Onco-dermatologie

11 Juin 2024

Palais de la Bourse

Caroline DUTRIAUX

4è Post-ASCO en Nouvelle-Aquitaine : les scoops de l'ASCO 2024

Liens d’intérêts

Frais de congrès, expertise, formation, investigation d’essais cliniques pour:

- BMS, MSD, Novartis, Pierre Fabre, Sanofi, Sun Pharma, Regeneron, Immunocore

Quoi de neuf?

ASCO 2024

MELANOME cutané

STADES PRECOCES

MELANOME cutané

STADES AVANCES

MELANOME Uvéal

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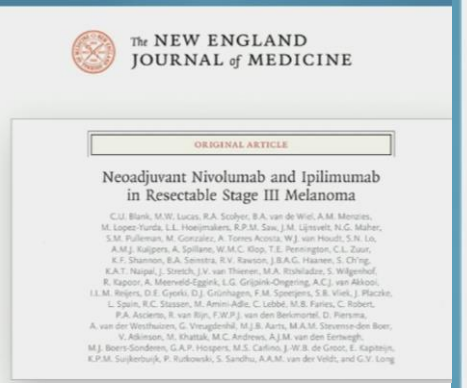
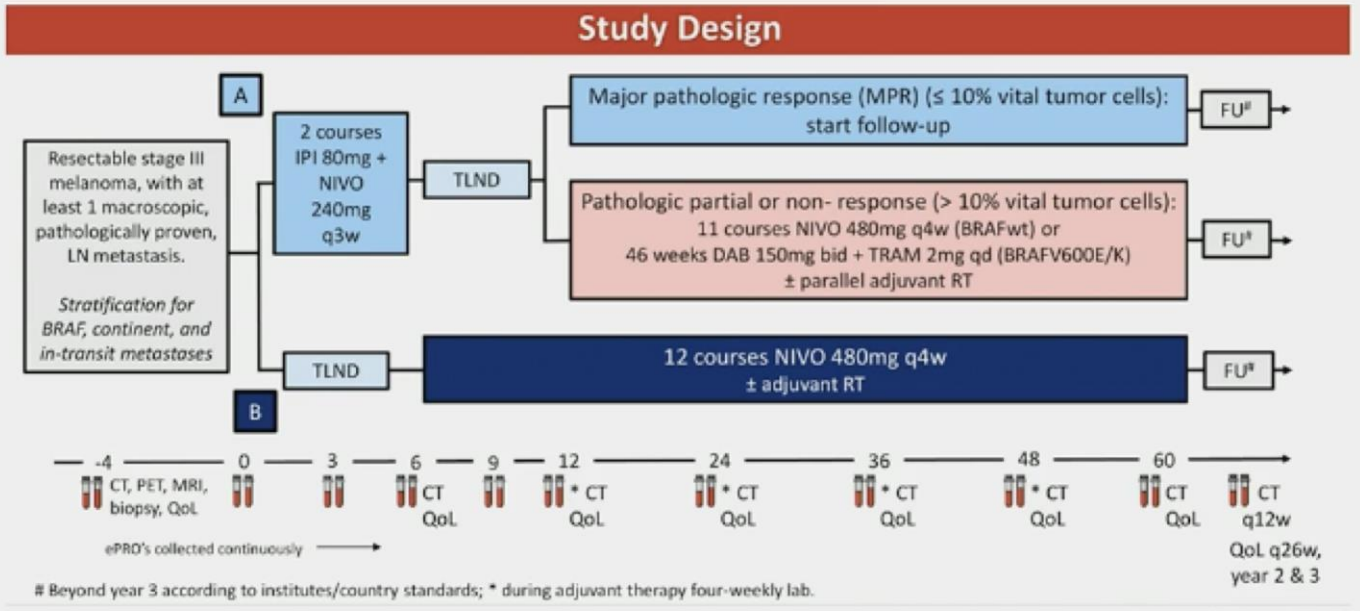
MELANOME uvéal

Le buzz en onco-dermatologie



NADINA trial

Response-driven **n**eo-**ad**juvant combination of **i**pilimumab + **n**ivolumab vs **a**djuvant nivolumab



Lucas MW et al, TPS9605, ASCO 2022.

LBA2: Sunday, June 2, 1:00 - 4:00 PM CT
Plenary Session, Hall B1

2024 ASCO ANNUAL MEETING #ASCO24

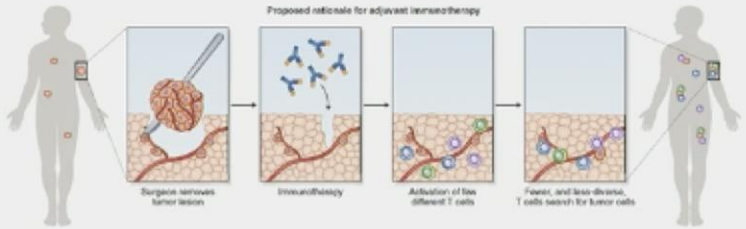
PRESENTED BY: Karakousis GC, Michielin O, Tetzlaff MT, Tsai KK

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

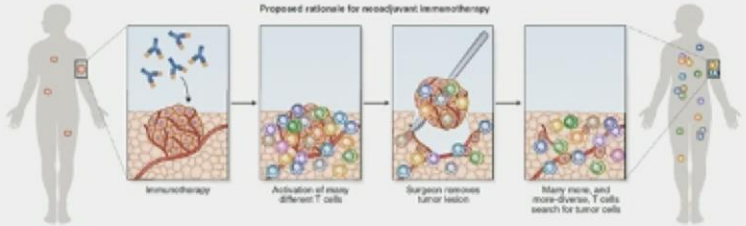
L’ère du néo-adjuvant dans le mélanome

Biological & Early Clinical Rationale for Neoadjuvant Immunotherapy

Adjuvant immunotherapy



Neoadjuvant immunotherapy



Versluis, Long and Blank, Nat Med 2020;

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Christian U. Blank, MD PhD

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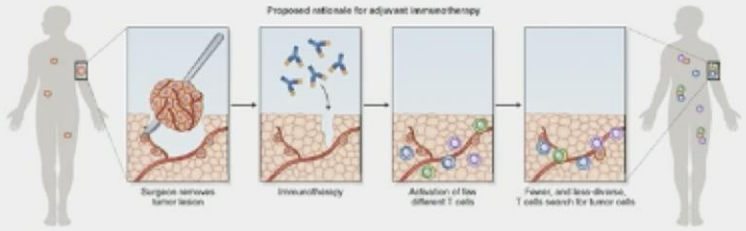
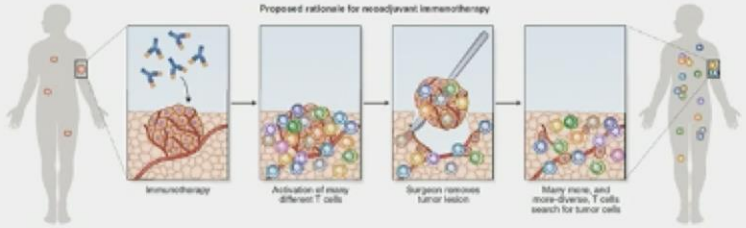
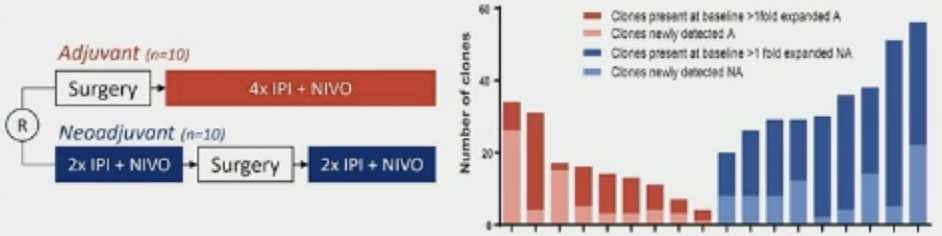


Neoadjuvant immunotherapy



OpACIN (Phase1)
neoadjuvant ipilimumab + nivolumab



Versluis, Long and Blank, Nat Med 2020;

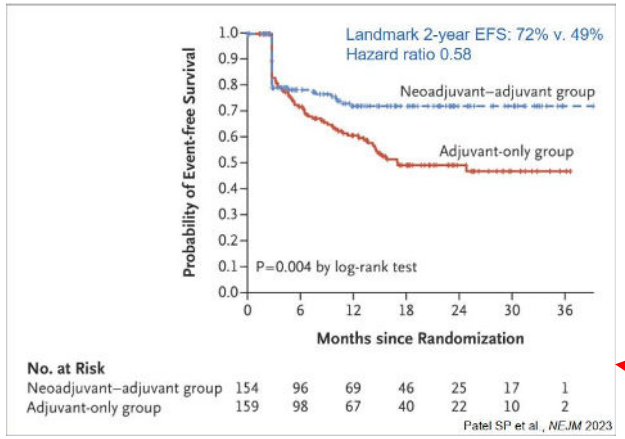
2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Christian U. Blank, MD PhD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

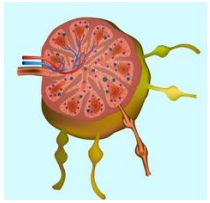
Quelles molécules? Quels schémas? Quel ratio B/R? Quelle attitude post-néo-adjuvante?

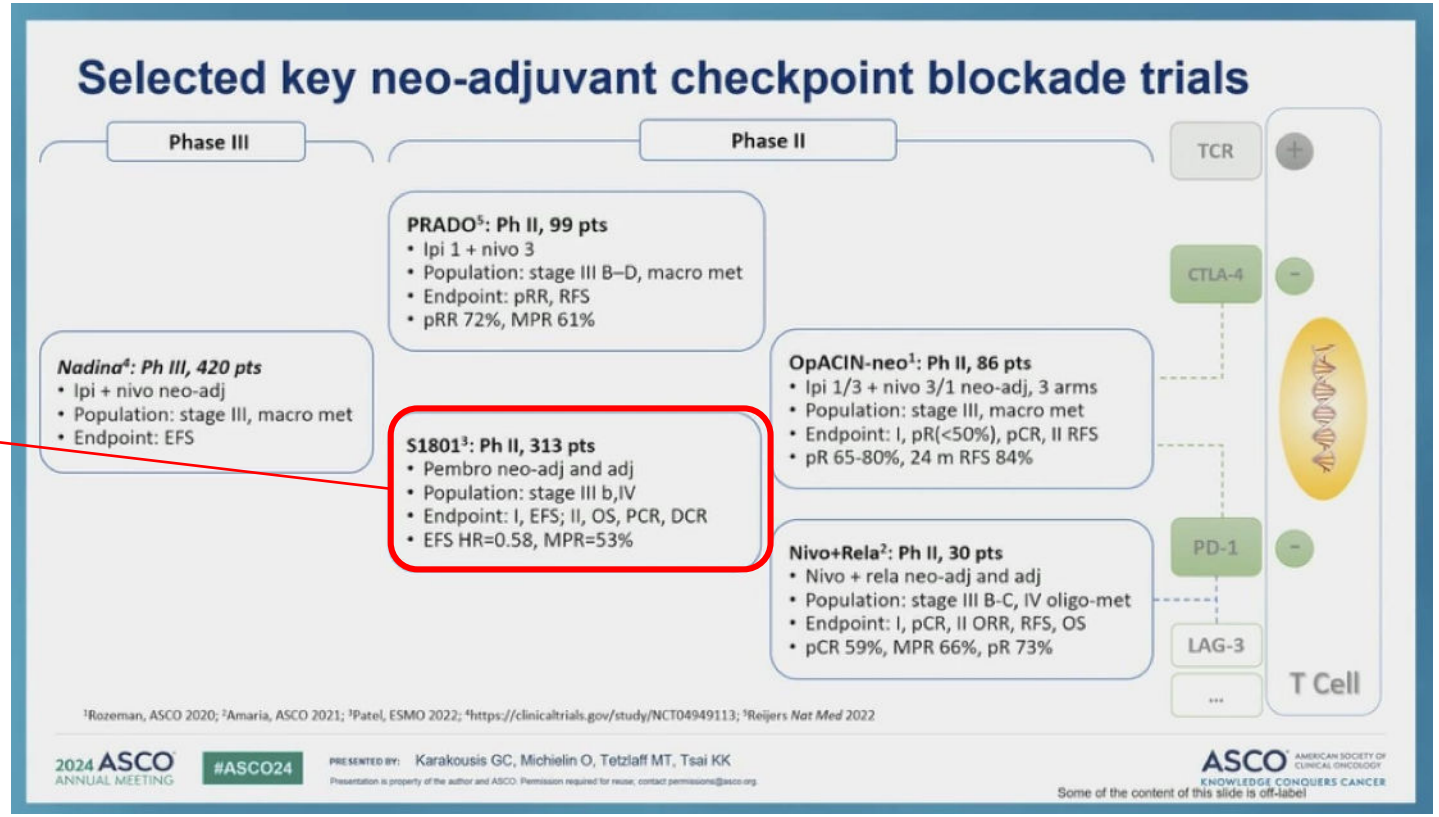
Plusieurs essais…dont l'essai SWOG 1801= modèle de l'approche néo-adj applicable en routine



Patel, NEJM 2023

Stades III
Macro-ganglionnaires (ou IV) résécables





1er essai néo-adj de phase 3 dans le mélanome

Bénéfice significatif sur l'EFS d'une combo par rapport au standard (antiPD1 adj)

HR à à 0.32

p<0.0001

Près de 60% des patients recevront seulement 2 cures d'ICI (6 semaines)

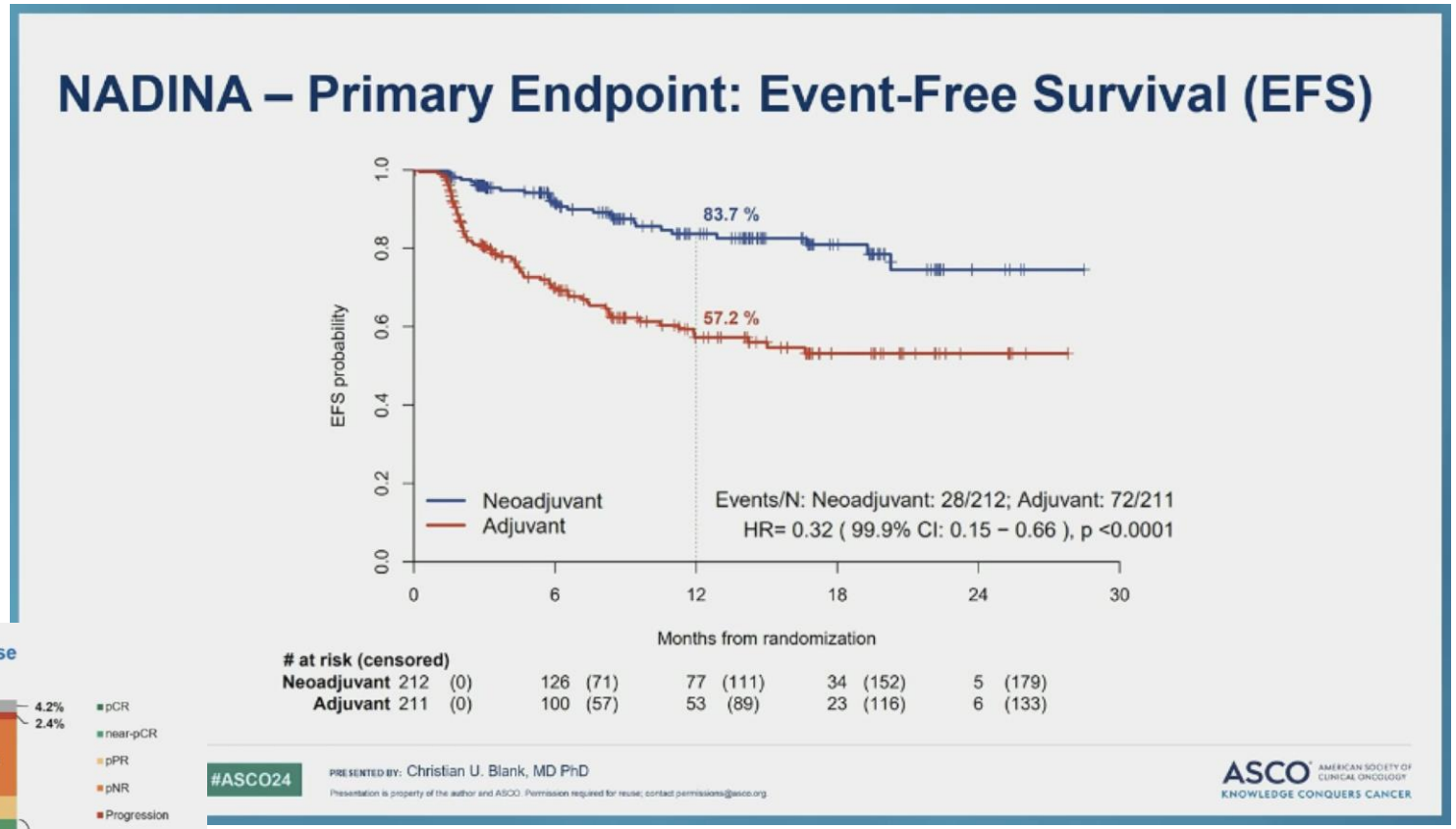
➔ Meilleure **réponse pathologique** -> meilleure survie sans rechute -> OS??

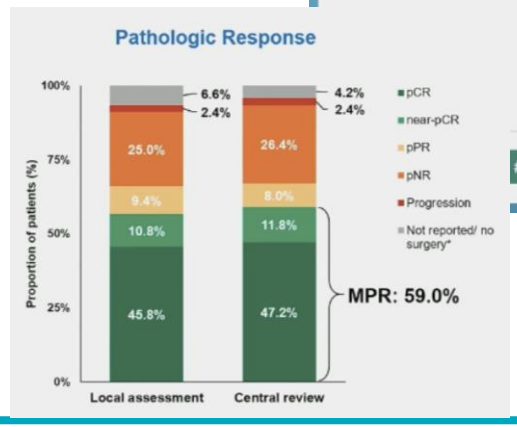
➔ **Désescalade thérapeutique** (pas d'adjuvant pour >50% des patients)

➔ Moins de toxicité*

➔ Gain en qualité de vie

➔ Réduction des coûts

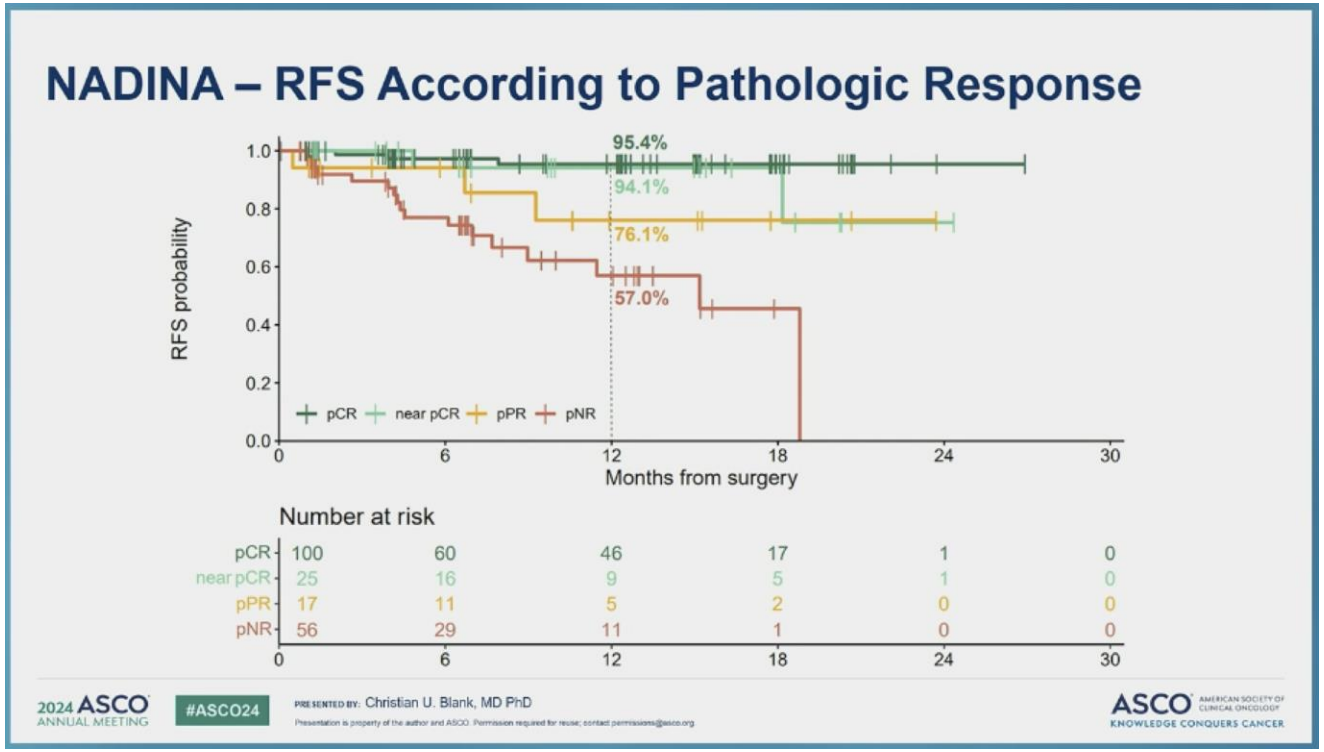




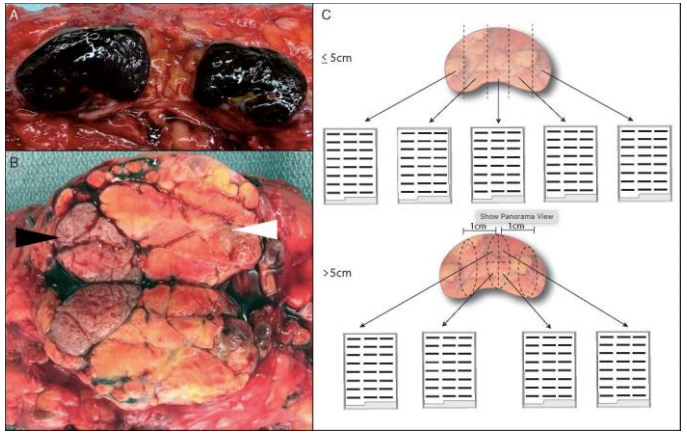
* Même si la combo double le % d'effets indésirables de grade 3-4 (30% vs 15%), 7% insuffisance corticotrope

Réponse pathologique= nouveau « biomarqueur de survie »

Ou comment prédire l'avenir…



Tetzlaff, Ann Oncol 2018



-% tumeur résiduelle viable
-Signes de régression tumorale : nécrose, fibrose, stroma inflammatoire, macrophages pigmentés
-Réponse pathologique: pCR, near pCR, pPR, pNR

- Consensus INMC: *Amaria, Lancet Oncol 2019*
  - **standardisation lecture histopathologique**
  - Rationalisation méthodologie des essais, identification biomarqueurs clinico-pathologiques, moléculaires et radiologiques

Pathologic Response category in melanoma	Residual viable tumor (as a % of total tumor bed)
Pathologic complete response (**pCR**)	0
Pathologic near complete response (**pnCR**)	1-10
Pathologic partial response (**pPR**)	11-50
Pathologic non-response (**pNR**)	51-100
Major pathologic response (**MPR**)	

L'adjuvant le grand perdant?

Stades III ou IV réséqués

Non… on peut booster l'adjuvant par un vaccin personnalisé à ARNm

- **Actualisation à 3 ans, phase 2, essai Keynote-942: Pembro+/- vaccin**
- ESMO 2023: avantage significatif sur la RFS et la DFMS

LBA9512

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]

[a]Manju Morrissey,[20] Igor Feldman,[20] Vasudha Sehgal,[20] Huzhang Mao,[20] Jia Guo,[20] Min Liu,[20] Anjali Rao,[20] Wei Zheng,[20] Praveen Aanur,[20] Lakshmi Srinivasan,[20] Mo Huang,[21] Tal Zaks,[20] Michelle Brown,[20] Tracey Posadas[20]

[1]Laura and Isaac Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]Hollywood Private Hospital and Edith Cowan University, Perth, Australia; [3]Melanoma Institute Australia and Westmead Hospital, Sydney, Australia; [4]Saint John of God Subiaco Hospital, Subiaco, Australia; [5]Earle A. Chiles Research Institute, Portland, OR, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Massachusetts General Hospital, Boston, MA, USA; [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [11]Yale-New Haven Hospital, New Haven, CT, USA; [12]Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [13]University of Colorado, Aurora, CO, USA; [14]University of Arizona Cancer Center, Tucson, AZ, USA; [15]Princess Alexandra Hospital, Woolloongabba, Australia; [16]Lombardi Comprehensive Cancer Center, Washington, DC, USA; [17]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [18]Dana-Farber Cancer Institute, Boston, MA, USA; [19]Melanoma Institute Australia, Sydney, Australia; [20]Moderna, Inc., Cambridge, MA, USA; [21]Merck & Co., Inc., Rahway, NJ, USA.

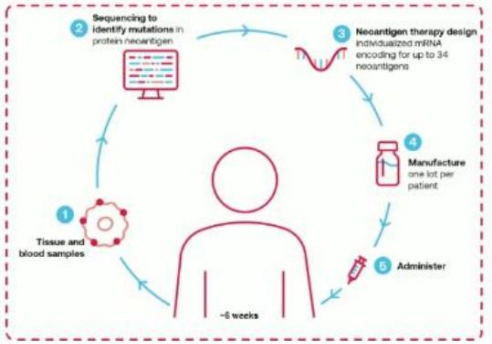
Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

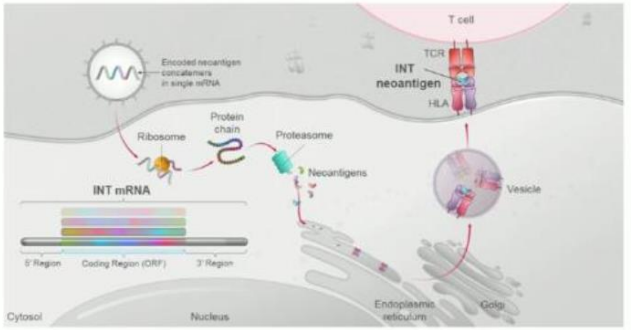
2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Jeffrey S. Weber, MD, PhD

ASCO KNOWLEDGE CONQUERS CANCER

Mécanisme d'action du V940

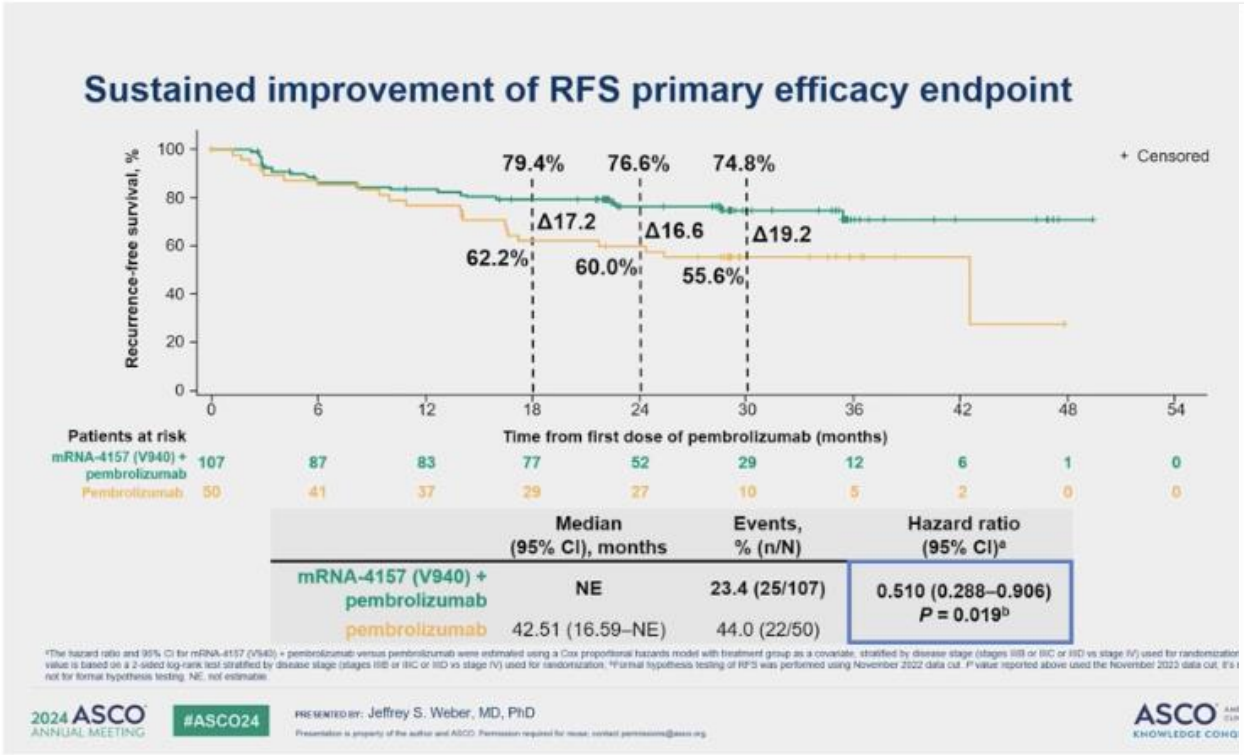
- Vaccin à ARNm personnalisé codant jusqu'à 34 néoantigènes
- Permet de potentialiser la réponse immunitaire médiée par les lymphocytes T spécifiques des néoantigènes produits

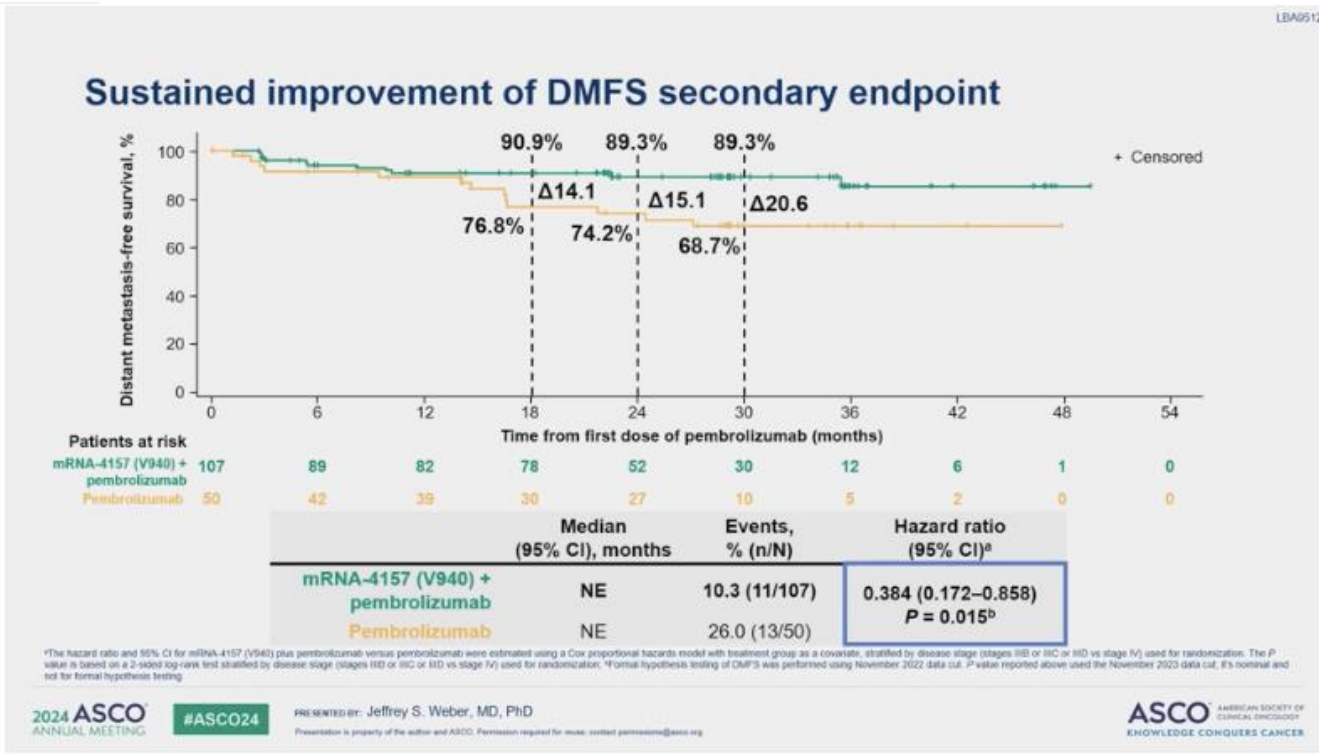




Weber JS, et al. Presented at ESMO 2023. Abstract LBA49; Weber JS, Lancet

Résultats actualisés pembro+ V940





Réduction de 49% du risque de récurrence ou de décès
Réduction de 62% du risque de métastase à distance ou de décès
Comparé au standard = pembrolizumab monothérapie
Pour les mélanomes à haut risque
Avec 3 ans de recul

Sans potentialisation des irAEs liés à l'antiPD1

=> Phase 3 V940-001 en cours
(IIB à IV réséqués)

Enseignement stades précoces

Mélanome « à haut risque »: IIB-IIC-III-IV résécables

- **Maladie microscopique (résiduelle) ou macro limitée**
- Ratio B/R à traiter à établir
- Considérer l'absence d'adjuvant dans certains cas
- Si TTT: préférer les approches moins toxiques basées sur antiPD1 seuls
- Quelques cures néo-adj up-front +++

- **Maladie macroscopique/facteurs péjoratifs**
- Très haut risque de rechute
- Ratio B/R à traiter: B>>R
- Préférer les approches les plus efficaces, basées sur combo
  - Adjuvant seul boosté?
  - Néo-adj ipi+nivo +/- adj?

NADINA= nouveau standard chez les « très haut risque »?

Quoi de neuf?

ASCO 2024

MELANOME
cutané

STADES
PRECOCES

MELANOME
cutané

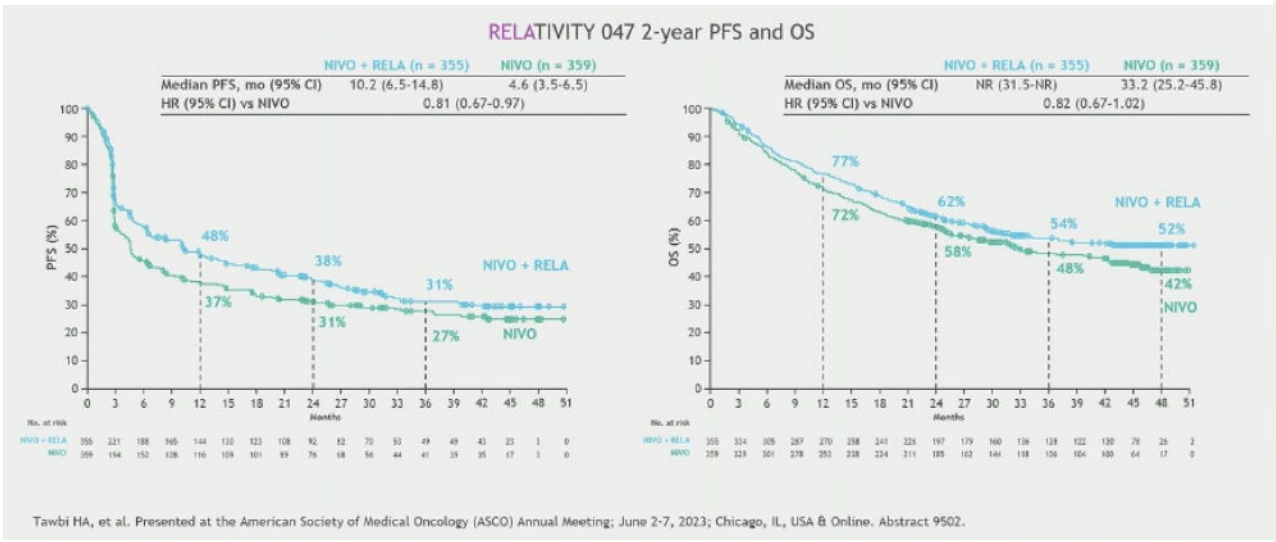
STADES
AVANCES

MELANOME
uvéal

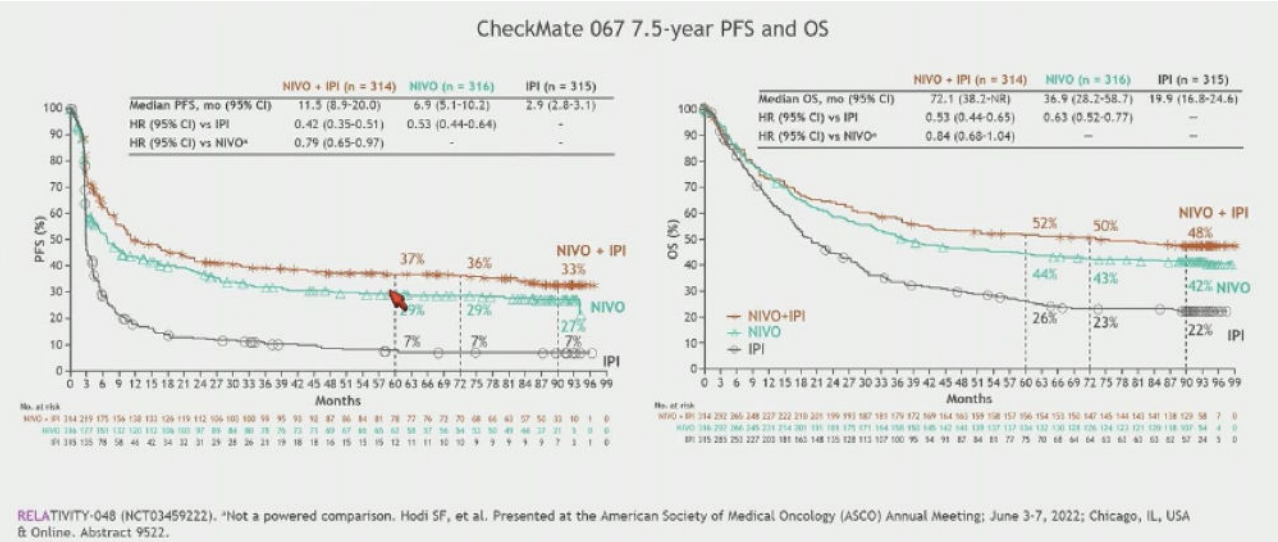
Comment optimiser le standard-of-care en 1ière L?

antiPD1 +/-antiCTLA4 ou antiLAG3

- Données actuelles



Tawbi HA, et al. Presented at the American Society of Medical Oncology (ASCO) Annual Meeting; June 2-7, 2023; Chicago, IL, USA & Online. Abstract 9502.



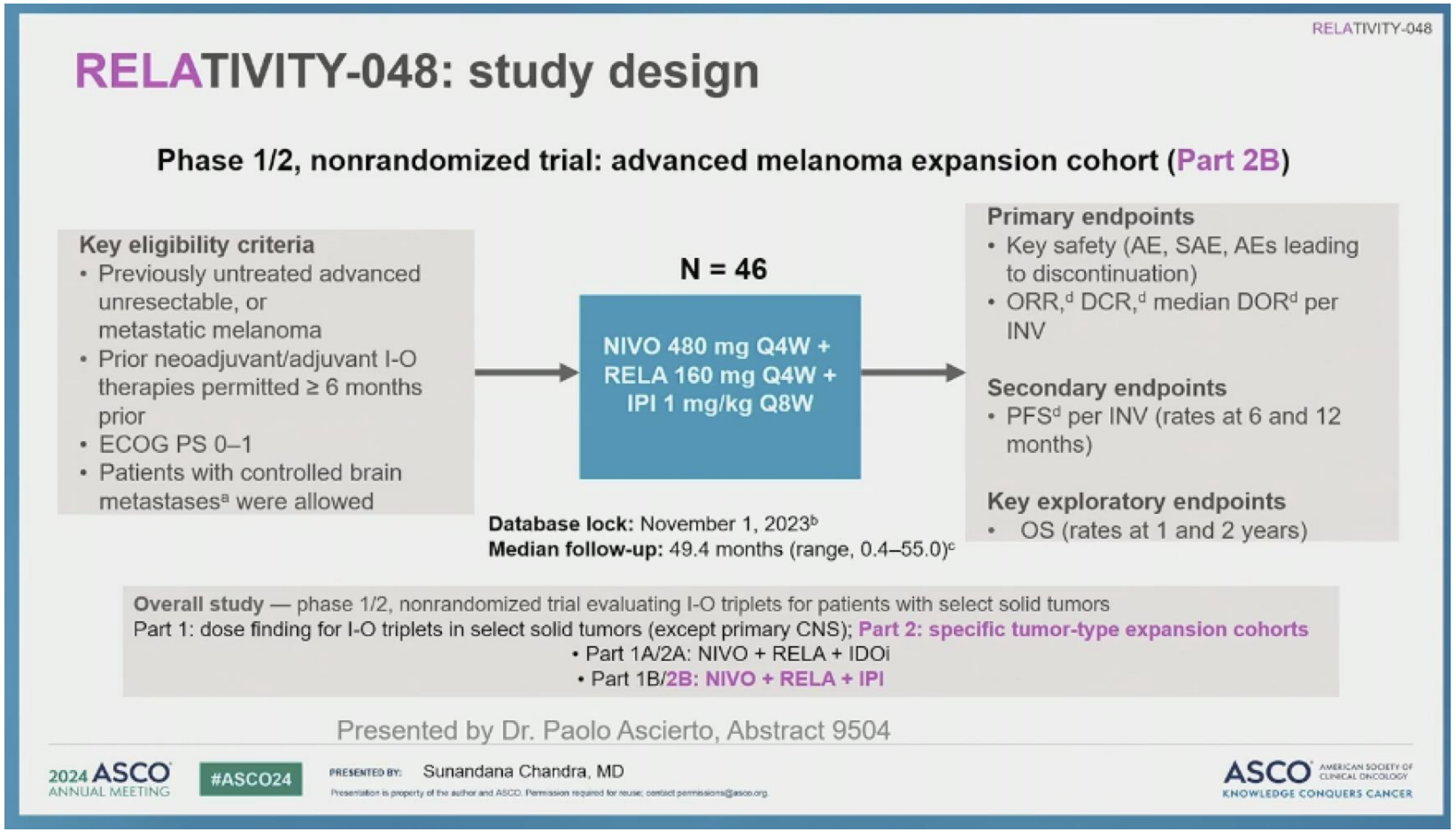
RELATIVITY-048 (NCT03459222). [a]Not a powered comparison. Hodi SF, et al. Presented at the American Society of Medical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL, USA & Online. Abstract 9522.

	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%

1-Triplette antiPD1 antiCTLA4 antiLAG3

IPI faible dose toutes les 8 semaines

- 16% ALM et muqueux
- 50% BRAFm
- 30% méta hépatique
- <10% maladie cérébrale contrôlée
- 52% M1c

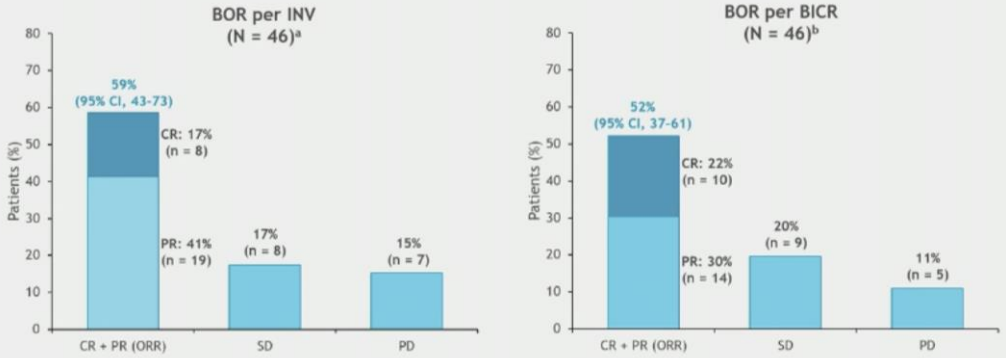


Résultats

Relativity-048

RELATIVITY-048

BOR per INV (primary endpoint) and BICR (exploratory endpoint)



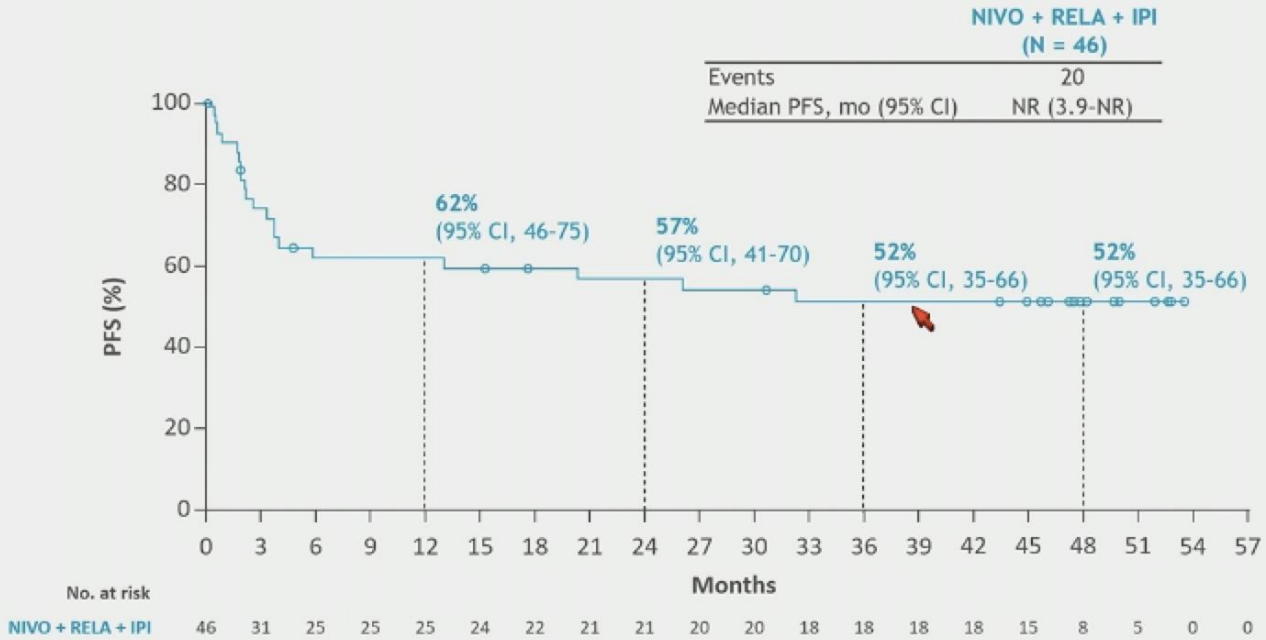
Safety summary

	NIVO + RELA + IPI (N = 46)	
	Any grade, n (%)	Grade 3-4, n (%)
Any AE	46 (100)	27 (59)
Any SAE	27 (59)	17 (37)
TRAE	44 (96)	18 (39)
TRAE leading to discontinuation	19 (41)	10 (22)
Most common TRAEs (≥ 20%)[a]		
Pruritus	16 (35)	0
Fatigue	14 (30)	0
Hypothyroidism	11 (24)	0
Asthenia	10 (22)	0
Colitis	10 (22)	2 (4)
Diarrhea	10 (22)	2 (4)
Lipase increased	10 (22)	6 (13)
Vitiligo	10 (22)	0
Deaths due to TRAEs	2 (4)	

- Treatment-related deaths occurring within 100 days of the last dose of study therapy were due to rectal hemorrhage and dyspnea (n = 1) and immune-mediated myositis (n = 1)

RELATIVITY-048

PFS per INV: secondary endpoint



ORR 59%, DCR 76%
PFS à 3 ans: 52% avec plateau au-delà de 36 mois
Tolérance acceptable: 39% irAE grades 3-4

Faible effectif <50 patients, phase 1-2
Données encore peu matures

Résultats

Relativity-048

Efficacy and safety in combination CPI 1L trials

Checkmate 067, Relativity 047, Relativity 048

	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, LBA44
Tawbi et al., NEJM, 2022; Tawbi et al., ASCO 2023, abstract 9502
Ascierto et al., abstract 9504

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Sunandana Chandra, MD

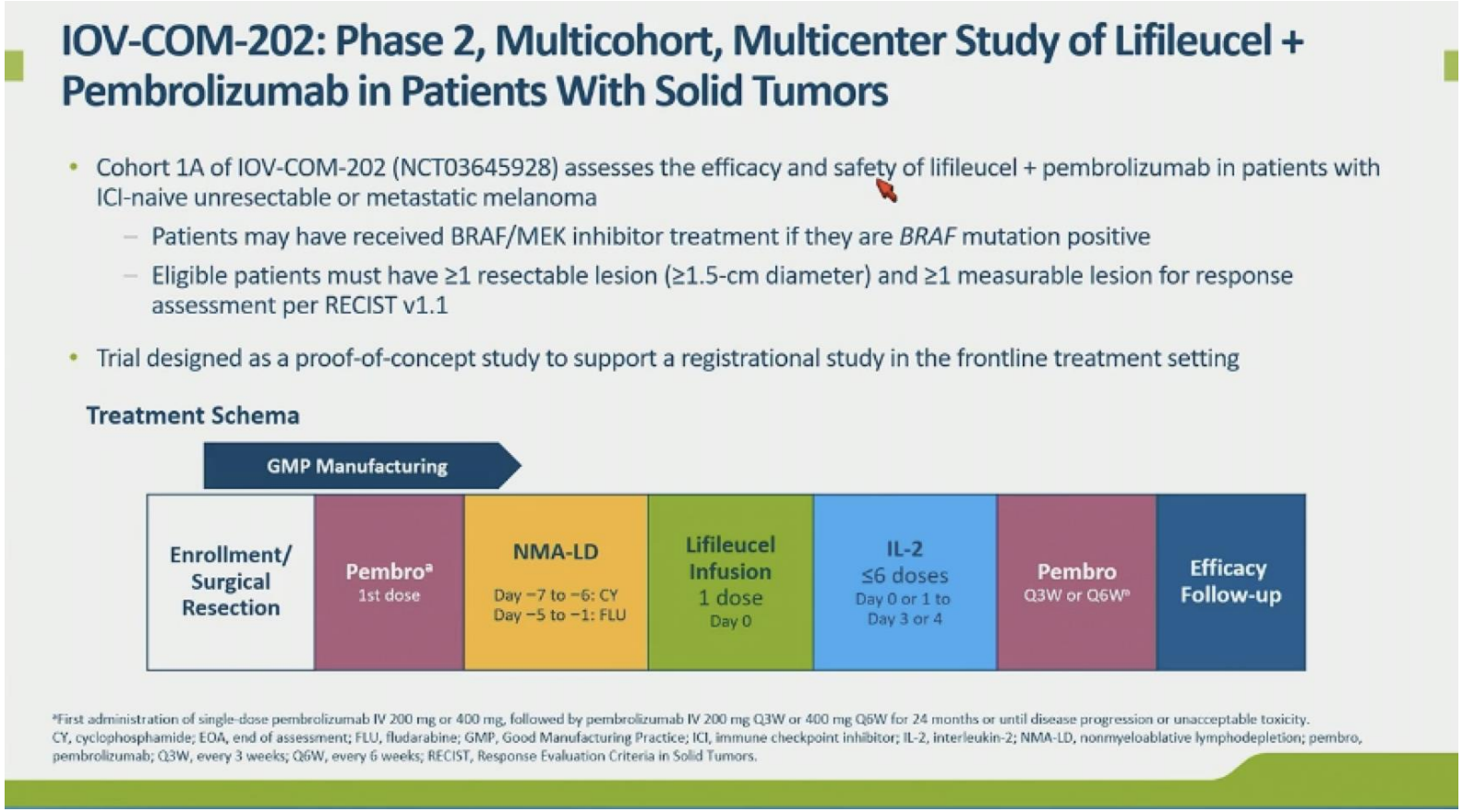
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Nouveau standard en 1ière L pour des sous-populations ou maladies « graves »?

2- Les thérapies cellulaires autologues par Lymphocytes infiltrant la tumeur

AntiPD1 + TIL

- Environ 50 % des patients connaîtront une résistance primaire ou secondaire à aux ICI
- Background:
  - Lifileucel : FDA-approval en 2ième L
  - Basé sur essai C-144-01, ORR 31.4%, DoR très longues chez certains patients au-delà de 2.5 ans
- Quid de son utilisation en première ligne?



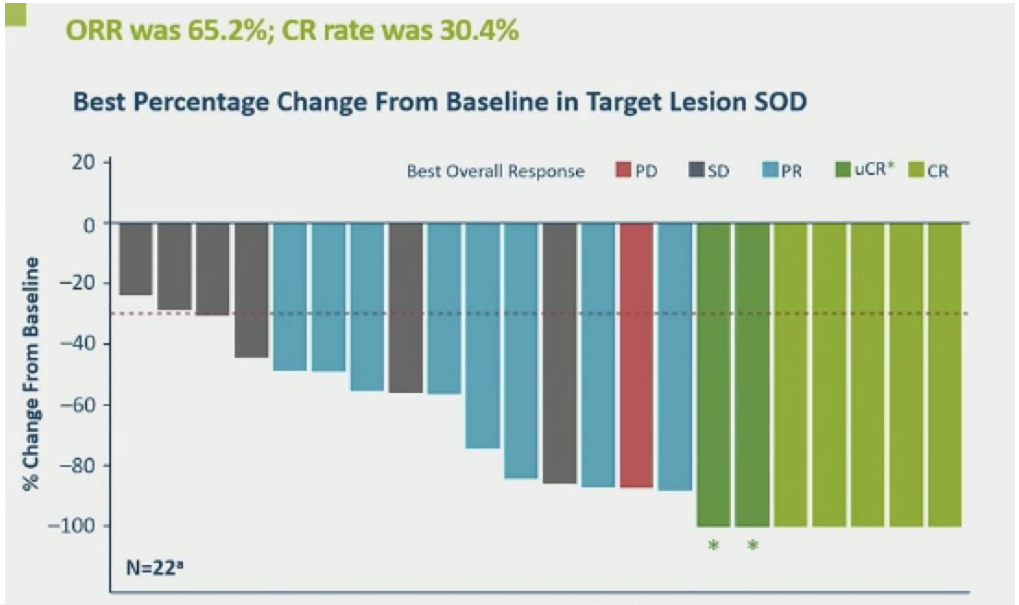
2- Les thérapies cellulaires autologues par Ly infiltrant la tumeur

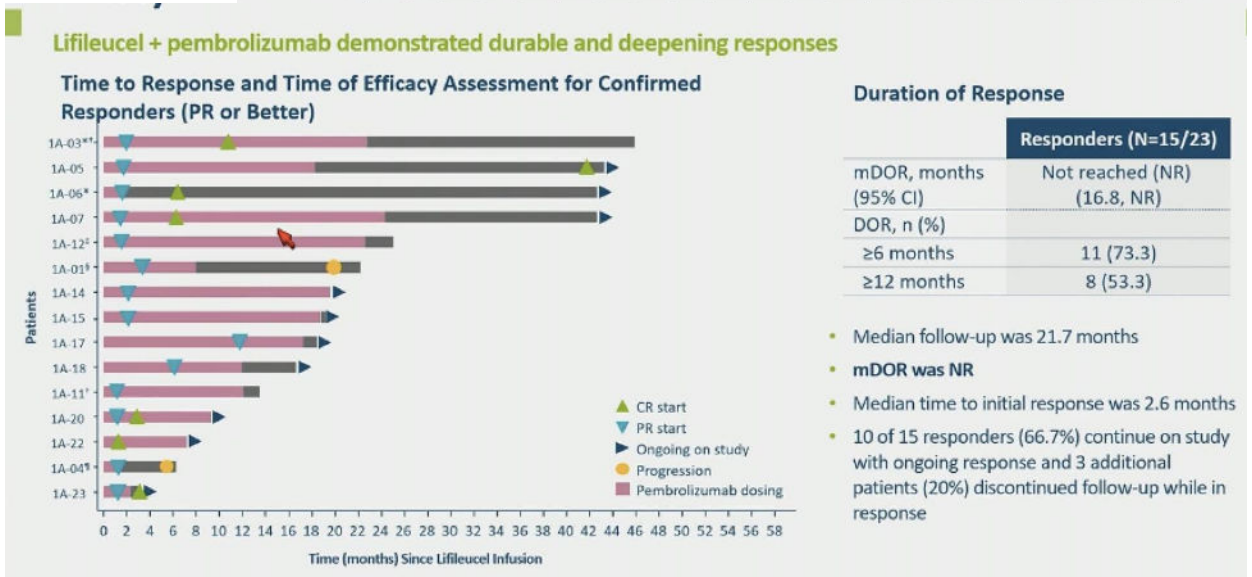
AntiPD1 + TIL

- ORR: 65%, CR 30%, DoR NR malgré suivi médian de 22 mois
- Tox hématologique sévère avec 43% neutropénies fébriles (lymphodéplétion), SRC (IL2); tox connue antiPD1 ensuite

TEAE/AEs	Grade 3/4 ≥10%
Chills	13%
Pyrexia	17.4%
Febrile neutropenia	43.5%
HTN	21.7%
Rash	13%
Neutropenia	100%
Lymphopenia	100%
Leukopenia	95.7%
Thrombocytopenia	95.7%
Anemia	43.5%

~80-90% resolved to Grade ≤2 by day 30



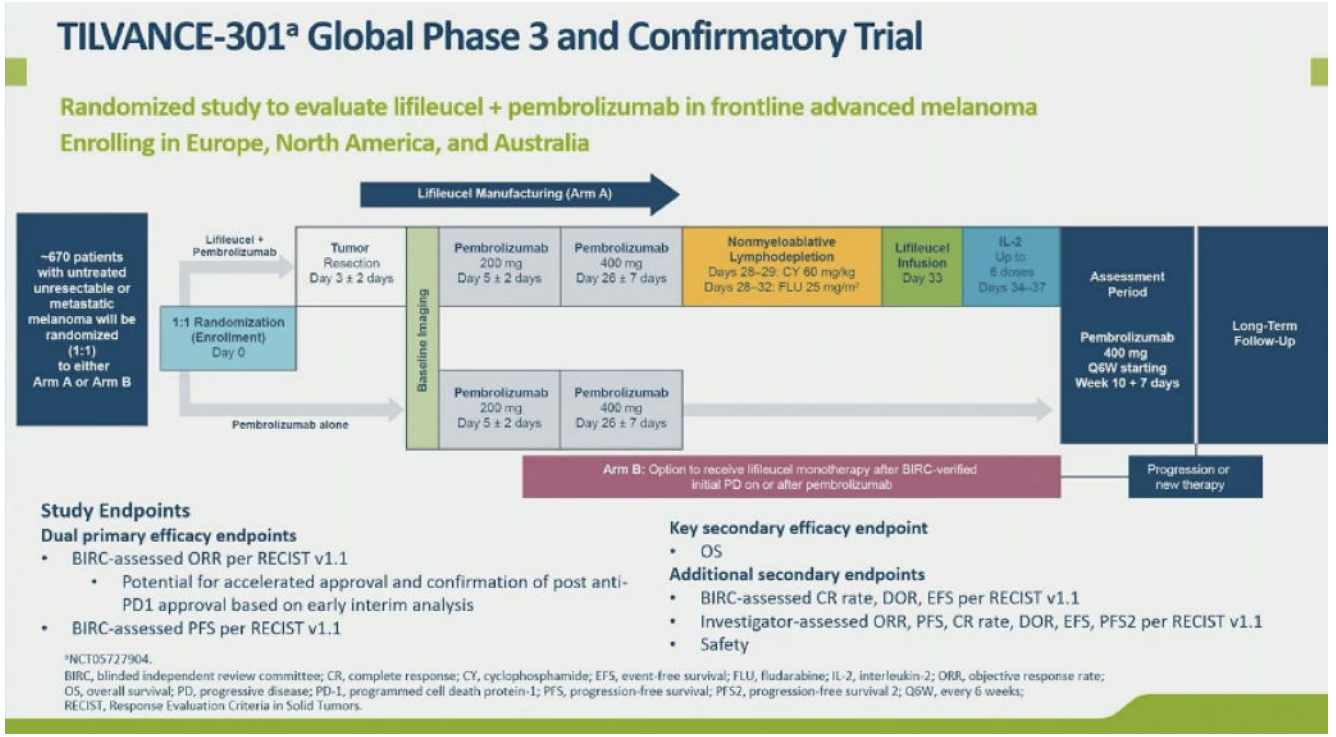


Phase 3 en cours

! Faiblesse du comparateur!

Intérêt pour: **patients jeunes, non comorbides, maladies à facteurs pronostiques péjoratifs**

- Problématique de la mise en œuvre pratique : collaboration nécessaire avec équipes d'hématologie et utilisation plus large multi-tumeurs



3- Rattrapage après échec ICI

PD-1 Refractory Melanoma: anti CTLA-4/PD-1

Ipilimumab +/- Nivolumab

Multicenter, Retrospective

- Advanced Melanoma (Cutaneous)
- Prior PD-1 Therapy with Progression

→ Nivolumab (1 or 3 mg/kg) + Ipilimumab (1mg or 3mg/kg OR Ipilimumab (3mg/kg)

- Ipilimumab + Nivolumab
  - ORR 23%
- Ipilimumab
  - ORR 17%

Zimmer et al, EJCA 2017

Ipilimumab +/- anti-PD-1

Multicenter, Retrospective

- Advanced Melanoma
- Prior PD-(L)1 Therapy with progression (innate or acquired resistance)

→ Ipilimumab OR Ipilimumab + PD-1 (Pembrolizumab or Nivolumab)

- Ipilimumab + PD-1
  - ORR 31%
- Ipilimumab
  - ORR 13%

Pires da Silva et al, Lancet Oncol

Ipilimumab +/- Nivolumab

- Advanced Melanoma (Cutaneous or Mucosal)
- Prior PD-1 Therapy with Progression

→ 1:3 Ipilimumab (3 mg/kg) | Ipilimumab (3 mg/kg) + Nivolumab (1 mg/kg)

- Ipilimumab + Nivolumab
  - ORR 28%
- Ipilimumab
  - ORR 9%

Ipilimumab +/- Pembrolizumab

- Advanced Melanoma (Cutaneous or Mucosal)
- Prior PD-1 Therapy with Progression

→ Pembrolizumab (200mg) + Ipilimumab (1 mg/kg)

- Ipilimumab + Pembrolizumab
  - ORR 29%

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PD-1 Refractory Melanoma: LAG-3/PD-1

Expansion Cohort:

- Advanced Melanoma
- Prior PD-1 +/- CTLA-4 Therapy with Progression

→ Nivolumab + Relatlimab

RELATIVITY-020: Nivolumab + Relatlimab

- ORR 9.2-12%

Ascierto et al, JCO 2023

Cemiplimab + Fianlimab

- ORR 13.3%

Hamid et al, ESMO 2022

Expansion Cohort:

- Advanced Melanoma
- Prior PD-1 +/- CTLA-4 Therapy with Progression

→ Cemiplimab + Fianlimab

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ASCO KNOWLEDGE

PD-1 Refractory Melanoma: TIL Therapy

M14TIL

- Advanced Melanoma
- Prior PD-1 Therapy with Progression

→ 1:1 TIL Treatment | Ipilimumab (3 mg/kg)

TIL: ORR 49%
Ipi: ORR 21%

Rohaan et al, NEJM 2022

Lifileucel

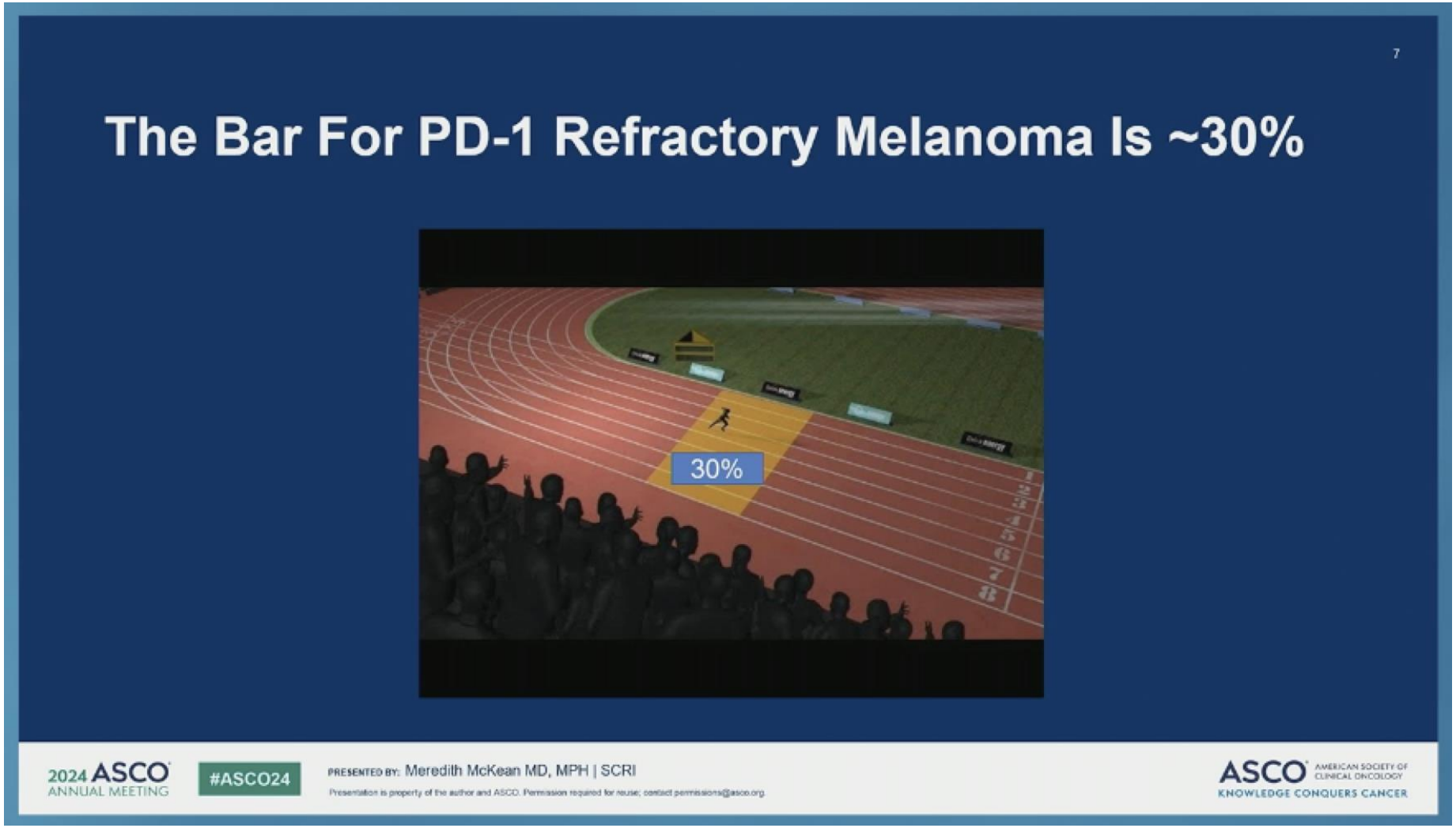
- Advanced Melanoma
- Prior PD-1 +/- CTLA-4 Therapy with Progression

→ Lifileucel (Cohorts 2 & 4 Pooled)

- ORR 31.4%

Chesney et al, JITC 2022

3- Rattrapage après échec ICI



3- Rattrapage après échec ICI: les pistes

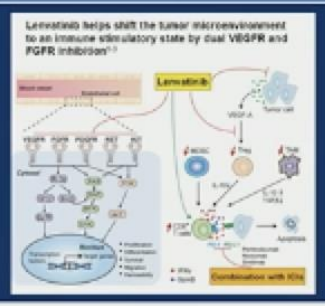
Approaches

Vibostolimab
- Anti-TIGIT

Quavonlimab
- Anti-CTLA-4

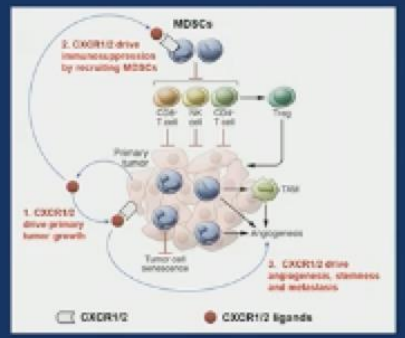
Lenvatinib
- Multitargeted-TKI
- 1st line: ORR 43.4% with pembro

ATRA
- Vitamin A derivative
- 1st line: ORR 71% with pembro



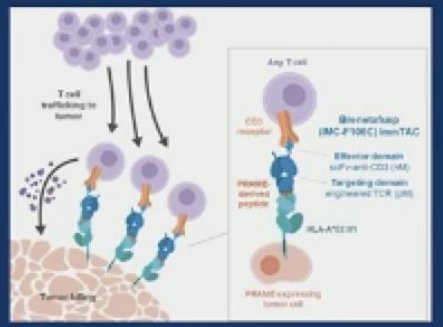
Arance et al, SMR 2023
Tobin et al, CCR 2023

SX-682
- CXCR1/2 small molecule inhibitor



Dunne et al, J Clin Oncol 2023

Brenetafusp (IMC-F106C)
- PRAMExCD3 bispecific antibody



KEYMAKER –U02A

Arm 1:
pembrolizumab 200 mg IV Q3W
+ quavonlimab 25 mg IV Q6W
+ vibostolimab 200 mg IV Q3W

ORR: 18%

Arm 2:
pembrolizumab 400 mg IV Q6W
+ quavonlimab 25 mg IV Q6W
+ lenvatinib 20 mg PO QD

ORR: 28%

Arm 3:
pembrolizumab 400 mg IV Q6W
+ ATRA 150 mg/m²/day PO for 3 days Q3W

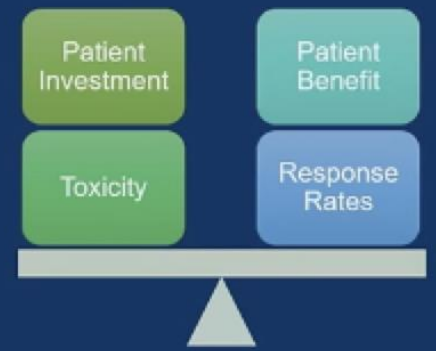
ORR: 0%

KEYNOTE-029: Phase 1b
Pembrolizumab + Quavonlimab
Melanoma with PD within 12 weeks of PD-(L)1; no prior CTLA4

Deva et al, AACR 2022

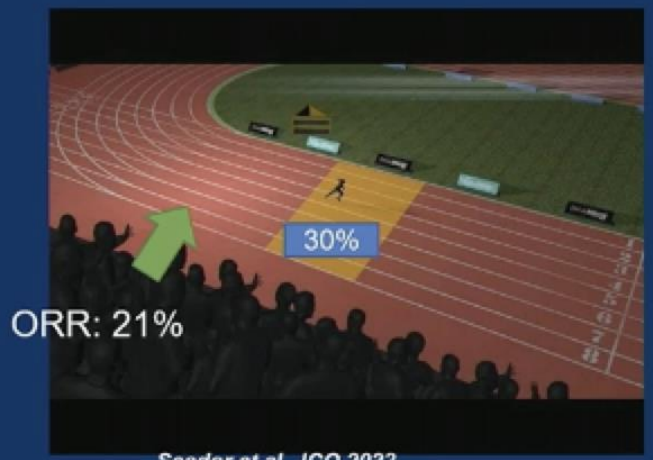
ORR: 9%

- Arm 1 & 2 response rates similar to 2nd line ipi/nivo
- Added tox without benefit with adding anti TIGIT and anti TKI
- Biomarker analysis needed



SX-682

- Cytopenias top tox but no increased infection risk
- 36 pts treated with 200mg BID combo
- 21% ORR at 200mg dose for 19 evaluable pts
- Most responders had progressed on ipi/nivo
- Ongoing responses > 1 year
- Included pts with mucosal melanoma and stable brain mets



Seedor et al, JCO 2023.
Ellis et al, Human Immunology 2000.

Brenetafusp: Targeting PRAME

Safety and immunogenicity of the PRAME cancer immunotherapeutic in metastatic melanoma: results of a phase I dose escalation study

R Gutzmer,[1] L Rivoltini,[2] E Levchenko,[3] A Teston,[4] J Utikal,[5,6] P A Ascierto,[7] L Demidov,[8] J J Grob,[9] R Ridolfi,[10] D Schadendorf,[11] P Queirolo,[12] A Santoro,[13] C Loquai,[14] B Dreno,[15] A Hauschild,[16] E Schultz,[17] T P Lesimple,[18] N Vanhoutte,[19] B Salaun,[19] M Gillet,[19] S Jamjak,[19] P M De Sousa Alves,[19,20] J Loushed,[19] V G Brichard,[19,21] F F Lehmann[19,20]

CLINICAL TRIALS | DECEMBER 01 2023

Abstract PR018: IMA203 TCR-T targeting PRAME demonstrates potent anti-tumor activity in patients with different types of metastatic solid tumors

Martin Wermke; Winfried Alsdorf; Dejka Araujo; Manik Chatterjee; Norbert Hilf; Tobias A.W. Holderried; Amir A. Jazaeri; Mamta Kalra; Andrea Mayer-Mokler; Regina Mendrzyk; Ali Mohamed; Sapna P. Patel; Ran Reshef; Arun Satelli; Harpreet Singh; Apostolia-Maria Tsimberidou; Steffen Walter; Toni Weinschenk; Cedrik M. Britten; Jason Luke

- HLA A02:01 present in 34-48% in Caucasian population and 20% in AA

Therapeutic targeting of PRAME with ^{mTCR}CAR T cells in acute myeloid leukemia

Danielle C. Kirkey,[1,2,*] Anisha M. Loeb,[1,*] Sommer Castro,[1] Cyd Nourigat McKay,[1] LaKeisha Perkins,[1] Laura Pardo,[3] Amanda R. Leonti,[1] Thao T. Tang,[1] Michael R. Loken,[3] Lisa Eidenschink Brodersen,[3] Keith R. Loeb,[1] David A. Scheinberg,[4] Quy Le,[1,*] and Soheil Meshinchi[1,2,†]

ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Paul Nathan, M.D., Ph.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Francois Baurain, M.D., Ph.D., Marcus O. Butler, M.D., Max Schlaak, M.D., Ryan J. Sullivan, M.D., Sebastian Ochsenreither, M.D., Reinhard Dummer, M.D.,

Seedor et al, JCO 2023.
Ellis et al, Human Immunology 2000.

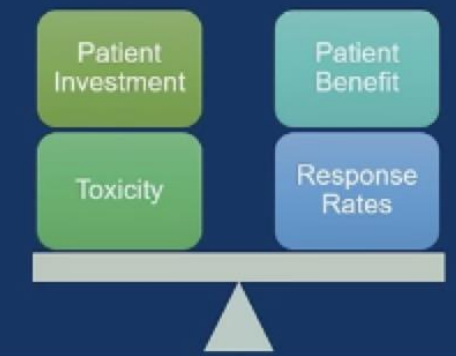
Abstract Summary

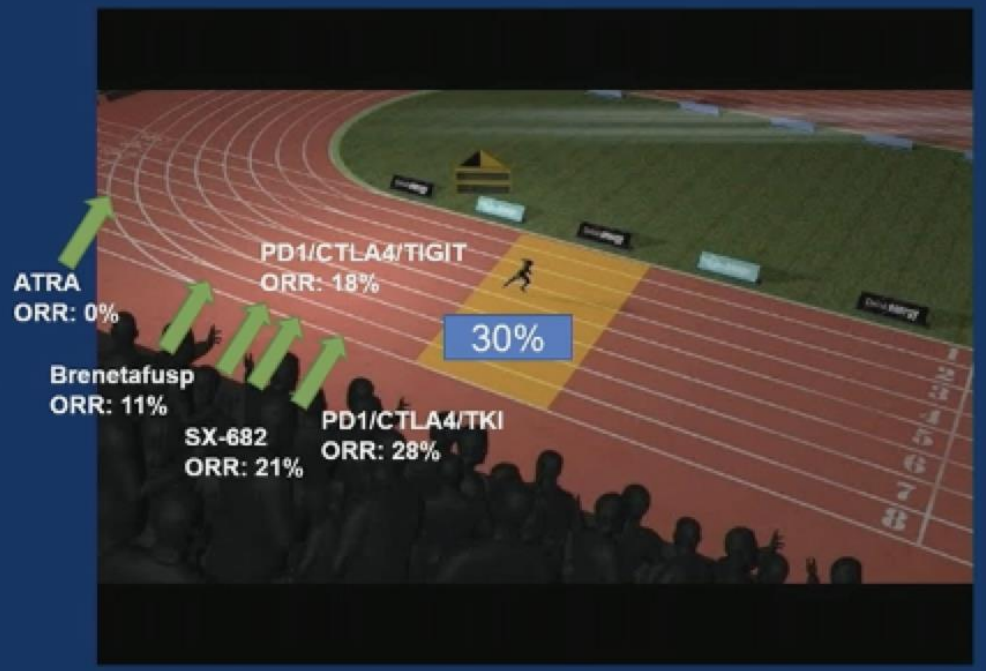
Phase 1/2 studies, signal-seeking

Patients that are heavily pretreated

Range of doses

Not uncommon to have high tox in the early phase setting





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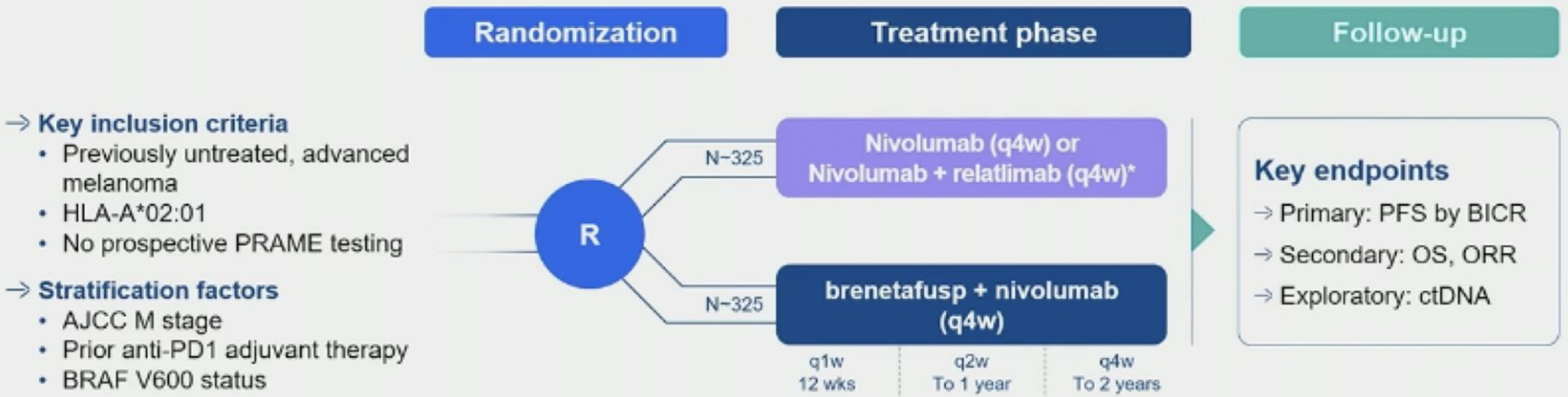
PRISM-MEL301: First-line advanced CM Phase 3



Initial randomization includes comparison of two brenetafusp regimens (~90 patients or 30/arm)

(PRISM-MEL301; NCT06112314); *see ASCO 2024 TiP poster #TPS9602*

*Use of nivolumab or nivolumab + relatlimab as control will be country specific

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Dr. Omid Hamid

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Enseignement stades avancés

Mélanome stade III-IV non résécables

- **En première ligne: gold-standard ipi+nivo (mais OS ns améliorée versus PD1 mono)…** place pour antiPD1 ou antiPD1+LAG3 (PDL1<1%)

- **En 2ième ligne et +:** maladie hétérogène et immuno-réfractaire

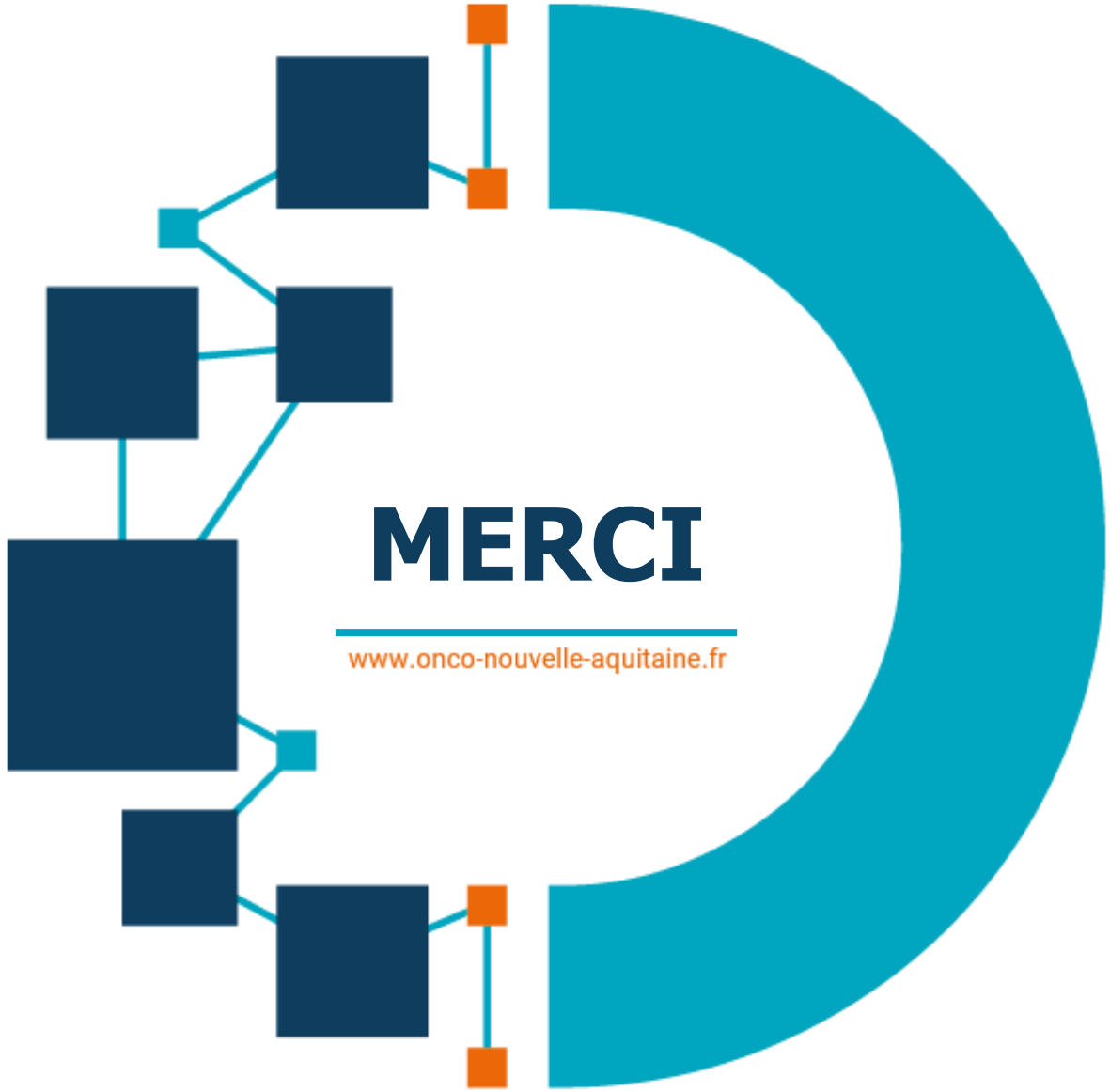
  -Toujours évaluer l'apport des *traitements locaux associés*

  -*Des pistes nombreuses mais restant sous la « barre des 30% »*

  -Pour l'instant rattrapage par ipi+nivo si maladie réfractaire aux antiPD1 seuls ou PD1+LAG

  -*Screening large, RCP moléculaire*

En espérant que cette population s'amenuise du fait des progrès considérables en phase précoce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www.onco-nouvelle-aquitaine.fr