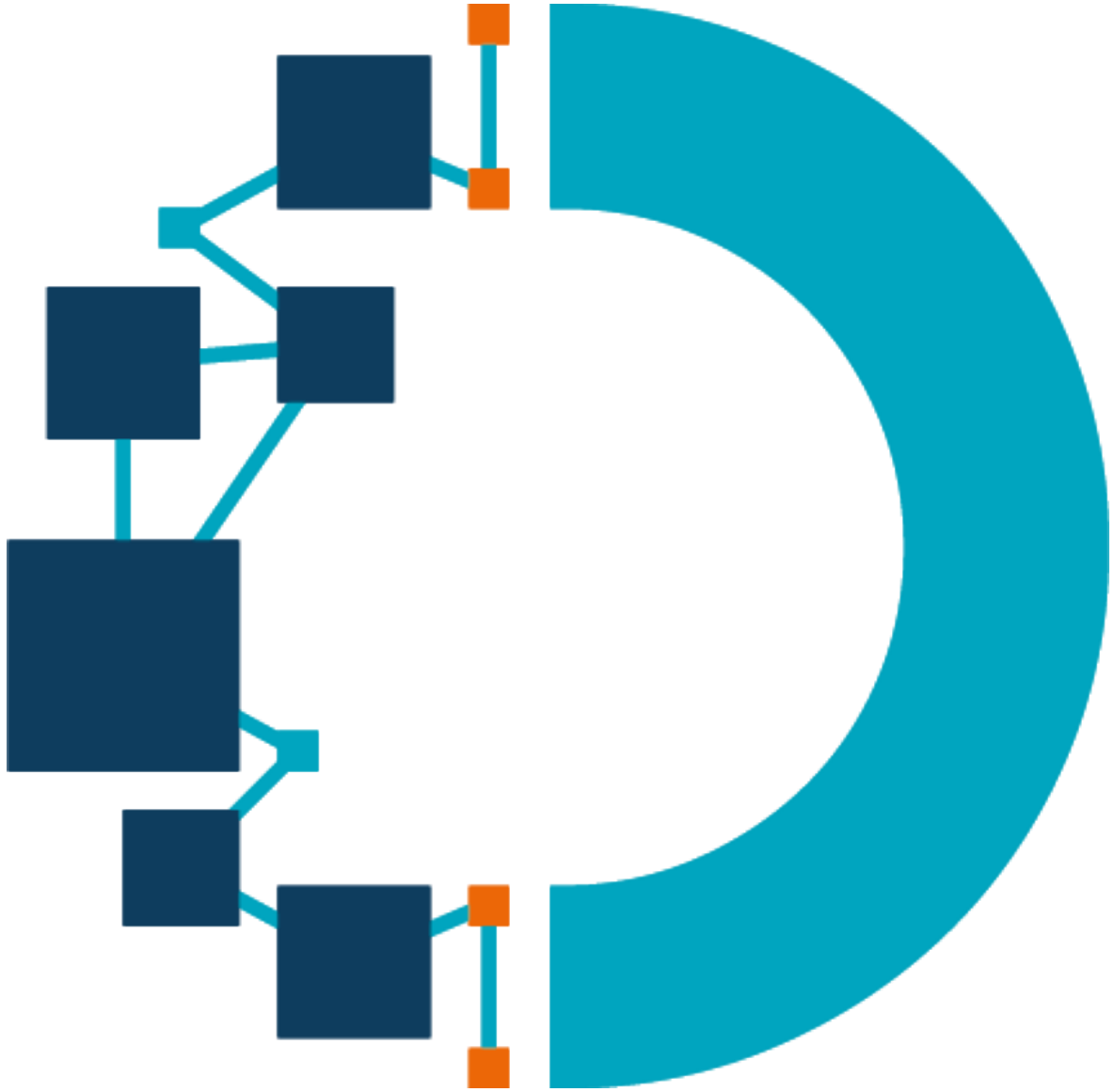
PRISE EN CHARGE DU MELANOME : RECOMMANDATIONS ET ACTUALITES

Pr. Henri Montaudié

CHU de Nice, INSERM U1065, C3M, UCA



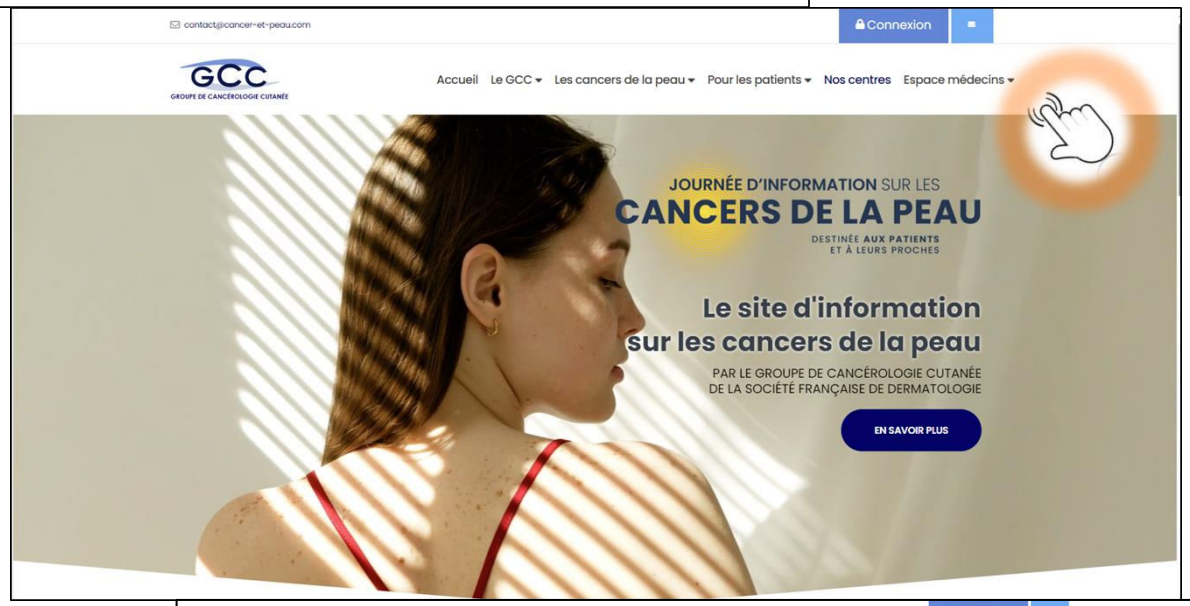
Liens d'intérêts

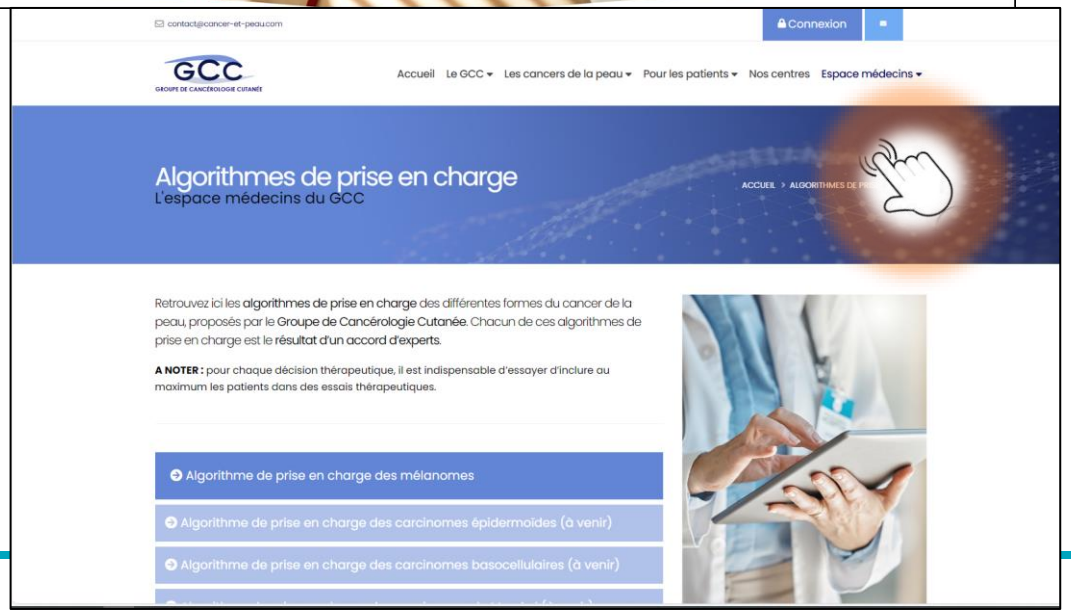
- « Le contenu et/ou les opinions exprimés lors de cette présentation, notamment celui ou celle(s) relatifs à la stratégie thérapeutique ont été réalisés en toute indépendance »
- Consultant occasionnel – participation à des boards pour les laboratoires : PFO, BMS, MSD, Novartis, Regeneron et Sun Pharma
- Participation à des essais cliniques : PFO, BMS, MSD, GSK, Novartis, Regeneron, Nektar, Therapeutics, 4SC, Incyte,IOVANCE
- Grant : Leo Pharma et BMS

Groupe de Cancérologie Cutanée
https://www.cancer-et-peau.com

Groupe de Cancérologie Cutanée (GCC)

Le Groupe de Cancérologie Cutanée (**GCC**) est un groupe thématique de la Société Française de Dermatologie. Il regroupe des dermatologues, oncologues et dermato- ...





Annales de dermatologie et de vénéréologie - FMC 4 (2024) 281–288

ELSEVIER
Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

PRATIQUES PROFESSIONNELLES

Algorithmes de prise en charge thérapeutique du mélanome du stade I au stade IV. Recommandations de prise en charge du Groupe de cancérologie cutanée de la Société française de dermatologie

Algorithms for the therapeutic management of melanoma stages I to IV. Management recommendations of the Cutaneous Oncology Group of the French Society of Dermatology

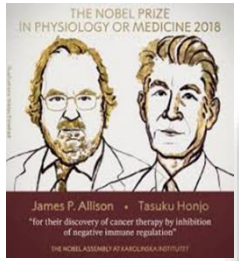
E. Funck-Brentano[a,1,*], H. Montaudié[b,1], C. Gaudy-Marqueste[c], E. Maubec[d,e], M. Samimi[f], M.-T. Leccia[g], T. Jouary[h], N. Meyer[i], C. Lebbé[j], S. Dalac[k], G. Quereux[l], L. Mortier[m], au nom du Groupe de cancérologie cutanée de la Société française de dermatologie

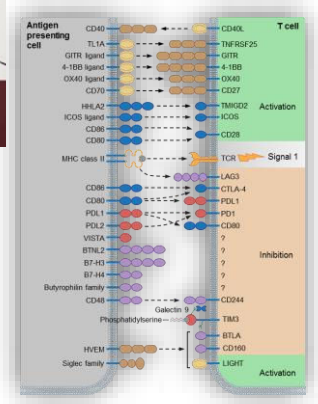
[a] *Service de dermatologie générale et oncologique, hôpital Ambroise-Paré, AP–HP, EA4340-BECCOH, université Paris-Saclay, UVSQ, 92104 Boulogne-Billancourt, France*
[b] *Service de cancérologie cutanée, CHU de Nice, Inserm U1065, équipe 12, centre méditerranéen de médecine moléculaire, université Côte d'Azur, Nice, France*
[c] *Service de dermatologie et de cancérologie cutanée, CHU Timone, Immunity and Cancer Team, centre de recherche en cancérologie de Marseille (CRCM), Inserm, U1068, CNRS, UMR7258, Aix-Marseille University, UM105, Marseille, France*
[d] *Service de dermatologie, hôpital Avicenne, AP–HP, 93000 Bobigny, France*
[e] *Université Sorbonne-Paris-Nord, Inserm UMR1124, université Paris Cité, Paris, France*
[f] *Service de dermatologie, CHU de Tours, Tours, France*
[g] *Service de dermatologie, allergologie et photobiologie, CHU Grenoble-Alpes, Inserm U1209, CNRS 5309, IAB, université Grenoble-Alpes, 38000 Grenoble, France*

[*] Auteur correspondant.
Adresse e-mail : elisa.funck-brentano@aphp.fr (E. Funck-Brentano).
[1] Contribution identique.

L'arsenal thérapeutique dans le mélanome en 2024…

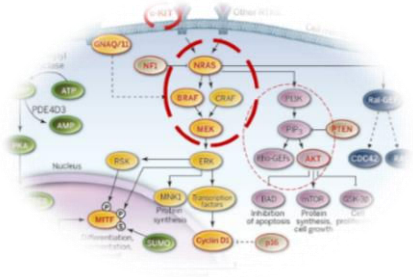
✓ **IMMUNOTHÉRAPIE:**





- Anti-PD1: nivolumab[1,2] – pembrolizumab[3]
- Anti-PD1+ anti-CTLA-4: nivolumab + ipilimumab[4,5]

✓ **THÉRAPIE CIBLÉE**: anti-BRAF + anti-MEK

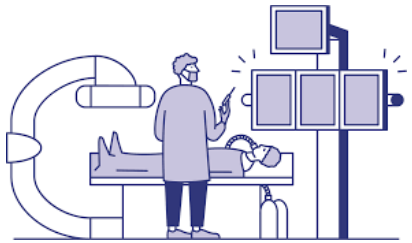


- vemurafenib + cobimetinib[6]
- dabrafenib + trametinib[7,8,9,10]
- encorafenib + binimetinib[11]
- inhibiteurs tyrosines kinases : imatinib…

✓ **CHIMIOTHÉRAPIE:**

- Dacarbazine, temodal, fotemustine…

✓ **Traitements locaux destructeurs**

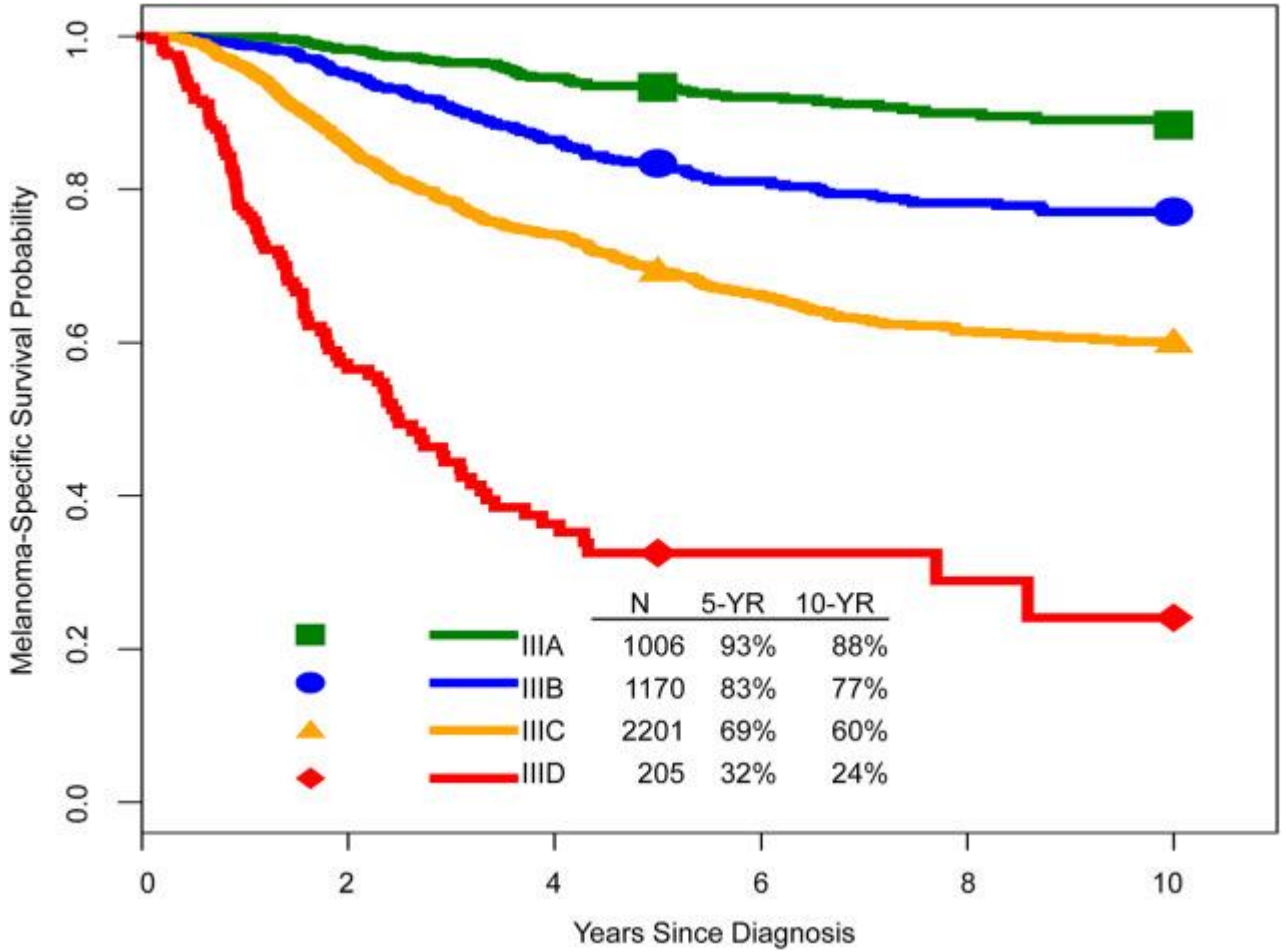


[1]Robert et al. N Engl J Med 2015;372:320-30
[2]Weber et al. Lancet Oncol 2015; 16: 375–84
[3]Robert al. N Engl J Med 2015;372:2521-32
[4]Wolchok JD et al. N Engl J Med 2017;377:1345-56
[5]Tawbi HA et al. N Engl J Med. 2018;23;379(8):722-730
[6]Larkin J et al. N Engl J Med. 2014; 13;371(20):1867-76
[7]Long GV et al. Lancet 2015;386:444-51
[8]Long GV et al. N Engl J Med 2014 13;371(20):1877-88
[9]Robert C. et al. N Engl J Med 2015;372:30-9.
[10]Davies M et al. Lancet Oncol 2017; 18: 863–73
[11]Dummer R et Lancet Oncol. 2018;19(5):603-615

ACTUALITÉS SUR LA PRISE EN CHARGE DU MÉLANOME À HAUT RISQUE DE RÉCIDIVE

Mélanome à haut risque de récidive (1)…

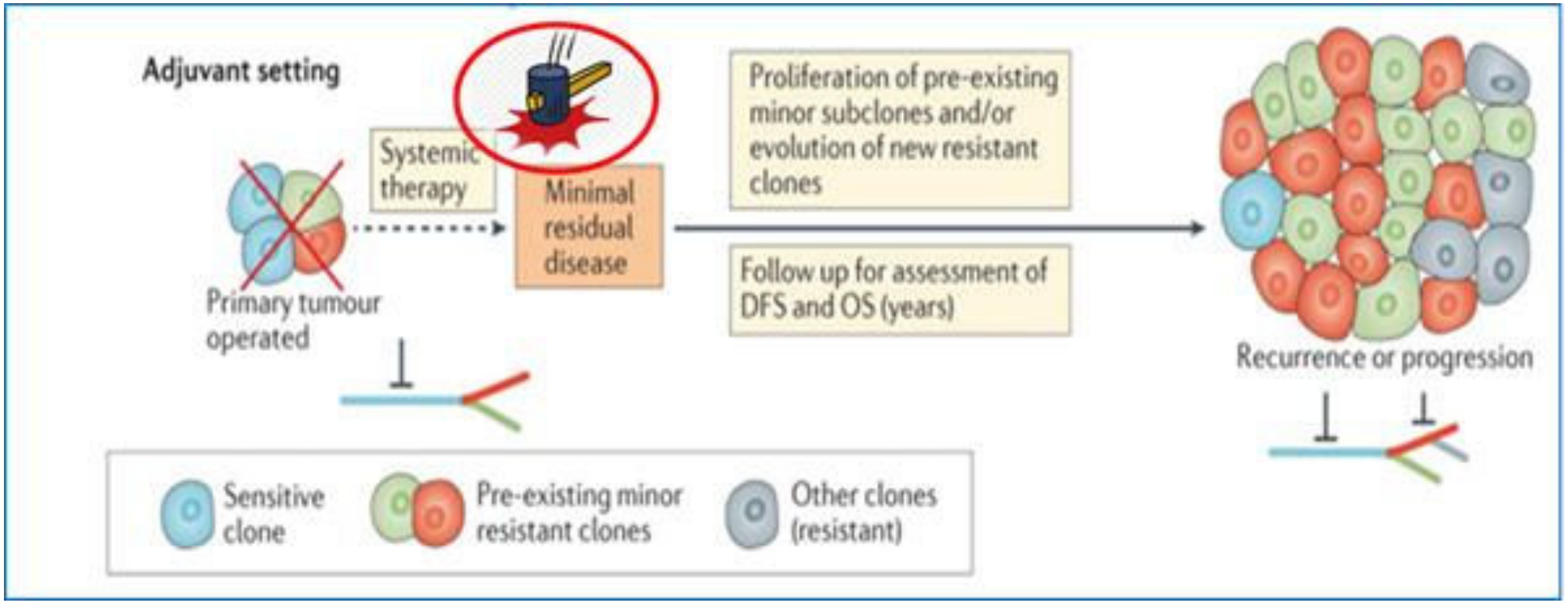
AJCC 8ème édition



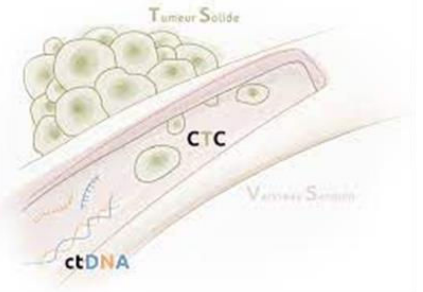
MÉLANOME STADE III
(ET STADE IV OPÉRÉ)

Gershenwald JE et al. CA Cancer J Clin. 2017

Traitement ADJUVANT
ou comment s'attaquer à la **maladie résiduelle?**



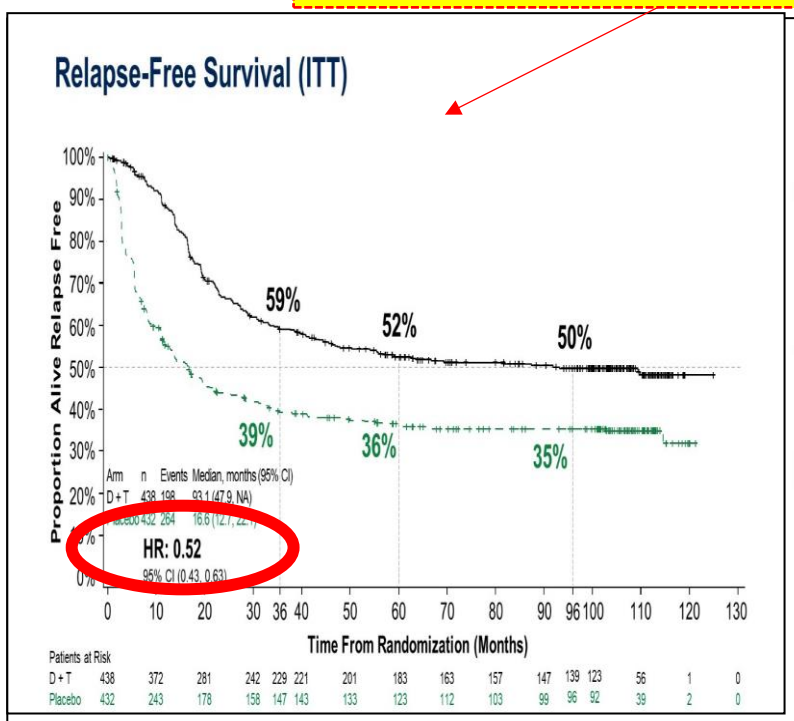
ADN tumoral circulant

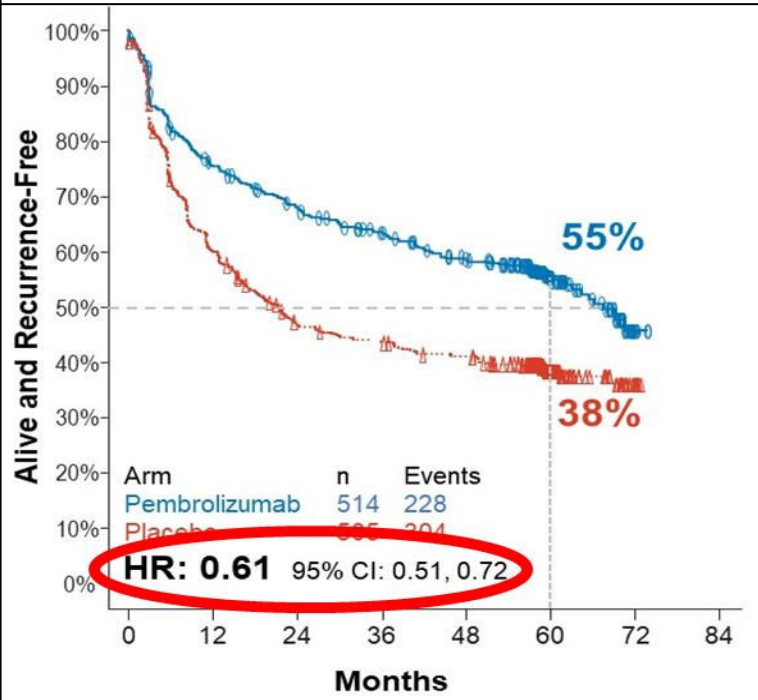


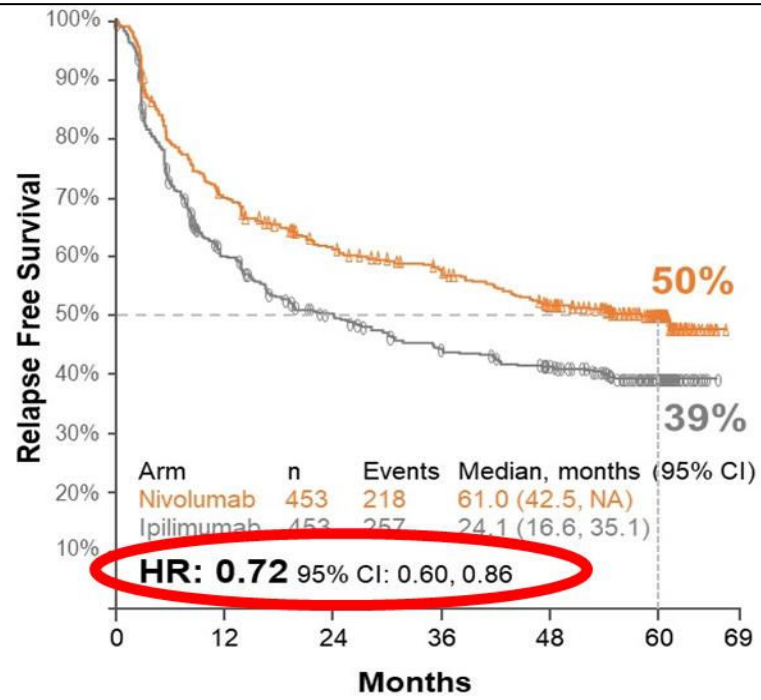
Gershenwald JE et al. CA Cancer J Clin. 2017

Données de Survie Sans Récidive (SSR = RFS) > 5 ans

Jusqu'à 10 ans pour COMBI-AD!!







COMBI-AD[1]	KEYNOTE-054[2]	CHECKMATE-238[3]
Dabrafenib plus trametinib vs placebo	Pembrolizumab vs placebo	Nivolumab vs ipilimumab

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.

III A-B-C

IIIB/C –IV
Comparateur actif

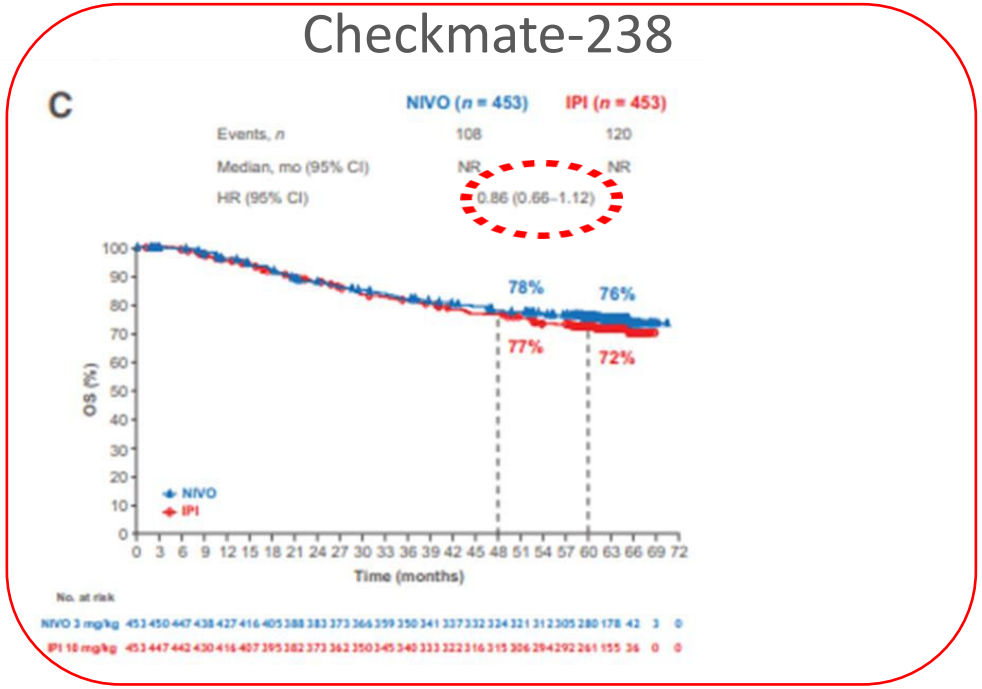
Long GV et al. NEJM 2024

Résultats similaires sur la survenue de métastase à distance

Données de Survie Globale (SG = OS)

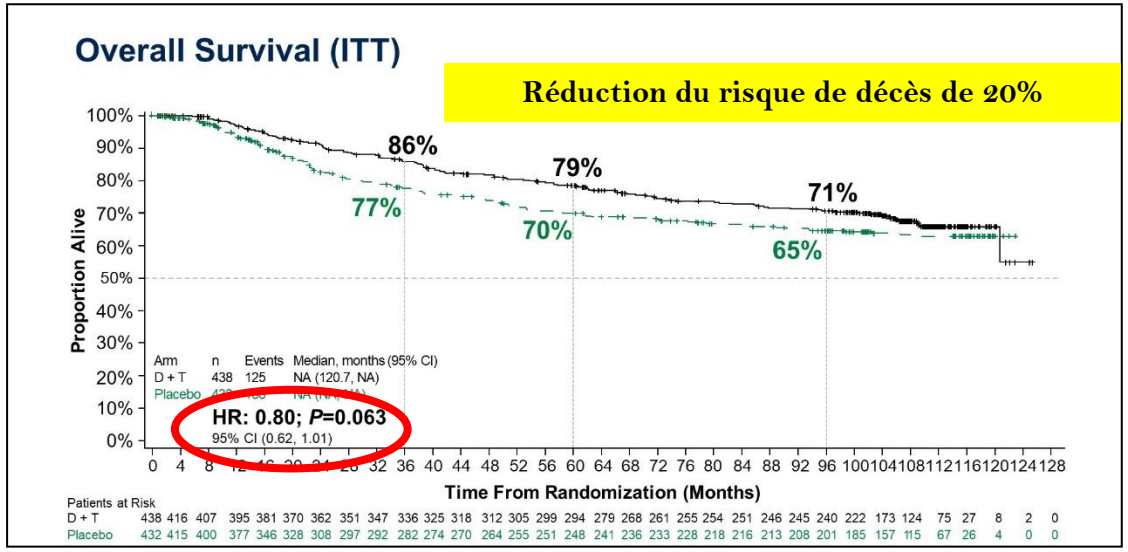
Amélioration OS mais non significative

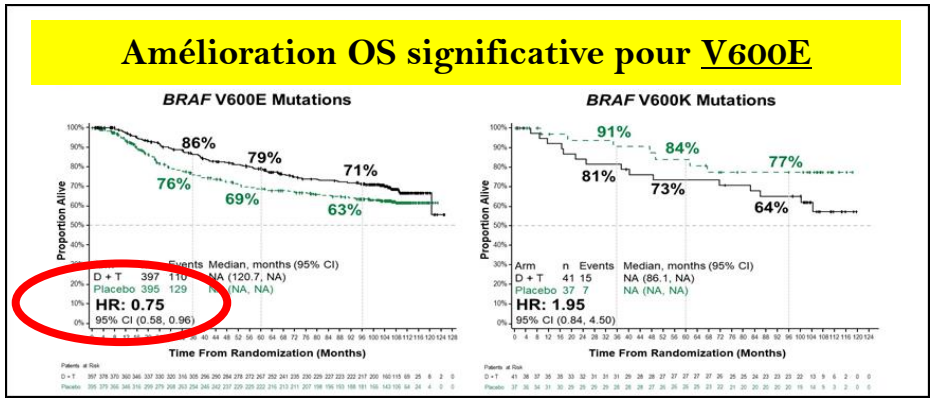
Checkmate-238



Larkin J et al. Clin Can Res 2023

COMBI-AD



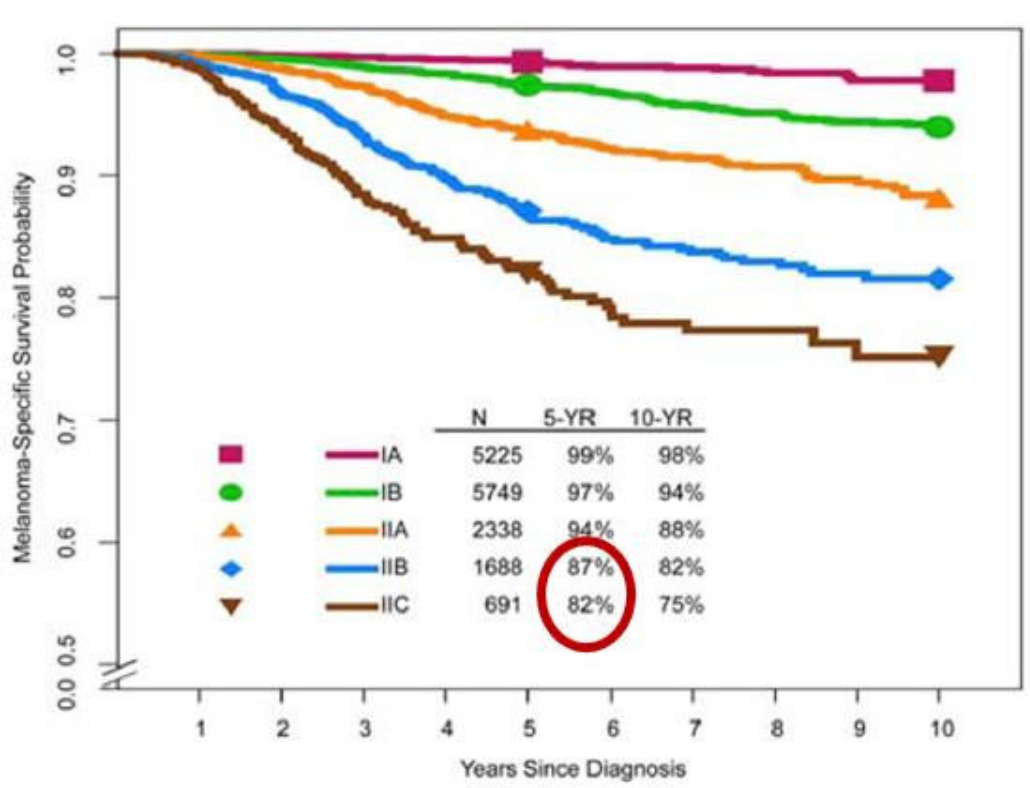


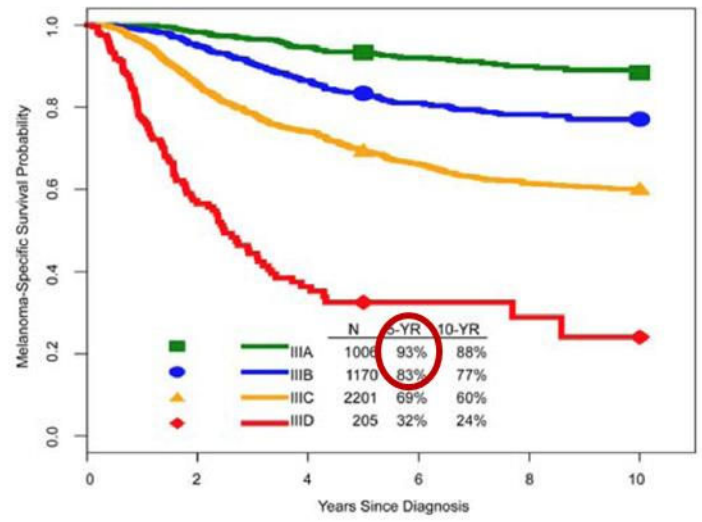
Long GV et al. NEJM 2024

Mélanome à haut risque de récidive (2)…
STADE IIB-IIC

Stade IIB:
- **Breslow 2-4mm ulcéré**
- **Breslow > 4mm non ulcéré**

Stade IIC: Breslow > 4mm ulcéré

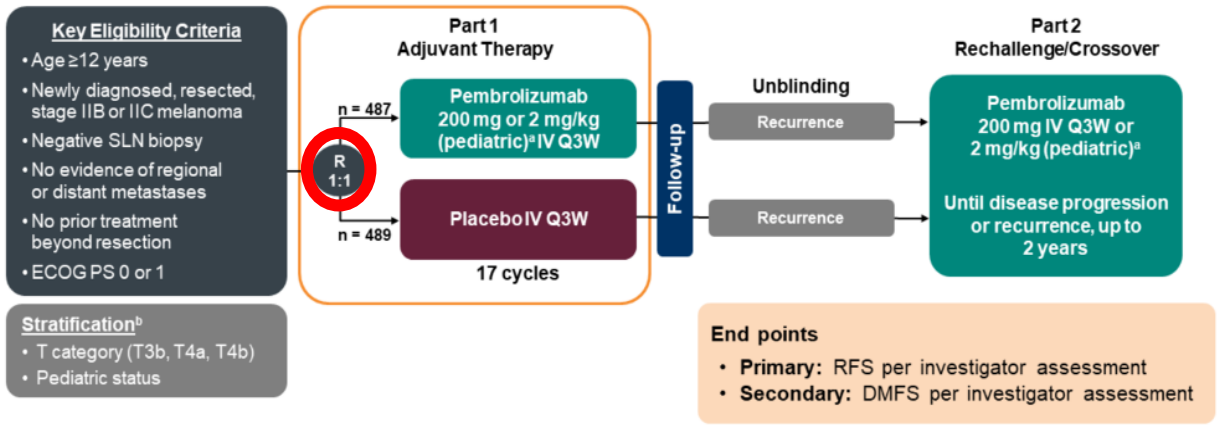




Gershenwald JE et al. CA Cancer J Clin. 2017

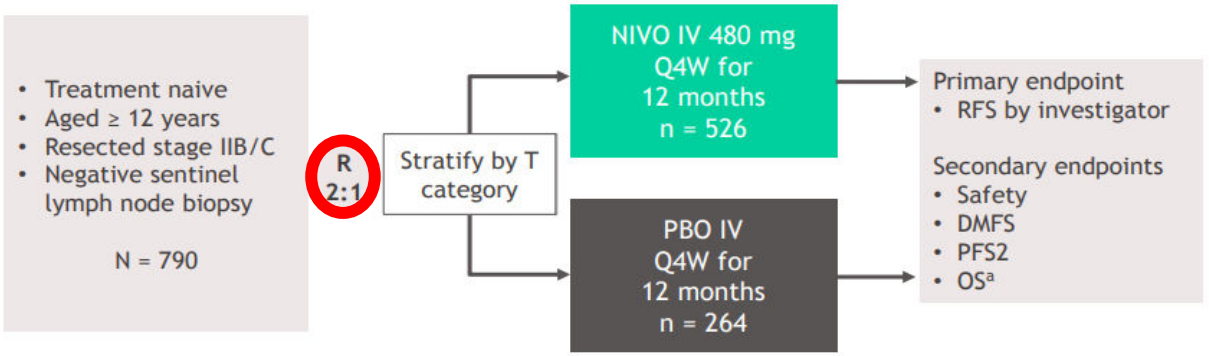
Thérapie adjuvante pour **les stades IIB-IIC** en 2024…

KEYNOTE-716 Study Design (NCT03553836)



CheckMate 76K

- CheckMate 76K is a global, randomized, double-blind, phase 3 study NIVO treatment in patients with resected stage IIB/C melanoma



Pembrolizumab vs Placebo as Adjuvant Therapy for High-Risk Stage II Melanoma: Long-Term Follow-Up, Rechallenge, and Crossover in KEYNOTE-716 4-year results

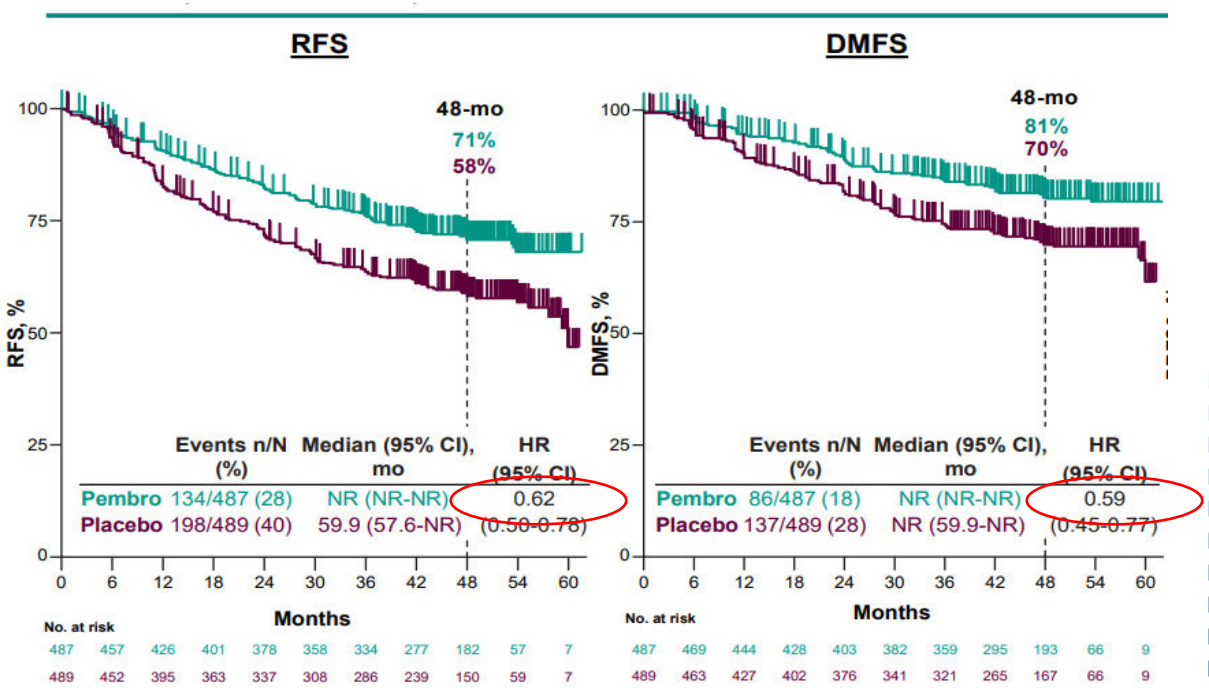
Adjuvant nivolumab vs placebo in stage IIB/C melanoma: 3-year results from CheckMate 76K

Georgina V. Long,[1] Michele Del Vecchio,[2] Christoph Hoeller,[3] Jeffrey Weber,[4] Jean-Jacques Grob,[5] Peter Mohr,[6] Stephan Grabbe,[7] Caroline Dutriaux,[8] Vanna Chiarion-Sileni,[9] Jacek Mackiewicz,[10] Piotr Rutkowski,[11] Petr Arenberger,[12] Gaëlle Quéreux,[13] Tarek Meniawy,[14] Paolo A. Ascierto,[15] Janis Taube,[16] Ayman Nassar,[17] Sonia Dolfi,[17] Wenjia Wang,[17] John M. Kirkwood[18]

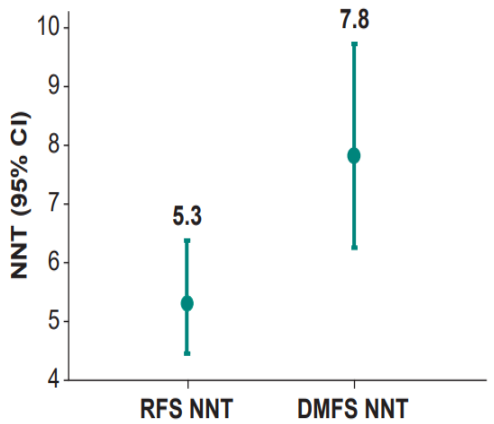
Luke JJ et al. Lancet Oncol 2023

Kirkwood JM et al. Nat Med 2023

Thérapie adjuvante pour **les stades IIB-IIC** en 2024…



Number Needed to Treat by RMST for RFS and DMFS



Calculation of NNT based on RMST

$$NNT_{RMST}(t) = \frac{1}{(RMST_P(t)/RMST_C(t)) - 1}$$

For this analysis:

$RMST_p(t)$ = Total area under the Kaplan-Meier curve to 60 months in the pembrolizumab arm

$RMST_c(t)$ = Total area under the Kaplan-Meier curve to 60 months in the placebo arm

Réduction du risque de récidive/de métastase à distance ~ 35-40%

Luke JJ et al. Lancet Oncol 2023

Kirkwood JM et al. Nat Med 2023

Est-il envisageable de faire mieux - différemment ?

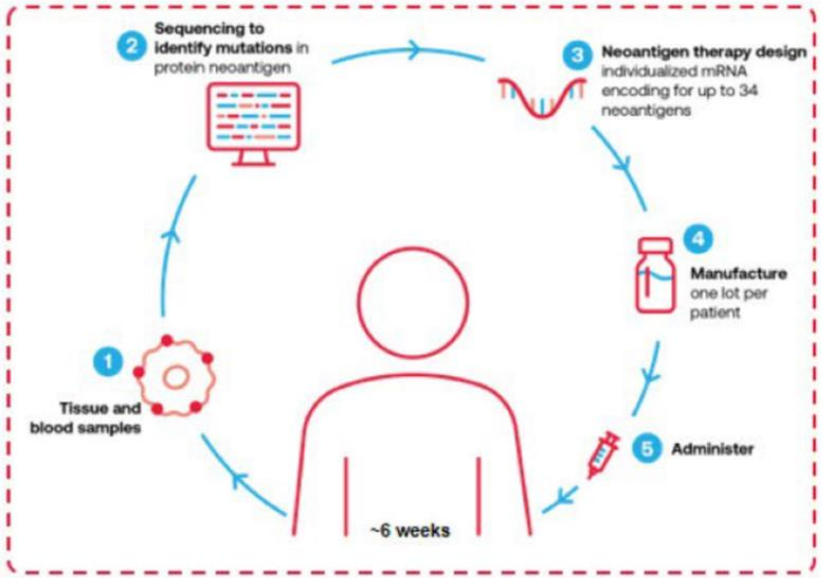
2024 ASCO ANNUAL MEETING

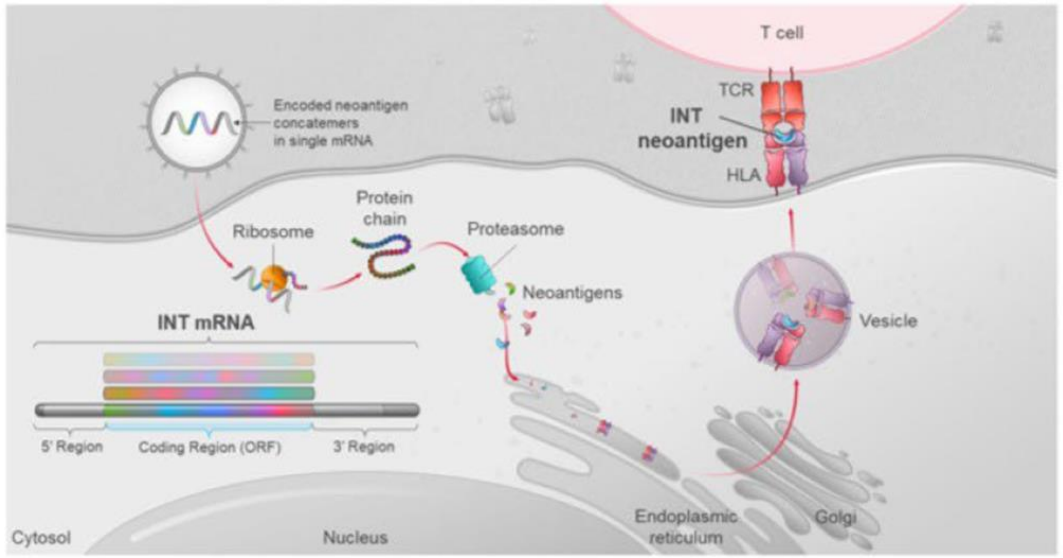
Individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from the mRNA-4157-P201 (KEYNOTE-942) trial

Jeffrey S. Weber,[1] Muhammad Adnan Khattak,[2] Matteo S. Carlino,[3] Tarek Meniawy,[4] Matthew H. Taylor,[5] George Ansstas,[6] Kevin B. Kim,[7] Meredith McKean,[8] Ryan J. Sullivan,[9] Mark B. Faries,[10] Thuy Tran,[11] C. Lance Cowey,[12] Theresa M. Medina,[13] Jennifer M. Segar,[14] Victoria Atkinson,[15] Geoffrey T. Gibney,[16] Jason J. Luke,[17] Elizabeth I. Buchbinder,[18] Georgina V. Long,[19] INT Research and Development Author Group,[20,21,a] Robert S. Meehan[20]

INT: *INDIVIDUALIZED NEOTANGEN THERAPY*

→ **ARN messager personnalisé** codant pour 34 neoantigènes spécifiques de la tumeur et du système HLA de chaque individu

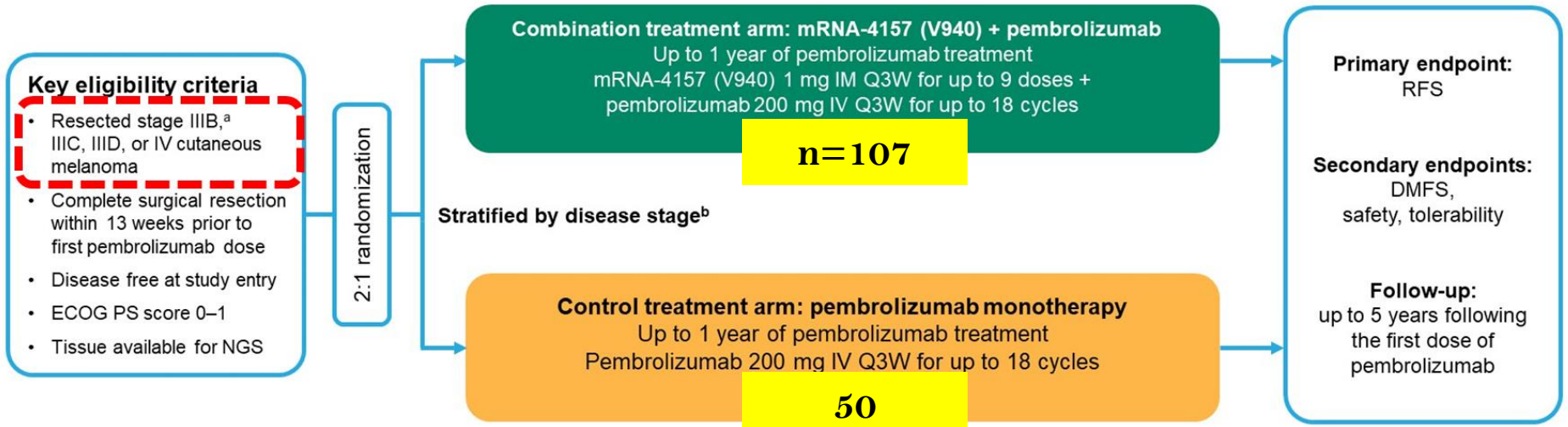




LBA9512

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design

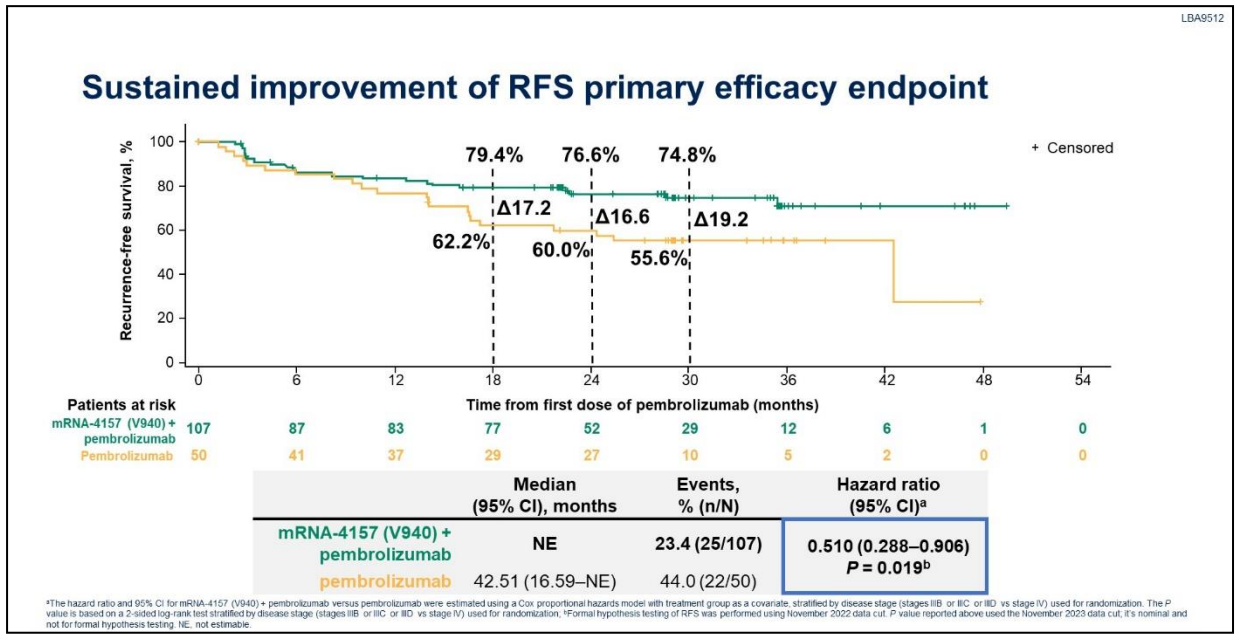
Randomized, phase 2, open-label study in patients with adjuvant resected melanoma at high risk of recurrence



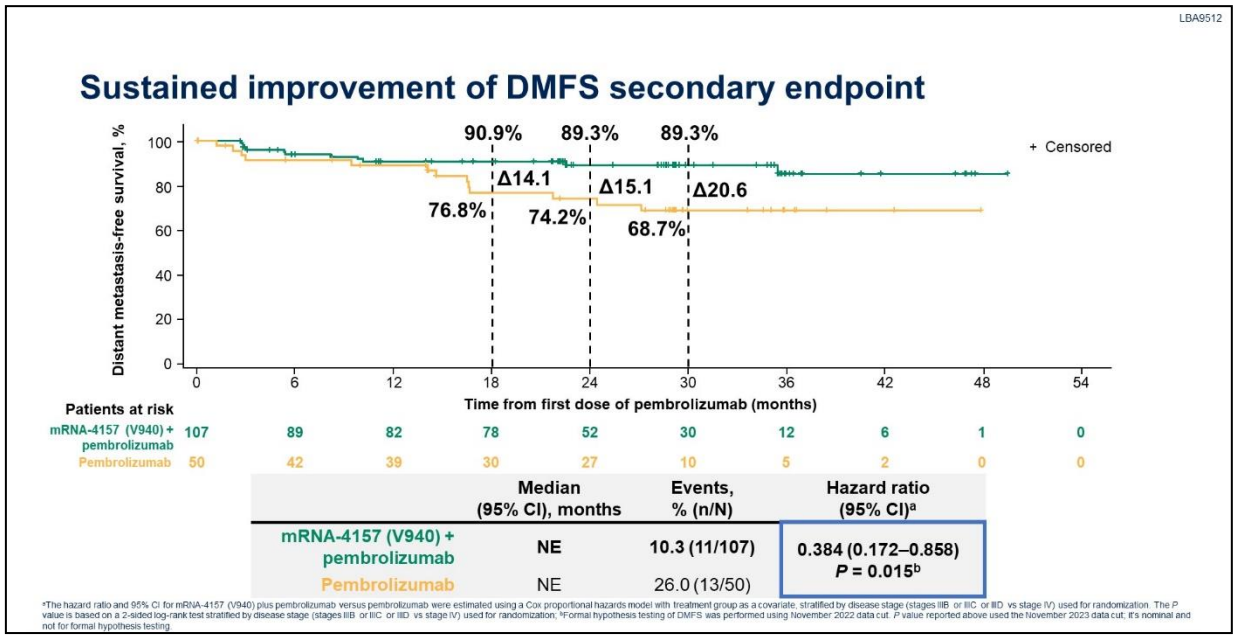
Designed with 80% power to detect a hazard ratio of 0.5 with 40 RFS events (with a 1-sided alpha of 0.1 per protocol)
Primary analysis **triggered after a minimum of 1-year planned follow-up[c]** (November 14, 2022 data cut) and at least 40 RFS events have been observed. DMFS analysis was prespecified for testing following positive RFS in the ITT population

Supportive analysis was **triggered after a minimum of 2 years of planned follow-up[c]** (November 3, 2023 data cut)
Median planned follow-up[c]: ~3yrs

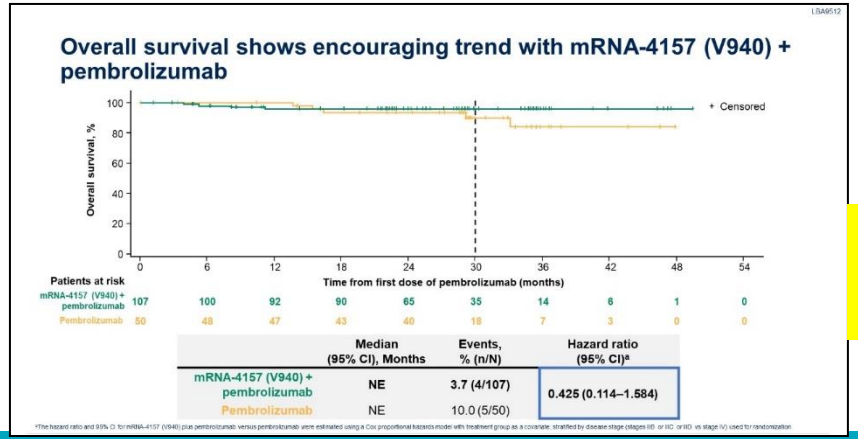
Suivi médian de 3 ans



Réduction du risque de récidive/décès de 49%

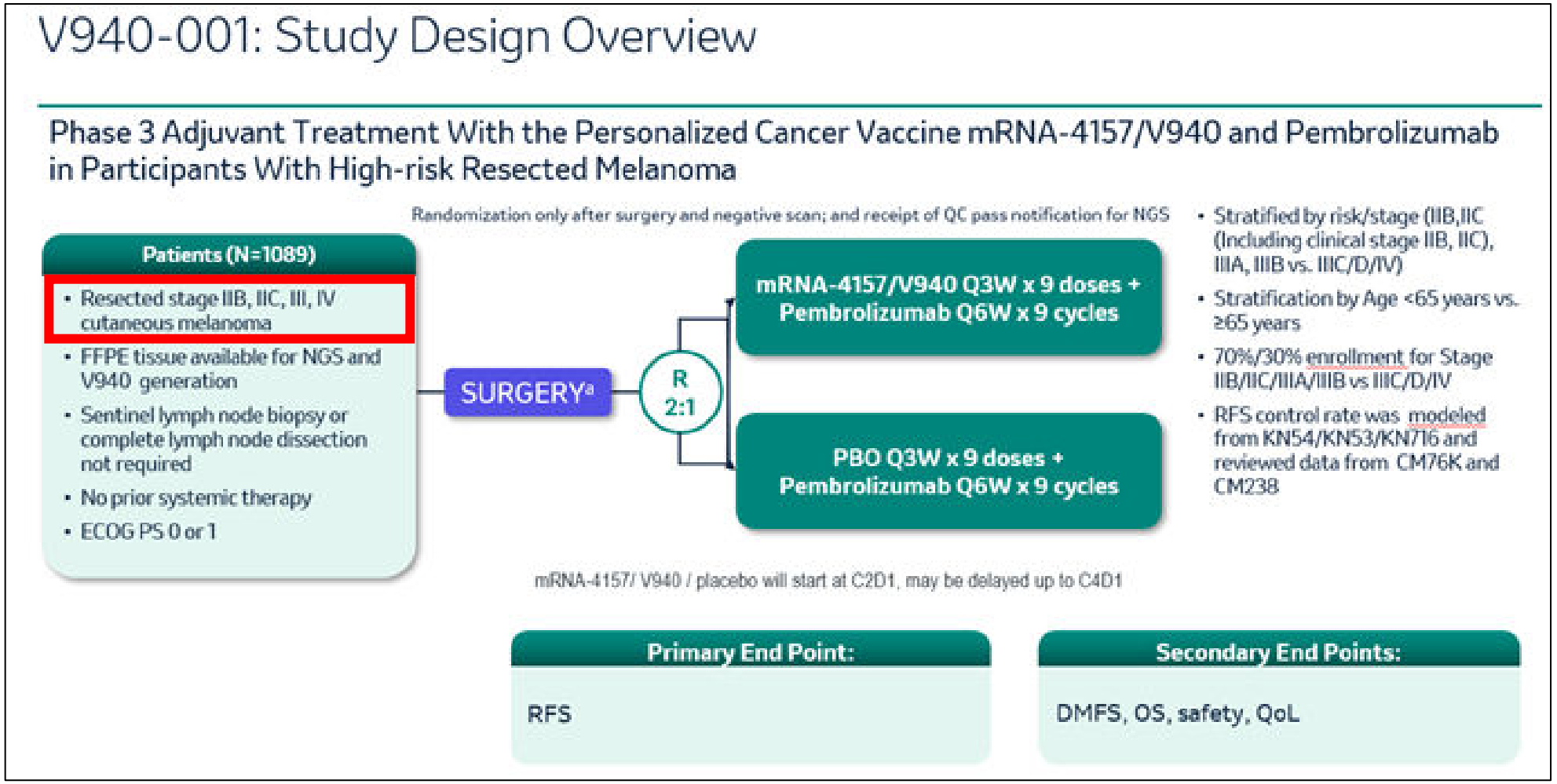


Réduction du risque de métastase à distance de 62%



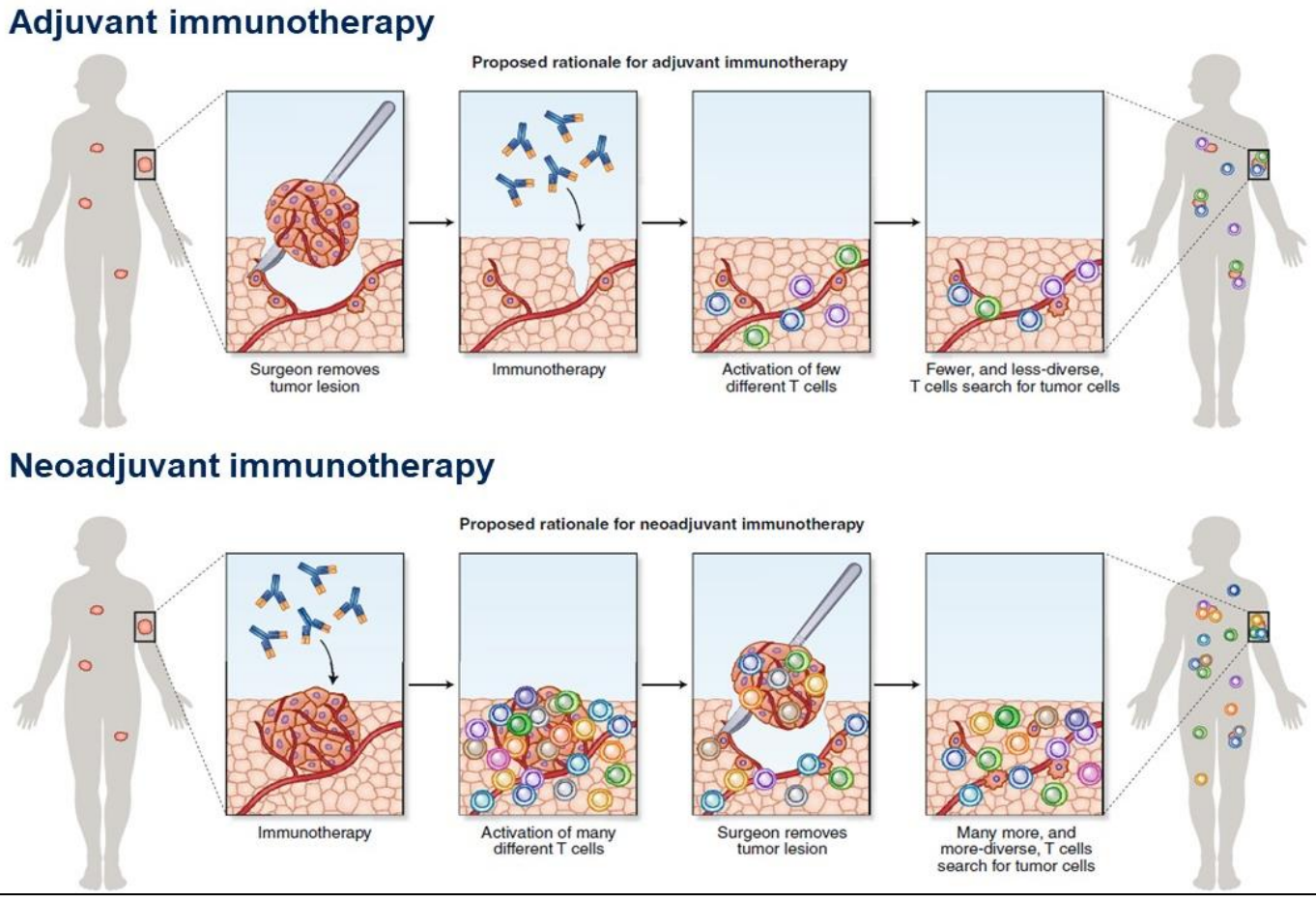
Trop immatures…

A confirmer…


V940-001: Study Design Overview
Phase 3 Adjuvant Treatment With the Personalized Cancer Vaccine mRNA-4157/V940 and Pembrolizumab in Participants With High-risk Resected Melanoma
Randomization only after surgery and negative scan; and receipt of QC pass notification for NGS
Patients (N=1089)
• Resected stage IIB, IIC, III, IV cutaneous melanoma
• FFPE tissue available for NGS and V940 generation
• Sentinel lymph node biopsy or complete lymph node dissection not required
• No prior systemic therapy
• ECOG PS 0 or 1
SURGERY[a]
R 2:1
mRNA-4157/V940 Q3W x 9 doses + Pembrolizumab Q6W x 9 cycles
PBO Q3W x 9 doses + Pembrolizumab Q6W x 9 cycles
• Stratified by risk/stage (IIB,IIC (Including clinical stage IIB, IIC), IIIA, IIIB vs. IIIC/D/IV)
• Stratification by Age <65 years vs. ≥65 years
• 70%/30% enrollment for Stage IIB/IIC/IIIA/IIIB vs IIIC/D/IV
• RFS control rate was modeled from KN54/KN53/KN716 and reviewed data from CM76K and CM238
mRNA-4157/ V940 / placebo will start at C2D1, may be delayed up to C4D1
Primary End Point:
RFS
Secondary End Points:
DMFS, OS, safety, QoL

Est-il envisageable de faire mieux - différemment ?

Stratégie NEOADJUVANTE



- Antigènes tumoraux abondants
- LT réactifs plus nombreux/diverses
- Expansion des LT résidents mémoires et réponse plus spécifique
- Réponse pathologique → (bio) marqueur pronostic, guide la stratégie thérapeutique ultérieure
- Réduction masse tumorale → réduction morbidité tumorale

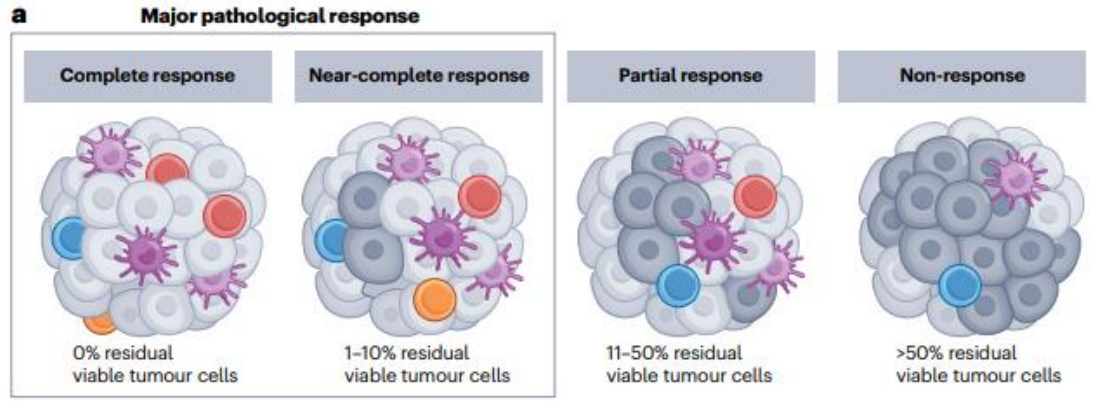
Krishnamoorthy M, Lenehan JG, Maleki Vareki S. Neoadjuvant Immunotherapy for High-Risk, Resectable Malignancies: Scientific Rationale and Clinical Challenges. JNCI J Natl Cancer Inst. 12 janv 2021;113(7):823-32.

Un (nouveau) concept: la réponse pathologique

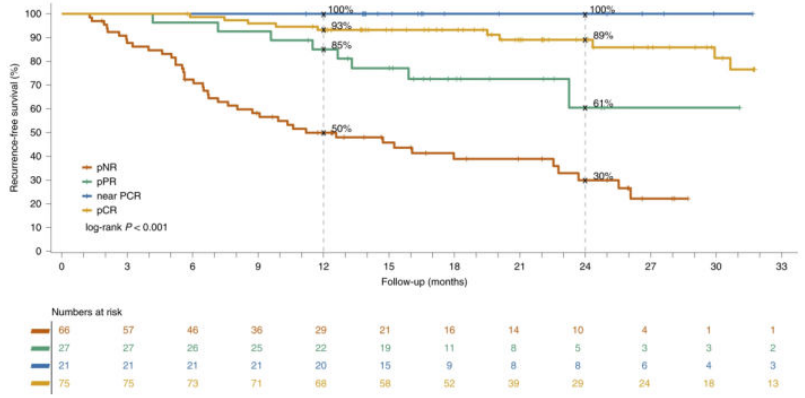
nature medicine ARTICLES
https://doi.org/10.1038/s41591-020-01188-3

Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

Alexander M. Menzies[1,2,3,12], Rodabe N. Amaria[4,12], Elisa A. Rozeman[5,12], Alexander C. Huang[6,7,12], Michael T. Tetzlaff[4,12], Bart A. van de Wiel[5,12], Serigne Lo[1,2,12], Ahmad A. Tarhini[8], Elizabeth M. Burton[4], Thomas E. Pennington[1,2,9], Robyn P. M. Saw[1,2,9], Xiaowei Xu[6], Giorgos C. Karakousis[6], Paolo A. Ascierto[10], Andrew J. Spillane[1,2,3], Alexander C. J. van Akkooi[5], Michael A. Davies[4,13], Tara C. Mitchell[6,13], Hussein A. Tawbi[4,13], Richard A. Scolyer[1,2,11,13], Jennifer A. Wargo[4,13], Christian U. Blank[5,13] and Georgina V. Long[1,2,3,13]



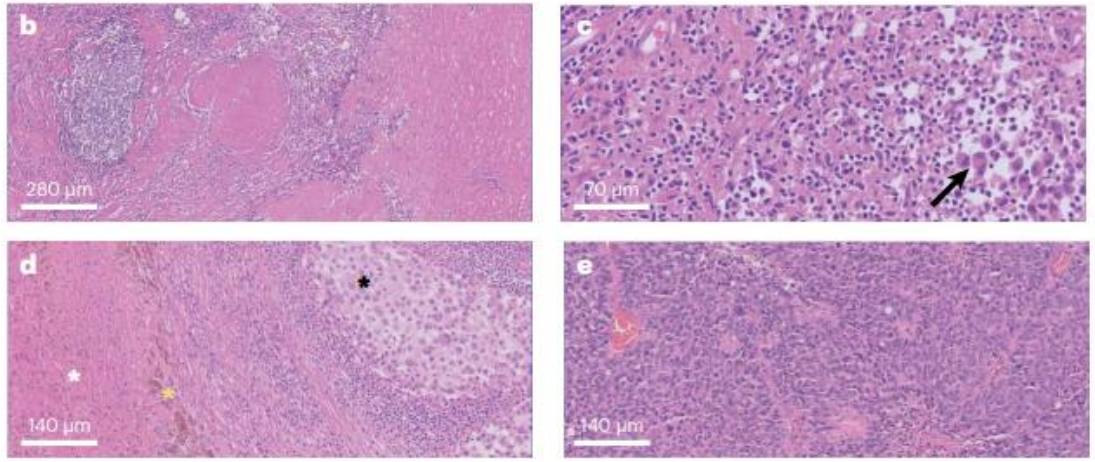
Neoadjuvant BRAF/MEK (n=51), PD-1 alone (n=35), or PD-1+CTLA-4 (n=103)[1]



INMC — International Neoadjuvant Melanoma Consortium

Pathological response[2]

pCR	0% vital tumour
near-pCR	>0 to ≤10% vital tumour
pPR	>10 to ≤50% vital tumour
pNR	>50% vital tumour



Menzies A et al. Nat Med. 2021
Lucas MW et al. Nat Rev Clin Oncol 2023
Tetzlaff MT, et al. Ann Oncol. 2018

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Patel SP et al. DOI: 10.1056/NEJMoa2211437

CLINICAL PROBLEM

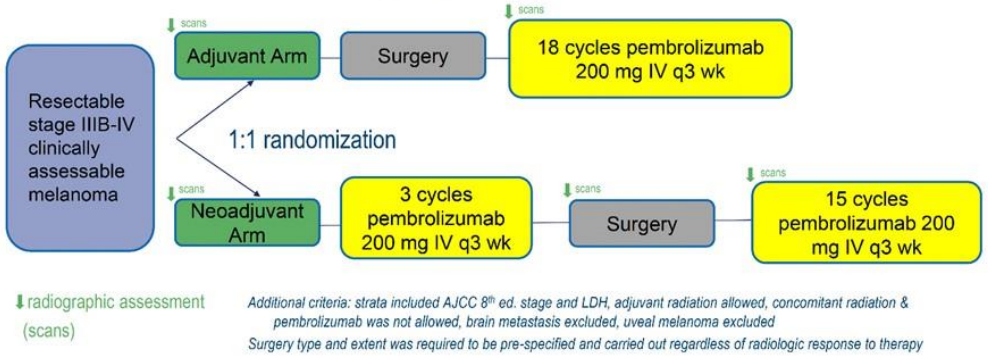
Patients with stage III or IV melanoma can benefit from treatment with a programmed death 1 (PD-1)–blocking antibody after surgical excision (adjuvant therapy). Whether PD-1 blockade both before surgery (neoadjuvant therapy) and afterward would further improve outcomes is unknown.

Etude de phase 2 SWOG S1801:

- **critère de jugement principal = survie sans évènement (progression/toxicité)**

S1801 Study Schema

Primary endpoint: Event-free survival

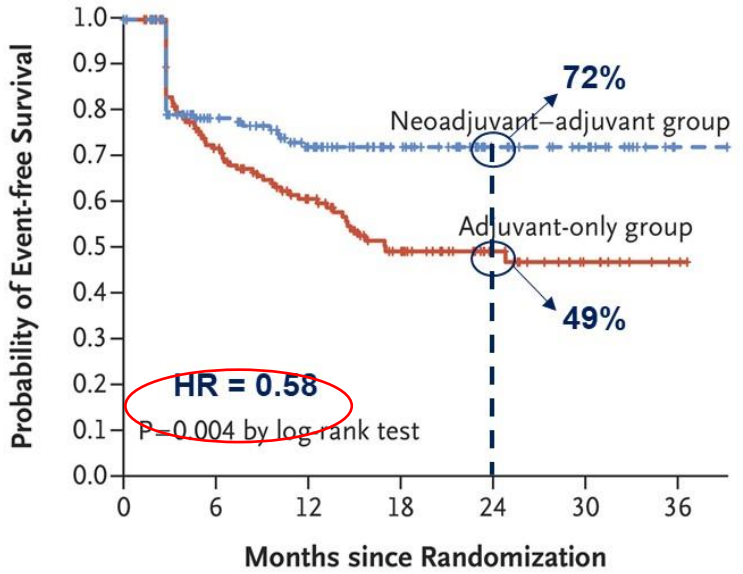


radiographic assessment (scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

Characteristic	Neoadjuvant–Adjuvant Group (N=154)	Adjuvant-Only Group (N=159)
Disease stage — no. (%)§		
IIIB	62 (40)	64 (40)
IIIC	69 (45)	74 (47)
IIID	9 (6)	10 (6)
IV	14 (9)	11 (7)



No. at Risk

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

Patel S et al. N Engl J Med. 2023

2024 ASCO ANNUAL MEETING

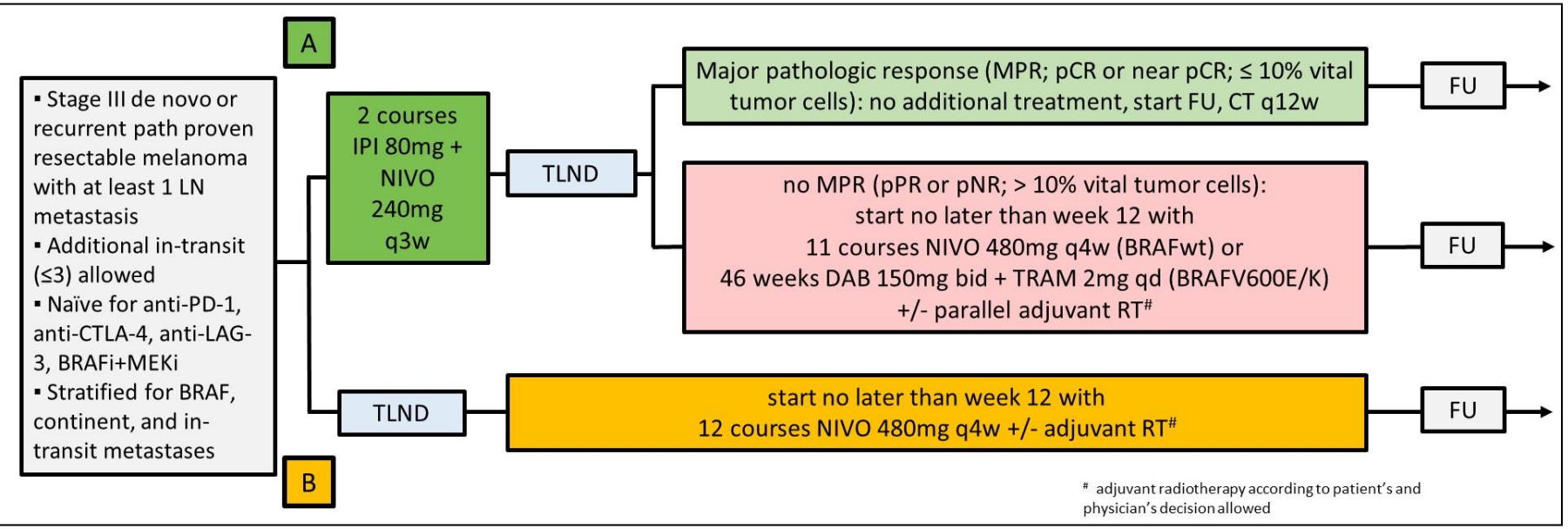
Neoadjuvant Nivolumab Plus Ipilimumab Versus Adjuvant Nivolumab in Macroscopic, Resectable Stage III Melanoma: The Phase 3 NADINA Trial

Christian U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, A.C.J. van Akkooi, W.J. van Houdt, R.P.M. Saw, A. Torres-Acosta, S.N. Lo, G.A.P. Hospers, M.S. Carlino, J.W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, G.V. Long

BARCELONA 2024 ESMO congress

Distant metastasis-free survival of neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable, macroscopic stage III melanoma: the NADINA trial

M.W. Lucas, A.M. Menzies, M. Lopez-Yurda, R.A. Scolyer, B.A. van de Wiel, R.P.M. Saw, W.J. van Houdt, N.G. Maher, A. Torres-Acosta, M.J. Boers-Sonderen, G.A.P. Hospers, M.S. Carlino, J.W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, G.V. Long, C.U. Blank

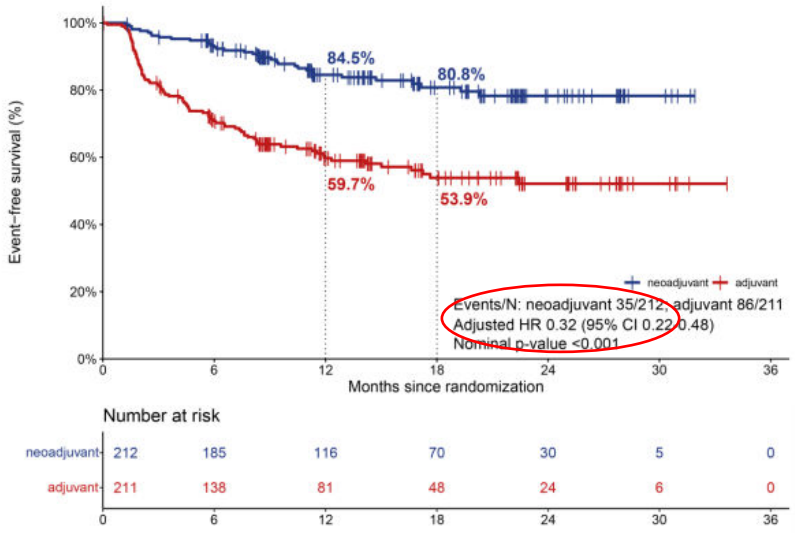


- **Primary endpoint**
  - Event-free survival: time from randomization until an event, being defined as progression, recurrence, or death due to melanoma/treatment.
- **Key secondary endpoint**
  - Overall survival
- **Secondary endpoints**
  - Pathological response rate: MPR (pCR + near pCR), pPR, pNR
  - Recurrence-free survival
  - Distant metastasis-free survival
  - Treatment related, and unrelated adverse events
  - Surgical complications
  - Health-related quality of life (ASCO 2024, LBA9584, poster #368)

Blank CU et al. NEJM 2024

Suivi médian 15,4 mois

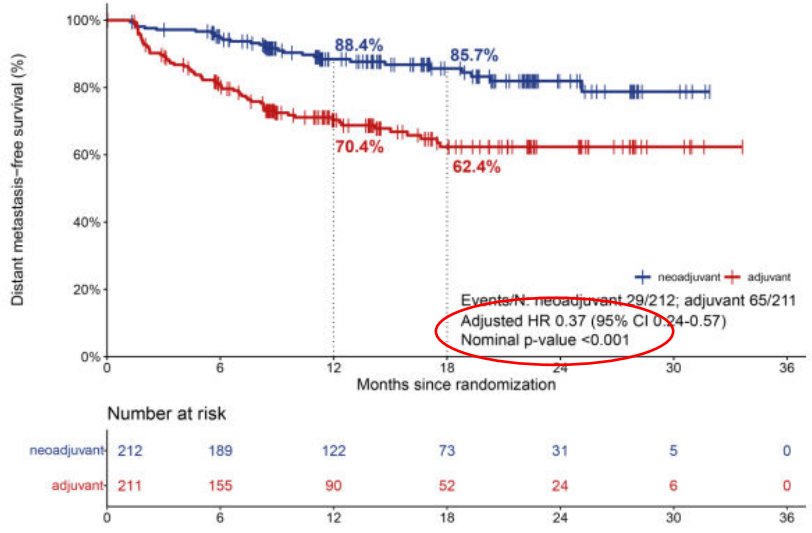
Updated event-free survival



Median follow-up of 15.4 months (95% CI 9.0-22.4).
Censoring at last CT scan or death

BARCELONA 2024 ESMO congress

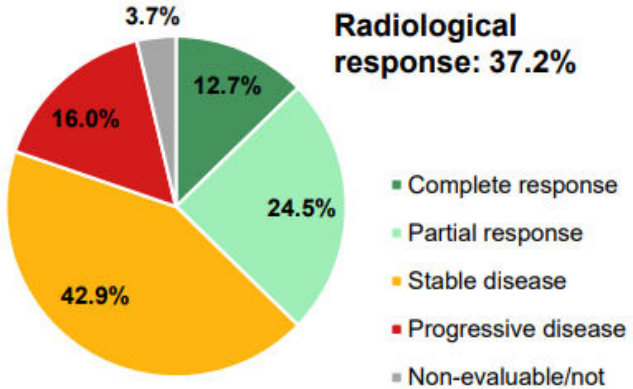
Distant metastasis-free survival



Median follow-up of 15.4 months (95% CI 9.0-22.4).
Censoring at last CT scan or death

BARCELONA 2024 ESMO congress

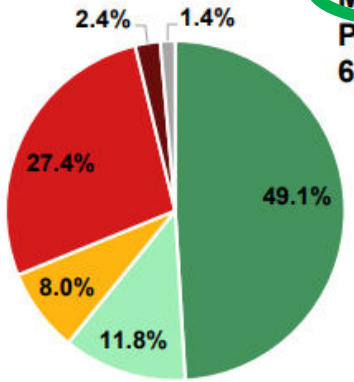
Radiological response



Radiological response: 37.2%

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Non-evaluable/not done

Pathological response



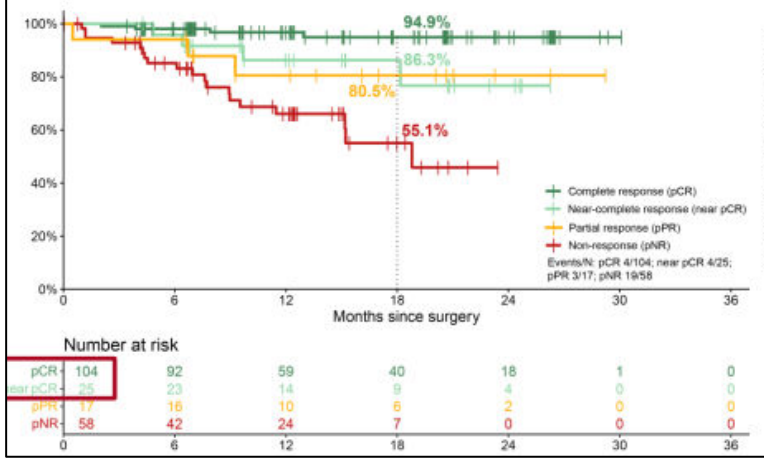
MPR: 60.8%

Pathological response: 68.8%

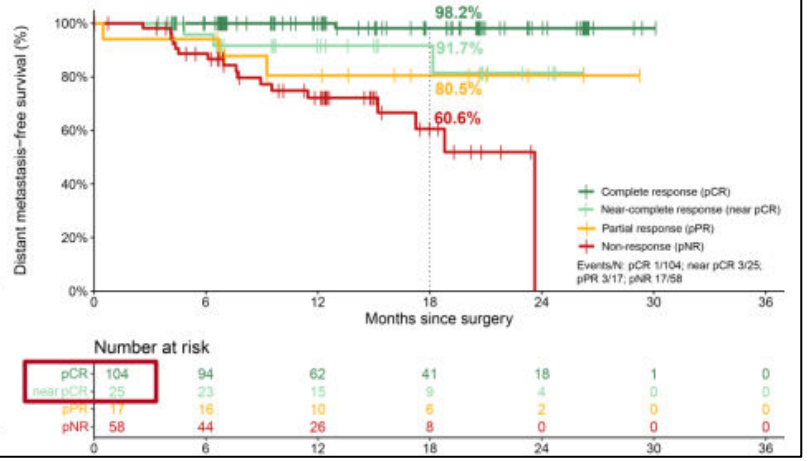
- Complete response
- Near complete response
- Partial response
- Non response
- Progression
- No surgery

RFS & DMFS based on pathological response in the neoadjuvant arm

Recurrence-free survival

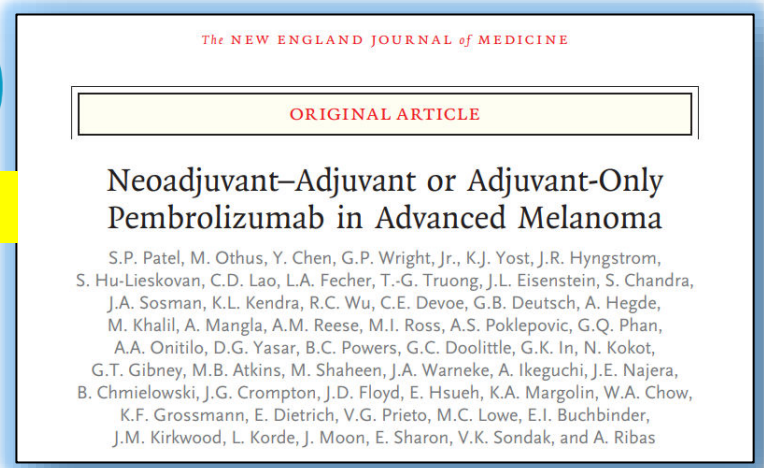


Distant metastasis-free survival



Stratégie NEOADJVANTE
Traitement de référence du mélanome stade III

SWOG 1801



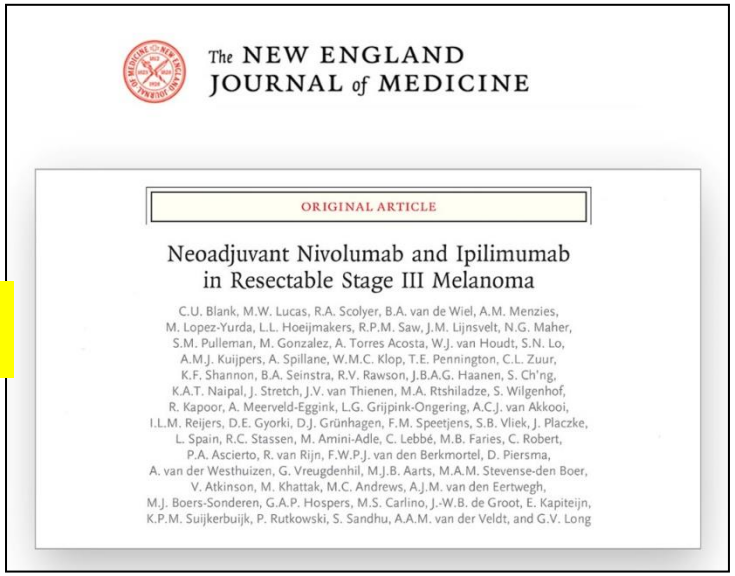
The NEW ENGLAND JOURNAL of MEDICINE

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

(NADINA)



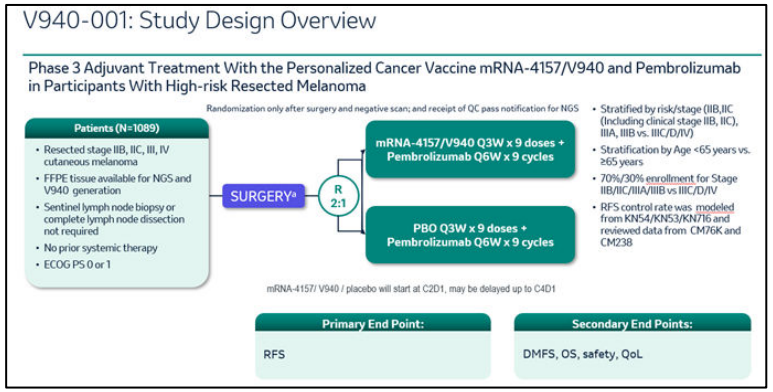
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

C.U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, L.L. Hoeijmakers, R.P.M. Saw, J.M. Lijnsvelt, N.G. Maher, S.M. Pulleman, M. Gonzalez, A. Torres Acosta, W.J. van Houdt, S.N. Lo, A.M.J. Kuijpers, A. Spillane, W.M.C. Klop, T.E. Pennington, C.L. Zuur, K.F. Shannon, B.A. Seinstra, R.V. Rawson, J.B.A.G. Haanen, S. Ch'ng, K.A.T. Naipal, J. Stretch, J.V. van Thienen, M.A. Rtshiladze, S. Wilgenhof, R. Kapoor, A. Meerveld-Eggink, L.G. Grijpink-Ongering, A.C.J. van Akkooi, I.L.M. Reijers, D.E. Gyorki, D.J. Grünhagen, F.M. Speetjens, S.B. Vliek, J. Placzke, L. Spain, R.C. Stassen, M. Amini-Adle, C. Lebbé, M.B. Faries, C. Robert, P.A. Ascierto, R. van Rijn, F.W.P.J. van den Berkmortel, D. Piersma, A. van der Westhuizen, G. Vreugdenhil, M.J.B. Aarts, M.A.M. Stevense-den Boer, V. Atkinson, M. Khattak, M.C. Andrews, A.J.M. van den Eertwegh, M.J. Boers-Sonderen, G.A.P. Hospers, M.S. Carlino, J.-W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, and G.V. Long

En attendant ???...

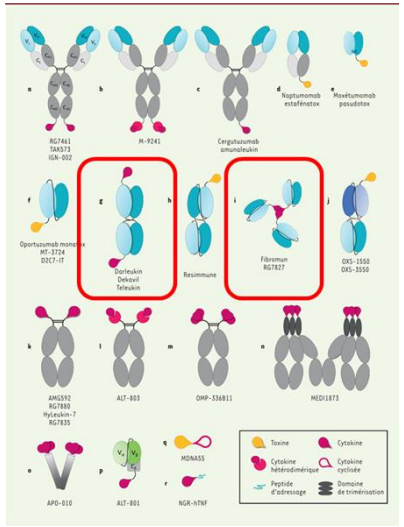


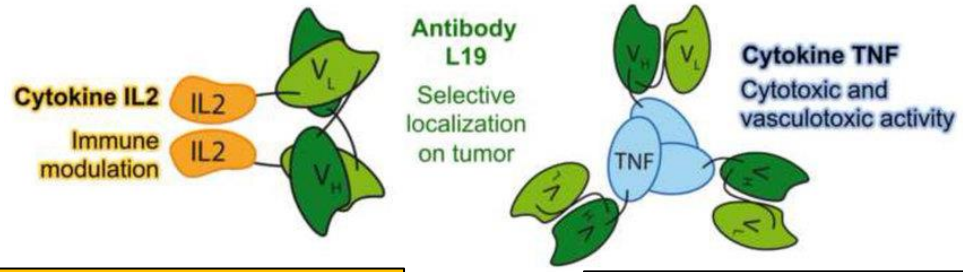
2024 ASCO ANNUAL MEETING

#LBA9501 - Phase 3 study (PIVOTAL) of neoadjuvant intralesional Daromun versus immediate surgery in fully resectable melanoma with regional skin and/or nodal metastases

Axel Hauschild, Jessica Cecile Hassel, Mirjana Ziemer, Piotr Rutkowski, Friedegund Meier, Lukas Flatz, Caroline Gaudy-Marqueste, Mario Santinami, Francesco Russano, Imke von Wasielewski, Thomas Eigentler, Michele Maio, Iris Zalaudek, Sebastian Haferkamp, Pietro Quaglino, Paolo Antonio Ascierto, Claus Garbe, Caroline Robert, Dirk Schadendorf, Katharina C. Kähler

DAROMUN®
immunocytokine ciblant la fibronectine



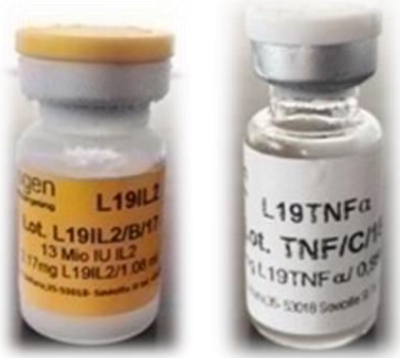


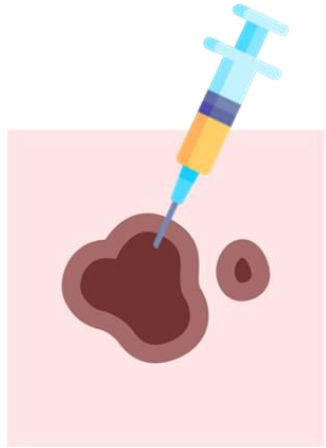
Darleukin®
combine 2 fragments scFv L19 fusionnés à l'IL-2

+

Fibromun®
assemble un trimère de TNF-α *via* trois fragments scFv L19

DAROMUN
(L19IL2 + L19TNF)





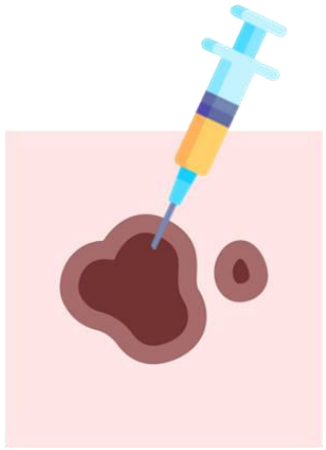
- utilisent le scFv L19 pour adresser les cytokines à la tumeur,
- induction d'une réponse immunitaire locale (et abscopale)

Inclusion criteria

1. Diagnosis of CMM with locally advanced disease (stage IIIB/C; AJCC 7th Ed.), eligible for complete surgical resection.
2. One injectable cutaneous, SC, or LN lesions (≥ 10 mm) or multiple injectable lesions (in aggregate ≥ 10 mm).
3. Prior anti-tumor treatments allowed, wash-out period 4 weeks.

Exclusion criteria

1. Uveal and mucosal melanoma or melanoma with unknown primary *(after study amendment)*.
2. Evidence of distant metastases at screening (FDG PET-CT).
3. Previous or concurrent cancer distinct in primary site or histology, except cervical carcinoma in situ, treated BCC, superficial bladder tumors, second primary melanoma in situ or any cancer curatively treated ≥5 years prior to study entry.



Chez 35% des patients dans le bras Daromun → ICI adjuvante dans 86% des cas

PIVOTAL - Trial design (1:1 Randomization)

Prior surgery, irradiation or any systemic treatment allowed!

ARM 1

- DAROMUN 1 weekly injection for 4 weeks
- Surgery of all lesions within 4 weeks

Randomization d1 d8 d15 d22 Safety visit < 4 weeks Surgery FU visits (Every 3 months)

ARM 2

- Surgery of all lesions within 4 weeks

Randomization < 4 weeks Surgery FU visits (Every 3 months)

Post-Adjuvant therapy at investigator´s discretion

Primary Endpoint

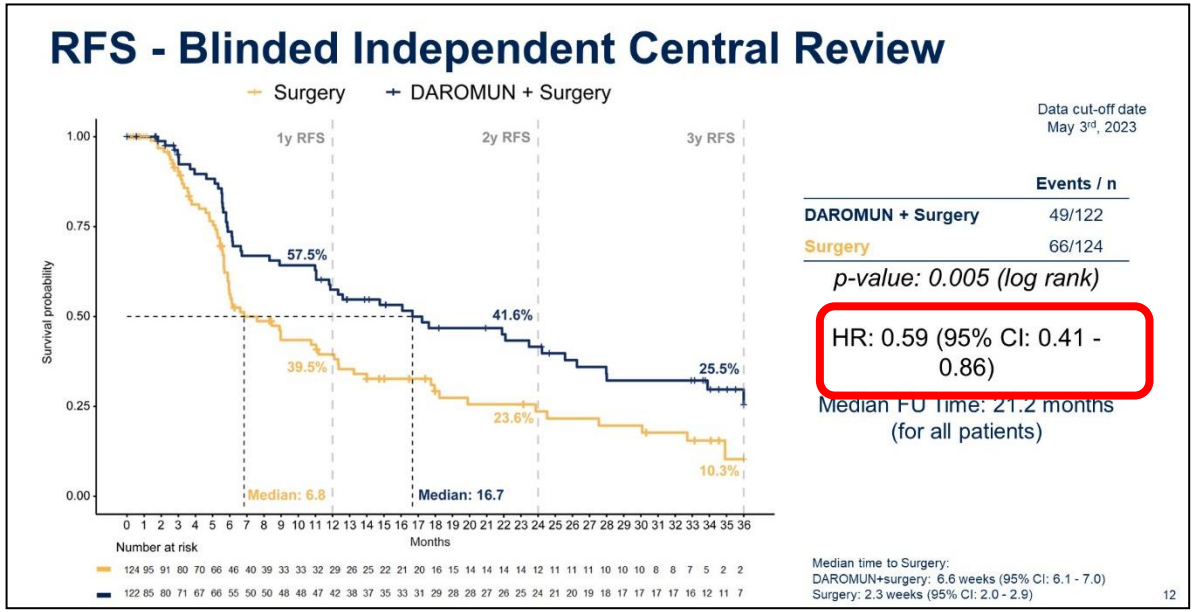
- **RFS (time from randomization to progression or death)**

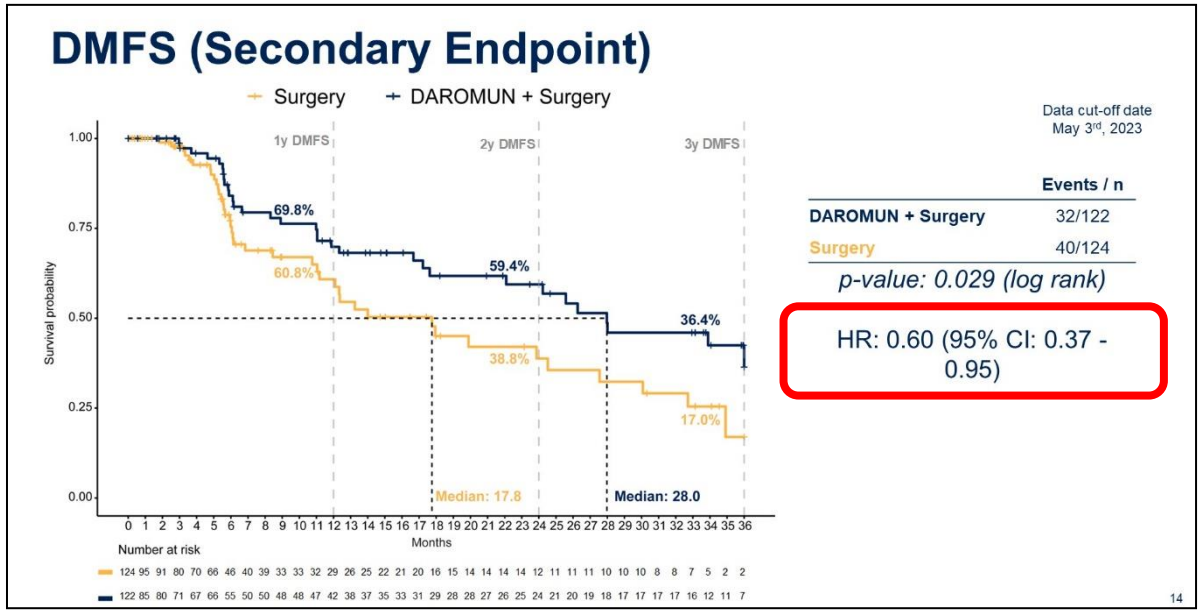
Secondary endpoints

- OS
- DMFS
- LRFS
- Safety (AEs, ADA*)
- Pathological response *(study amendment)*

**Anti-Drug Antibody*

Danielli *et al., Cancer Immunol Immunother*, **2015**, 64, 999;





Traitement adjuvant

- **pour 30% dans le bras DAROMUN**
- **Pour 40% dans le bras chirurgie**

Effet systémique des injections intra-lésionnelles

TRAEs in >10% of patients, n (%)	DAROMUN + Surgery (n=118)			Surgery (n=119)		
	ANY GR	GR = 3	GR = 4	ANY GR	GR = 3	GR = 4
Any	110 (93.2)	31 (26.3)	1 (0.8)	40 (33.6)	8 (6.7)	0
Injection site reaction	79 (66.9)	13 (11.0)	-	0	-	-
Pyrexia	57 (48.3)	1 (0.8)	-	0	-	-
Chills	57 (48.3)	-	-	0	-	-
Nausea	26 (22.0)	-	-	0	-	-
Fatigue	18 (15.3)	1 (0.8)	-	0	-	-
Headache	16 (13.6)	-	-	0	-	-
Influenza like illness	14 (11.9)	-	-	0	-	-
Vomiting	14 (11.9)	-	-	0	-	-
Alanine aminotransferase increased	12 (10.2)	1 (0.8)	-	0	-	-

Conclusion (1)

- Pour **les stades III** la stratégie adjuvante est plus que menacée **par la stratégie néoadjuvante**, d'autant plus avec les données de survie globale décevantes…
- La combo-ICI néoadjuvante va t-elle/doit-elle être le standard?

- L'intérêt des anti-PD1 en adjuvant pour **les stades IIB-IIC** se confirme:
  - réduction du risque de récidive/décès ~ 40%
  - réduction du risque de métastases à distance ~ 30-40%
  - **Profil de tolérance connu/attendu, acceptable (mais à considérer ++)**

  - En attendant les données de Survie Globale….

- En attendant les données avec le vaccin à ARN….

- Enfin une stratégie intra-tumorale disponible?

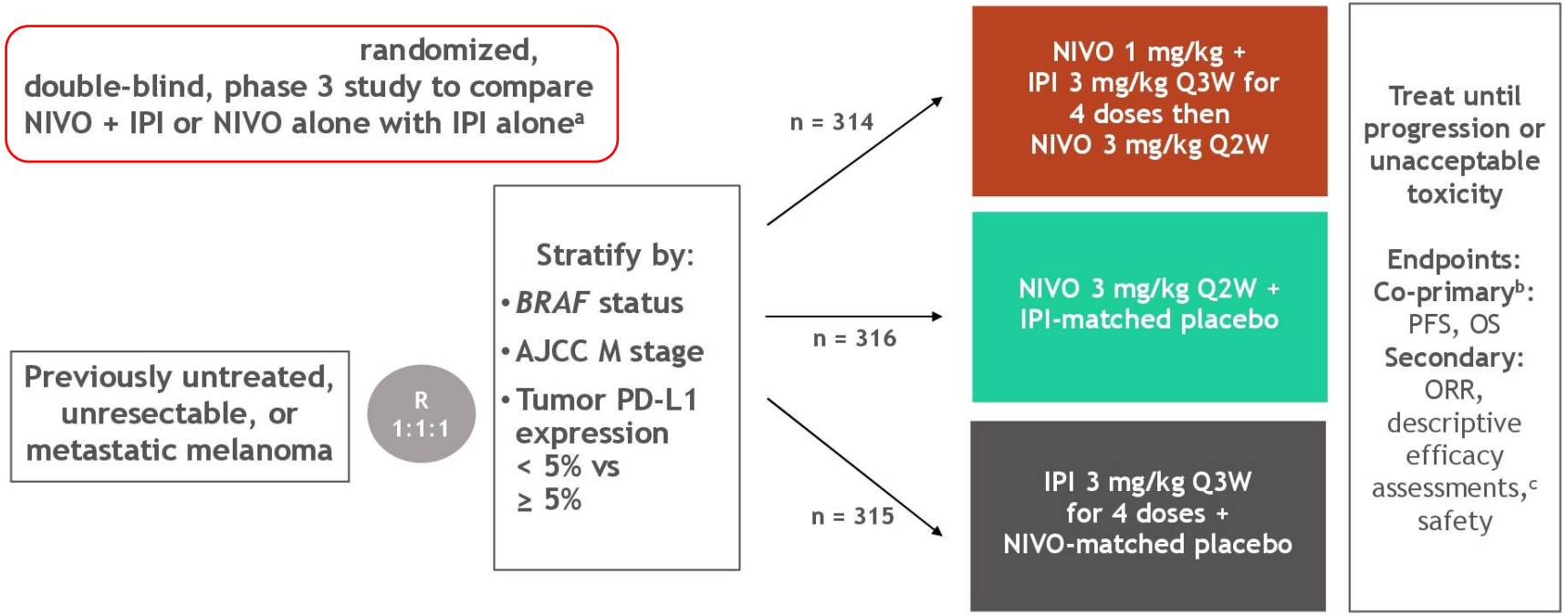
ACTUALITÉS SUR LA PRISE EN CHARGE DU MÉLANOME AVANCE

ORIGINAL ARTICLE

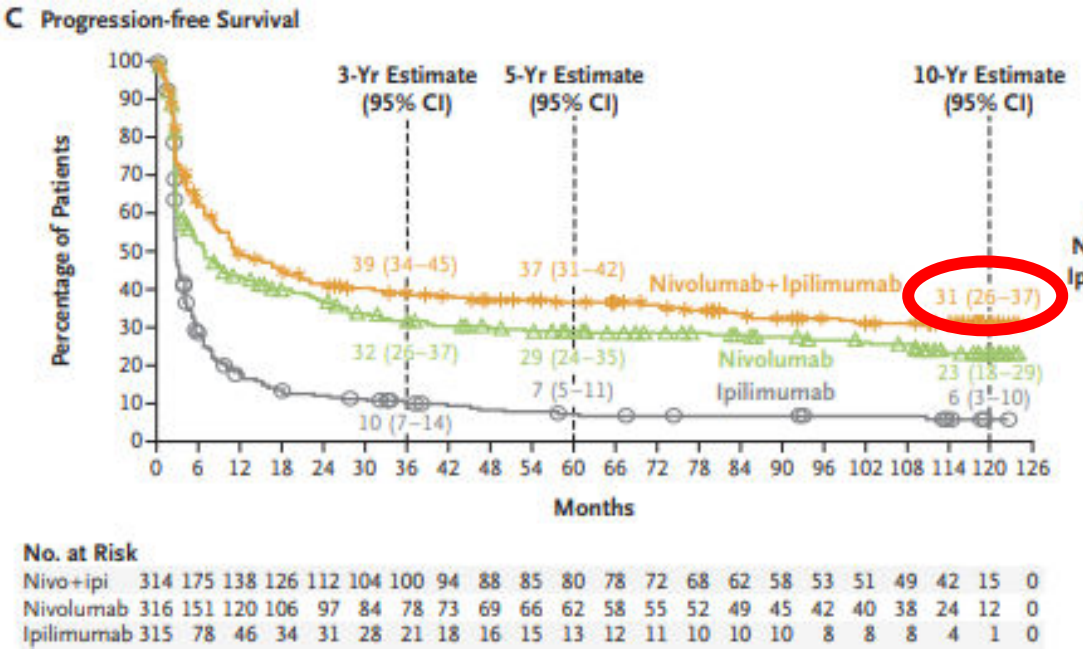
Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, P. Rutkowski, C.L. Cowey, D. Schadendorf, J. Wagstaff, P. Queirolo, R. Dummer, M.O. Butler, A.G. Hill, M.A. Postow, C. Gaudy-Marqueste, T. Medina, C.D. Lao, J. Walker, I. Márquez-Rodas, J.B.A.G. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, S. Sandhu, C. Lebbé, P.A. Ascierto, G.V. Long, C. Ritchings, A. Nassar, M. Askelson, M.P. Benito, W. Wang, F.S. Hodi, and J. Larkin, for the CheckMate 067 Investigators*

CheckMate 067: study design



Wolchok JD et al. NEJM 2024

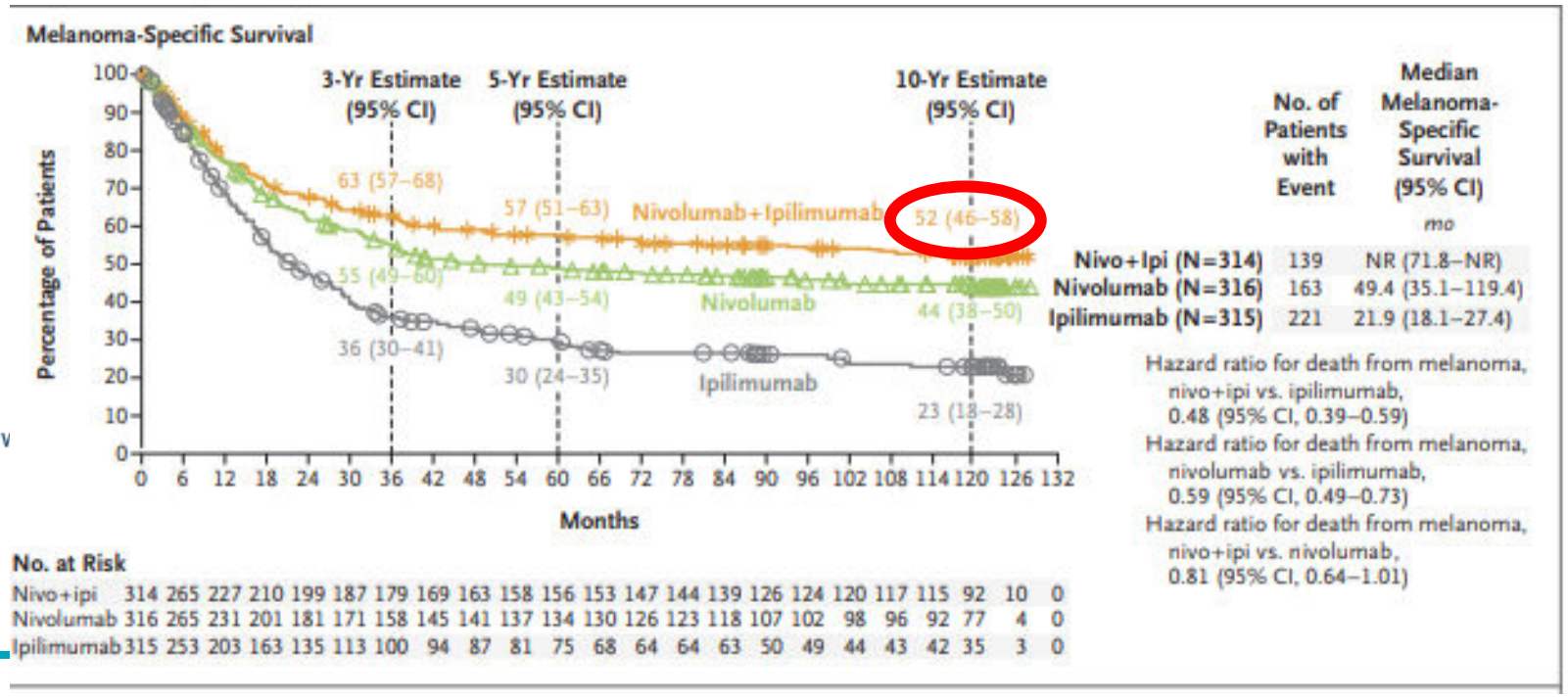


No. at Risk																						
Nivo+ipi	314	175	138	126	112	104	100	94	88	85	80	78	72	68	62	58	53	51	49	42	15	0
Nivolumab	316	151	120	106	97	84	78	73	69	66	62	58	55	52	49	45	42	40	38	24	12	0
Ipilimumab	315	78	46	34	31	28	21	18	16	15	13	12	11	10	10	10	8	8	8	4	1	0

	No. of Patients with Event	Median Progression-free Survival (95% CI)
		mo
Nivo+Ipi (N=314)	192	11.5 (8.9–20.0)
Nivolumab (N=316)	212	6.9 (5.1–10.2)
Ipilimumab (N=315)	262	2.9 (2.8–3.1)

Hazard ratio for disease progression or death, nivo+ipi vs. ipilimumab, 0.42 (95% CI, 0.35–0.51)
Hazard ratio for disease progression or death, nivolumab vs. ipilimumab, 0.54 (95% CI, 0.45–0.65)
Hazard ratio for disease progression or death, nivo+ipi vs. nivolumab, 0.79 (95% CI, 0.65–0.96)

- **Plus d'un patient sur deux en vie à 10 ans dans le groupe IPI + NIVO**
- **1/3 des patients n'ont pas progressé à 10 ans**



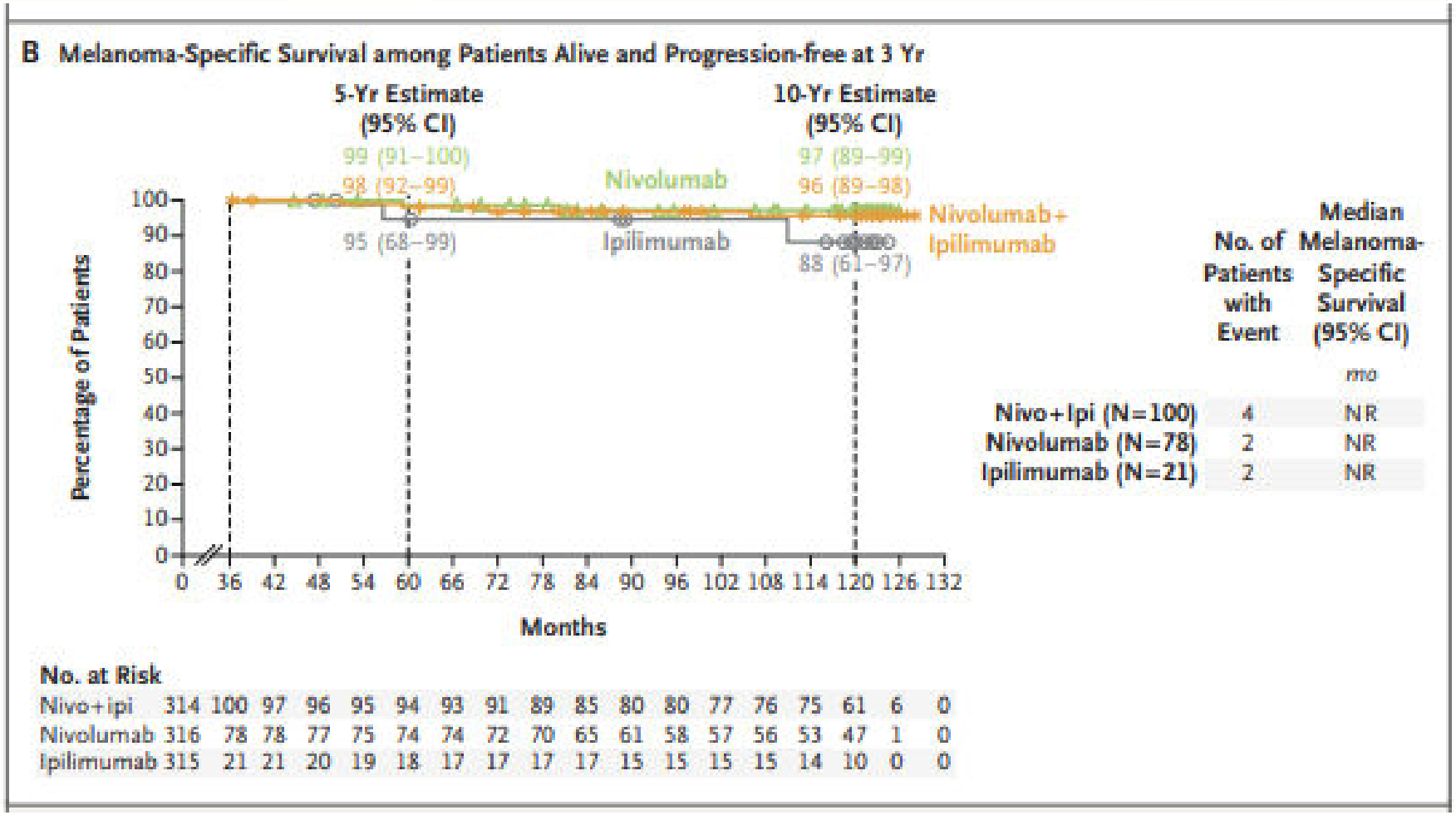
No. at Risk																						
Nivo+ipi	314	265	227	210	199	187	179	169	163	158	156	153	147	144	139	126	124	120	117	115	92	10	0
Nivolumab	316	265	231	201	181	171	158	145	141	137	134	130	126	123	118	107	102	98	96	92	77	4	0
Ipilimumab	315	253	203	163	135	113	100	94	87	81	75	68	64	64	63	50	49	44	43	42	35	3	0

	No. of Patients with Event	Median Melanoma-Specific Survival (95% CI)
		mo
Nivo+Ipi (N=314)	139	NR (71.8–NR)
Nivolumab (N=316)	163	49.4 (35.1–119.4)
Ipilimumab (N=315)	221	21.9 (18.1–27.4)

Hazard ratio for death from melanoma, nivo+ipi vs. ipilimumab, 0.48 (95% CI, 0.39–0.59)
Hazard ratio for death from melanoma, nivolumab vs. ipilimumab, 0.59 (95% CI, 0.49–0.73)
Hazard ratio for death from melanoma, nivo+ipi vs. nivolumab, 0.81 (95% CI, 0.64–1.01)

Wolchok JD et al. NEJM 2024

Pour les patients n'ayant pas progressé après *3* ans survie très prolongée espacement des surveillances par imageries +++



Wolchok JD et al. NEJM 2024

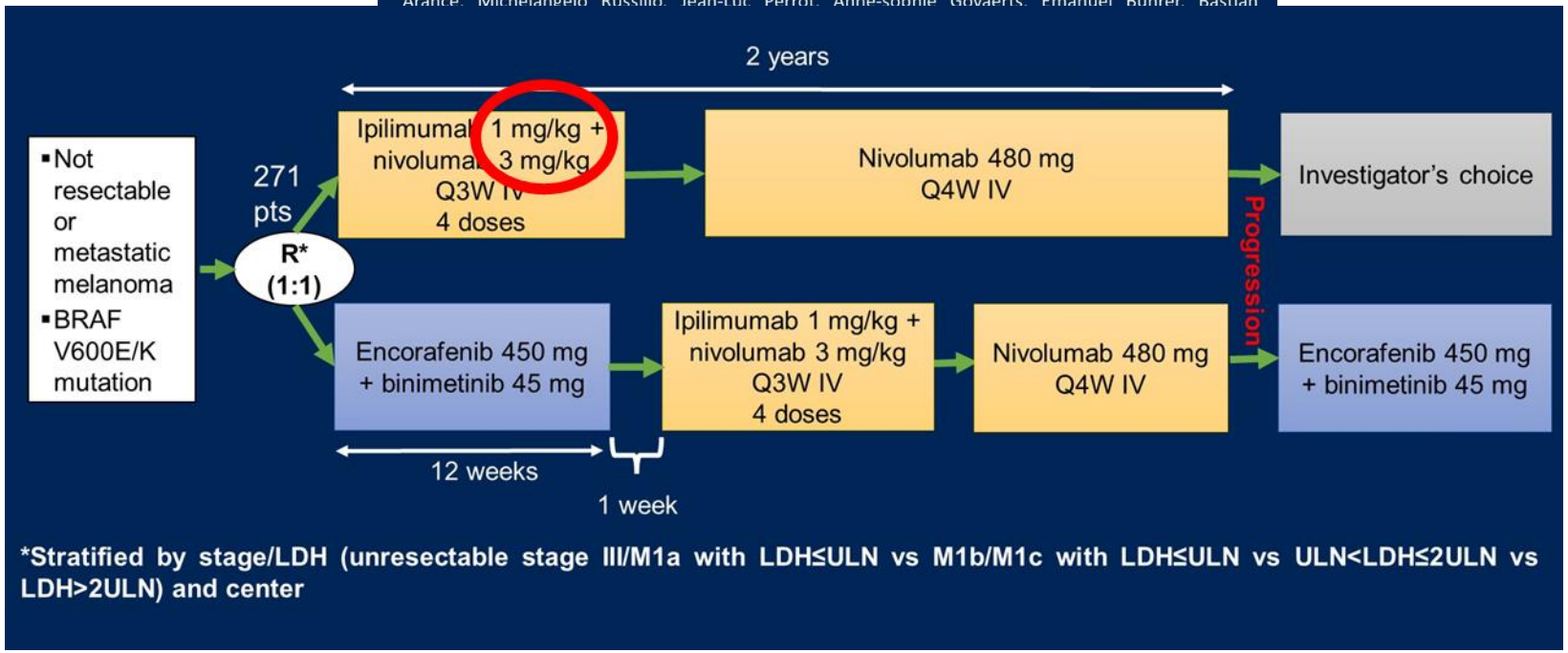
Qui commence en cas de mutation *BRAF600* ?

2024 ASCO ANNUAL MEETING #ASCO24

2024 ASCO ANNUAL MEETING

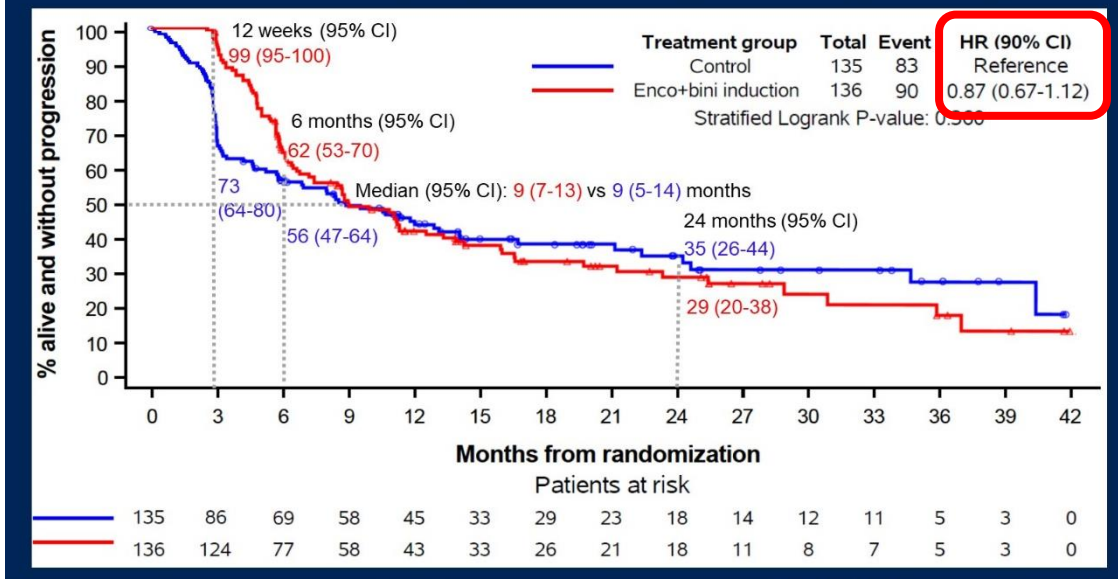
Combination of encorafenib and binimetinib followed by ipilimumab and nivolumab versus ipilimumab and nivolumab in patients with advanced BRAF-V600E/K melanoma: the primary analysis of an EORTC randomized phase II study (EBIN)

Caroline Robert, Caroline Dutriaux, Felix Oppong, Michal Kicinski, Émilie Routier, Eve-Marie Neidhardt, Xavier Durando, Barouyr Baroudjian, Philippe Saiag, Caroline Gaudy-Marqueste, Paolo A. Ascierto, Ana Arance, Michelangelo Russillo, Jean-Luc Perrot, Anne-sophie Govaerts, Emanuel Bührer, Bastian

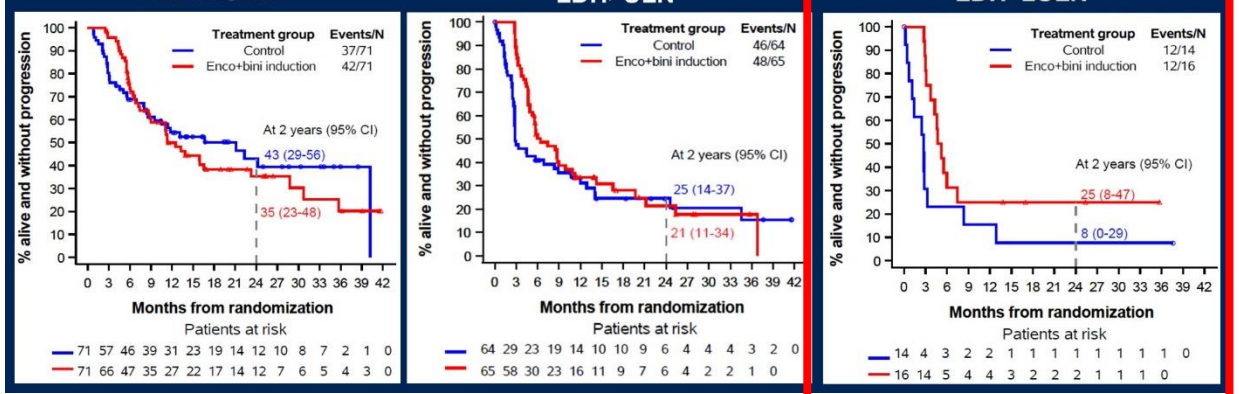


Objectif principal: Evaluer le bénéfice en terme de survie sans progression de l'induction par TC avec la double-immuo

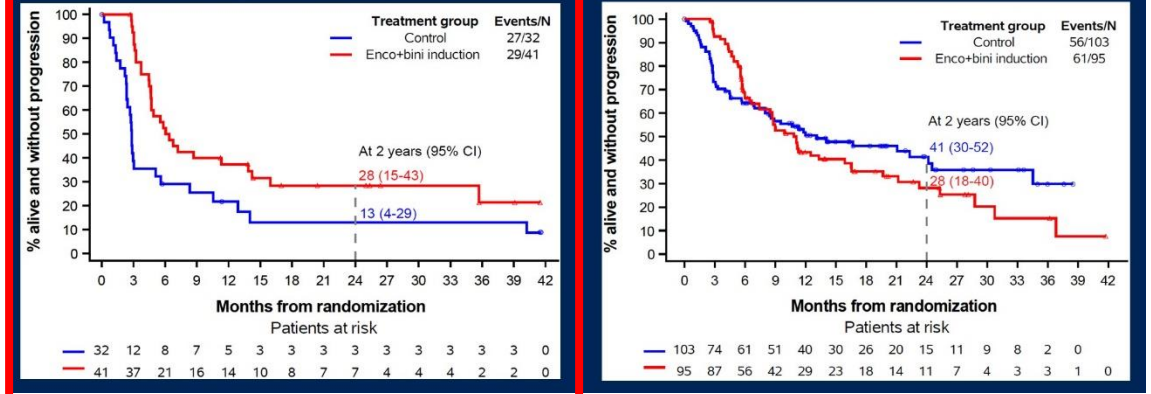
PFS in the ITT population (primary analysis)



PFS in LDH subgroups



PFS in subgroups of liver metastasis at baseline



Qui commence en cas de mutation *BRAF600* ?

	Trial	Arm	2-year PFS	2-year OS
Phase II	Ebin EORTC (n=270)	Arm A: ipi1/nivo3	35%	74%*
		Arm B: E+B x 12 weeks → ipi1/nivo3 → E+B	29%	68%*
Phase II	SECOMBIT (n=209)	Arm A: E+B → ipi/nivo	46%	65%
		Arm B: ipi/nivo → E+B	65%	73%
		Arm C: E+B x 8 weeks → ipi/nivo → E+B	57%	69%
Phase III	DREAMSeq (n=265)	Arm A: ipi/nivo → D+T	42%	72%
		Arm B: D+T → ipi/nivo	19%	52%

Robert et al., abstract LBA9503
Ascierto et al., JCO, 2023
Atkins et al., JCO, 2023

2024 ASCO ANNUAL MEETING #ASCO24

Comparaisons indirectes!!!

2024 ASCO ANNUAL MEETING

Efficacy and safety of triplet nivolumab, relatlimab, and ipilimumab in advanced melanoma: results from RELATIVITY-048

Paolo Antonio Ascierto,[1] Reinhard Dummer,[2] Caroline Gaudy-Marqueste,[3] Samantha Bowyer,[4] Evan J. Lipson,[5] Eleonora Ghisoni,[6] Mark R. Middleton,[7] Barbara Ratto,[8a] William Joseph Jackson,[8] Alicia M. Y. Cheong,[9] Sourav Mukherjee,[8] Jenny Wu,[8] Georgina V. Long[10]

Phase 1/2, nonrandomized trial: advanced melanoma expansion cohort (Part 2B)

Key eligibility criteria
- Previously untreated advanced unresectable, or metastatic melanoma
- Prior neoadjuvant/adjuvant I-O therapies permitted ≥ 6 months prior
- ECOG PS 0-1
- Patients with controlled brain metastases[a] were allowed

N = 46

NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W

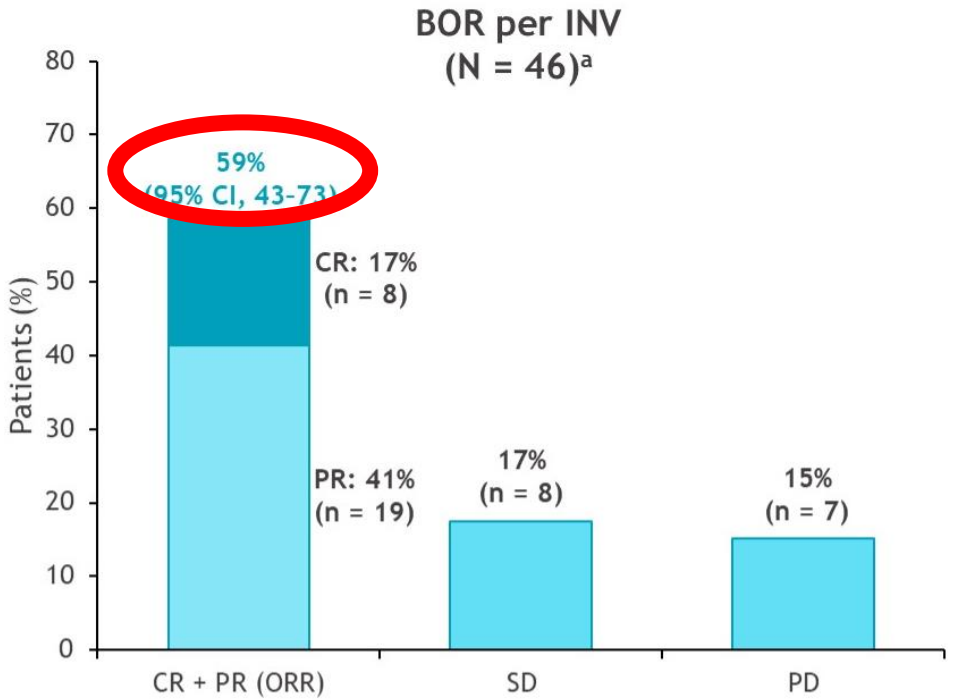
Primary endpoints
- Key safety (AE, SAE, AEs leading to discontinuation)
- ORR,[d] DCR,[d] median DOR[d] per INV

Secondary endpoints
- PFS[d] per INV (rates at 6 and 12 months)

Key exploratory endpoints
- OS (rates at 1 and 2 years)

Database lock: November 1, 2023[b]
Median follow-up: 49.4 months (range, 0.4-55.0)[c]

Overall study — phase 1/2, nonrandomized trial evaluating I-O triplets for patients with select solid tumors
Part 1: dose finding for I-O triplets in select solid tumors (except primary CNS); Part 2: specific tumor-type expansion cohorts
- Part 1A/2A: NIVO + RELA + IDOi
- Part 1B/2B: NIVO + RELA + IPI



	OS at 48 mos	PFS at 36 mos	Grade 3/4 TRAEs
CM 067 Ipi+Nivo (n=314)	53%	39%	59%
RELA 047 Nivo+Rela (n=355)	52%	31%	21%
RELA 048 Ipi+Nivo+Rela (n=46)	72%	52%	39%

Wolchok et al., NEJM, 2017; Hodi et al., ESMO 2018, LBA4
Tawbi et al., NEJM, 2022; Tawbi et al., ASCO 2023, abstract
Ascierto et al., abstract 9504

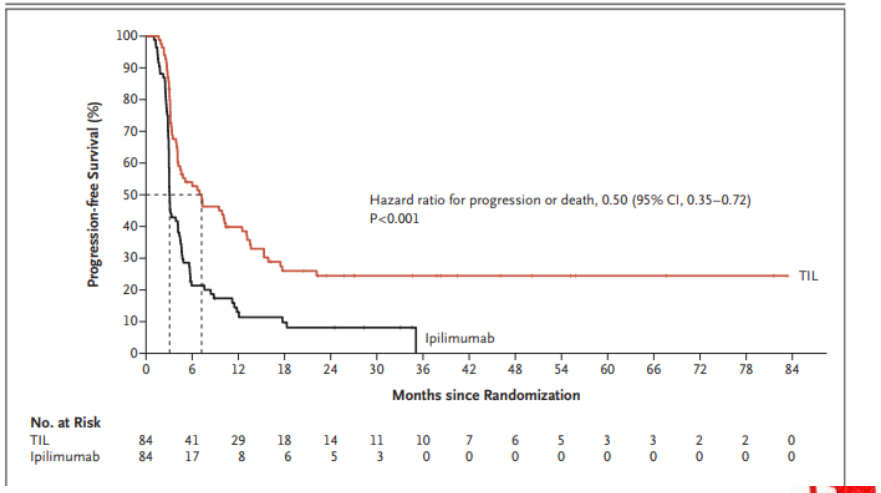
Comparaisons indirectes!!!

2024 ASCO Annual Meeting
May 31–June 4, 2024 | Chicago, IL, USA

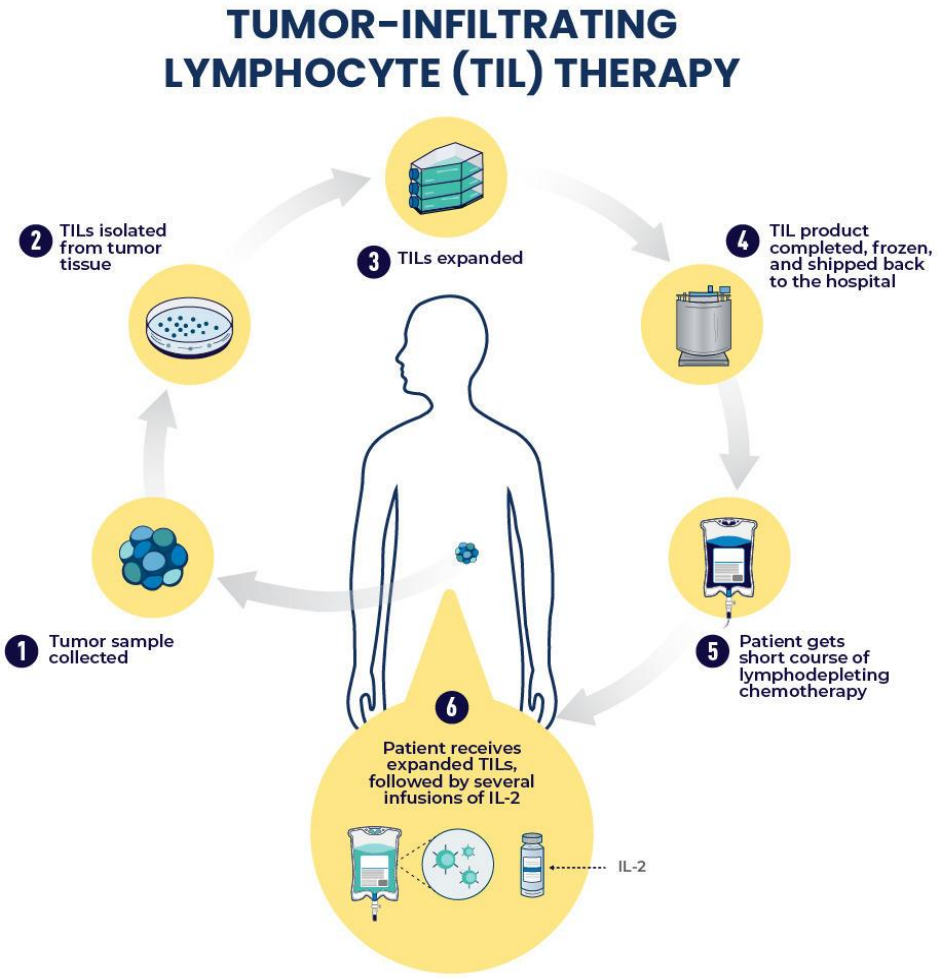
Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naive unresectable or metastatic melanoma: updated results from IOV-COM-202 Cohort 1A

Sajeve Thomas,[1] Helen Gogas,[2] Young Ki Hong,[3] Gino K. In,[4] Bernard Doger de Speville Uribe,[5] Andrew J.S. Furness,[6] Almudena Garcia Castano,[7] Simon Häfliger,[8] Kai He,[9] Theresa Medina,[10] Donald Lawrence,[11] Sylvia Lee,[12] Juan Martin-Liberal,[13] Friedrich Graf Finckenstein,[14] Brian Gastman,[14] Jeffrey Chou,[14] Rana Fiaz,[14] Melissa Catlett,[14] Guang Chen,[14] Patrick Terheyden[15]

- Lifileucel approuvé par la FDA en deuxième ligne de traitement dans les mélanomes avancés
- Taux de réponse 31,4% chez les patients pré-traités



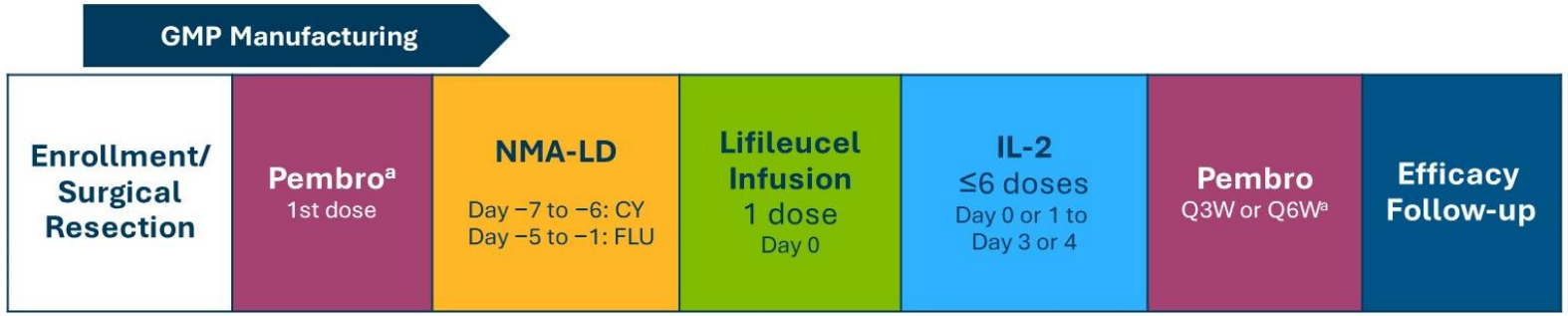
Rohaan MW et al. NEJM 2022



FDA APPROVED

En 2ème ligne

✓ **Patients naifs d'immunothérapie**
✓ **+/- BRAFi + MEKi**

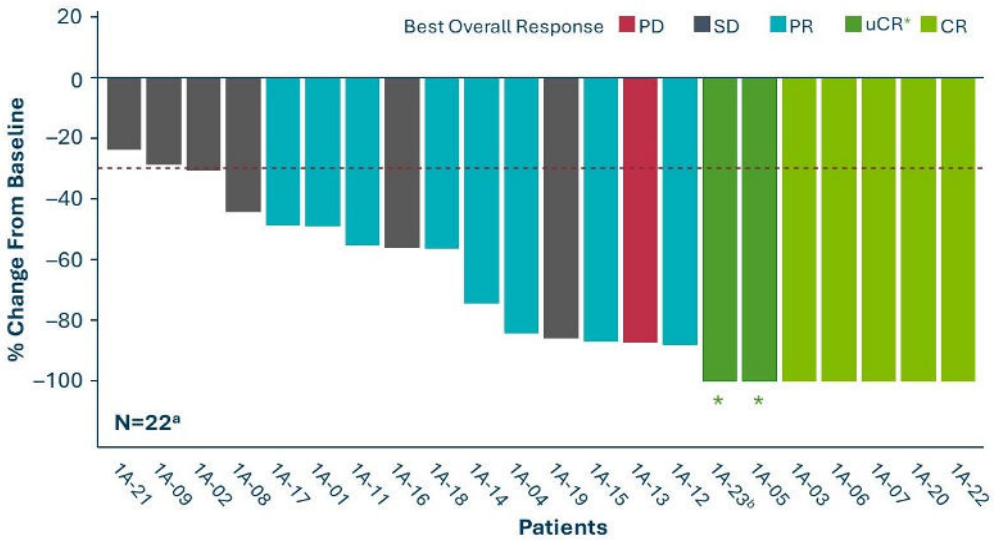


[a]First administration of single-dose pembrolizumab IV 200 mg or 400 mg, followed by pembrolizumab IV 200 mg Q3W or 400 mg Q6W for 24 months or until disease progression or unacceptable toxicity.
CY, cyclophosphamide; EOA, end of assessment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; pembro, pembrolizumab; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Suivi médian 21,7 mois

Taux de réponse objective 65,2 %

Taux de réponse complète 30,4 %



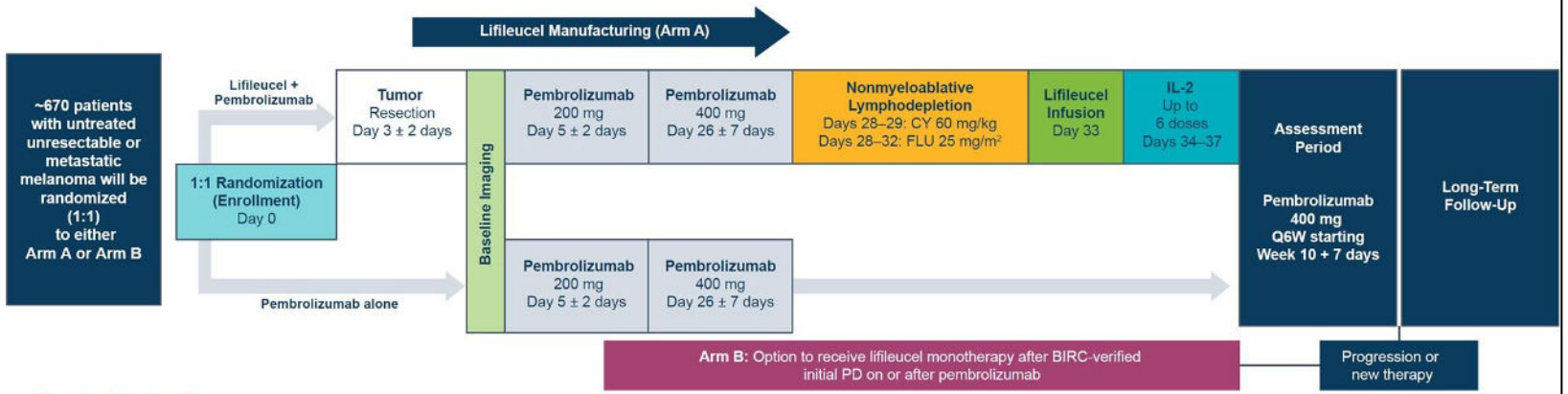
Nonhematologic TEAEs in ≥30% of Patients[a]

	N=23	
Preferred Terms, n (%)	**Any grade**	**Grade 3/4**
Chills	19 (82.6)	3 (13.0)
Pyrexia	18 (78.3)	4 (17.4)
Nausea	18 (78.3)	0
Vomiting	15 (65.2)	0
Fatigue	14 (60.9)	1 (4.3)
Febrile neutropenia	11 (47.8)	10 (43.5)
Headache	11 (47.8)	0
Diarrhea	10 (43.5)	1 (4.3)
Cough	10 (43.5)	0
Dyspnea	9 (39.1)	1 (4.3)
Alopecia	9 (39.1)	0
Decreased appetite	9 (39.1)	0
Hypertension	8 (34.8)	5 (21.7)
Rash maculopapular	8 (34.8)	3 (13.0)
Peripheral edema	8 (34.8)	1 (4.3)
Hypokalemia	8 (34.8)	0
Abdominal pain	7 (30.4)	0

- ❑ 100% de toxicité hémato grade3-4
- ❑ Un décès (sepsis)

TILVANCE-301[a] Global Phase 3 and Confirmatory Trial

Randomized study to evaluate lifileucel + pembrolizumab in frontline advanced melanoma Enrolling in Europe, North America, and Australia



Study Endpoints

Dual primary efficacy endpoints

- BIRC-assessed ORR per RECIST v1.1
  - Potential for accelerated approval and confirmation of post anti-PD1 approval based on early interim analysis
- BIRC-assessed PFS per RECIST v1.1

Key secondary efficacy endpoint

- OS

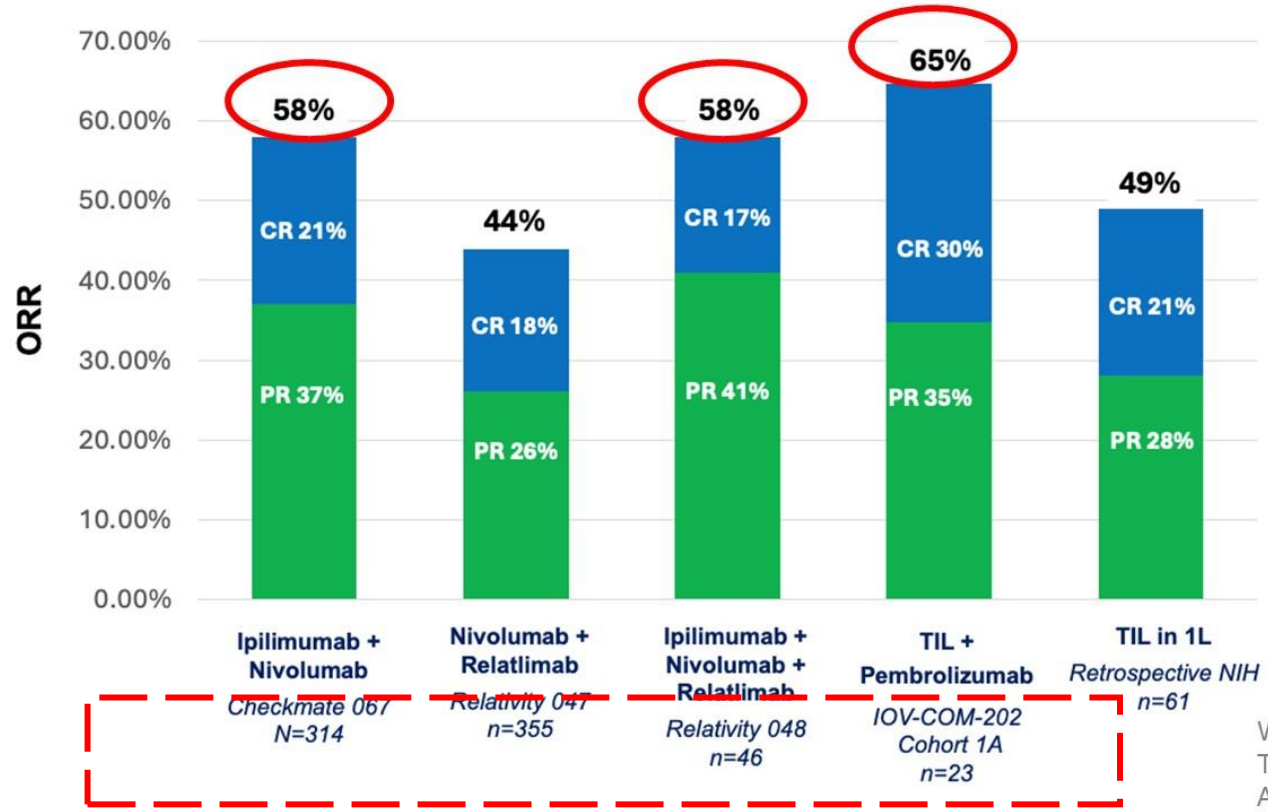
Additional secondary endpoints

- BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
- Investigator-assessed ORR, PFS, CR rate, DOR, EFS, PFS2 per RECIST v1.1
- Safety

[a]NCT05727904.

BIRC, blinded independent review committee; CR, complete response; CY, cyclophosphamide; EFS, event-free survival; FLU, fludarabine; IL-2, interleukin-2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFS2, progression-free survival 2; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

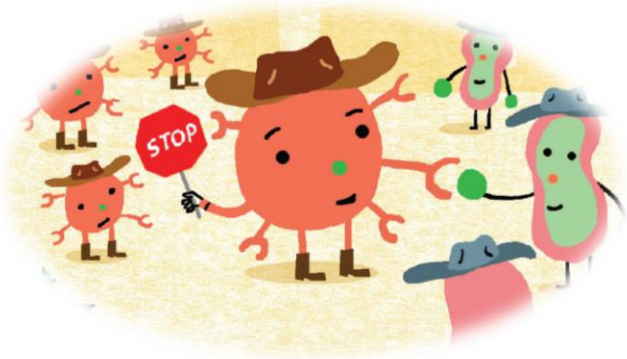
ORR in 1L with combination immunotherapy and TIL trials



Wolchok et al., JCO, 2022
Tawbi et al., NEJM, 2022
Ascierto et al., abstract 9504
Thomas et al., abstract 9505
Goff and Rosenberg et al., unpublished

Comparaisons indirectes!!!

Conclusion



- Confirmation de l'utilisation en 1ère ligne IPI NIVO y compris si mutation *BRAFV600*
- Traitements séquentiels avec induction par TC chez les patients avec LDH élevés et/ou métastases hépatiques??…. données à confirmer
- Triplette IPI + NIVO + RELA à confirmer dans un essai de phase III, données prometteuses (ORR 59 %)
- TIL thérapie innovante
  - en 1ère ligne ? (à réserver pour les patients réfractaires ?)
  - phase III versus anti-PD1 seul
- Pour les mélanomes réfractaires à l'immunothérpaie +/ TC??
  - RP-1/NIVO avec taux de réponse de 32,7% avec réponse prolongée
  - Lenvatinib + anti-PD1 avec taux de réponse de 21-30% mais réponse courte < 6 mois

MERCI

www.onco-nouvelle-aquitaine.fr