CNCP | CONFÉRENCE NATIONALE DES COMITÉS DE PROTECTION DES PERSONNES

Vaccins en Oncologie

Dr. Carlos Gomez-Roca

- Département d'Oncologie Médicale - Unité des Essais Précoces, IUCT – Oncopole Claudius Regaud
- Antitumor Immunity and Immunotherapy Team (T2i) CRCT, UMR1037 Inserm / UMR5071 CNRS
- Responsable du groupe « Patient Advocacy » au FITC

T2i :
Immunité Anti-Tumorale Et Immunothérapie

Oncopole CLAUDIUS REGAUD

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

CRCT Centre de Recherches en Cancérologie de Toulouse ONCOPOLE

FITC Société Française d'Immuno-Thérapie du Cancer

Bases de l'immunité des cancers

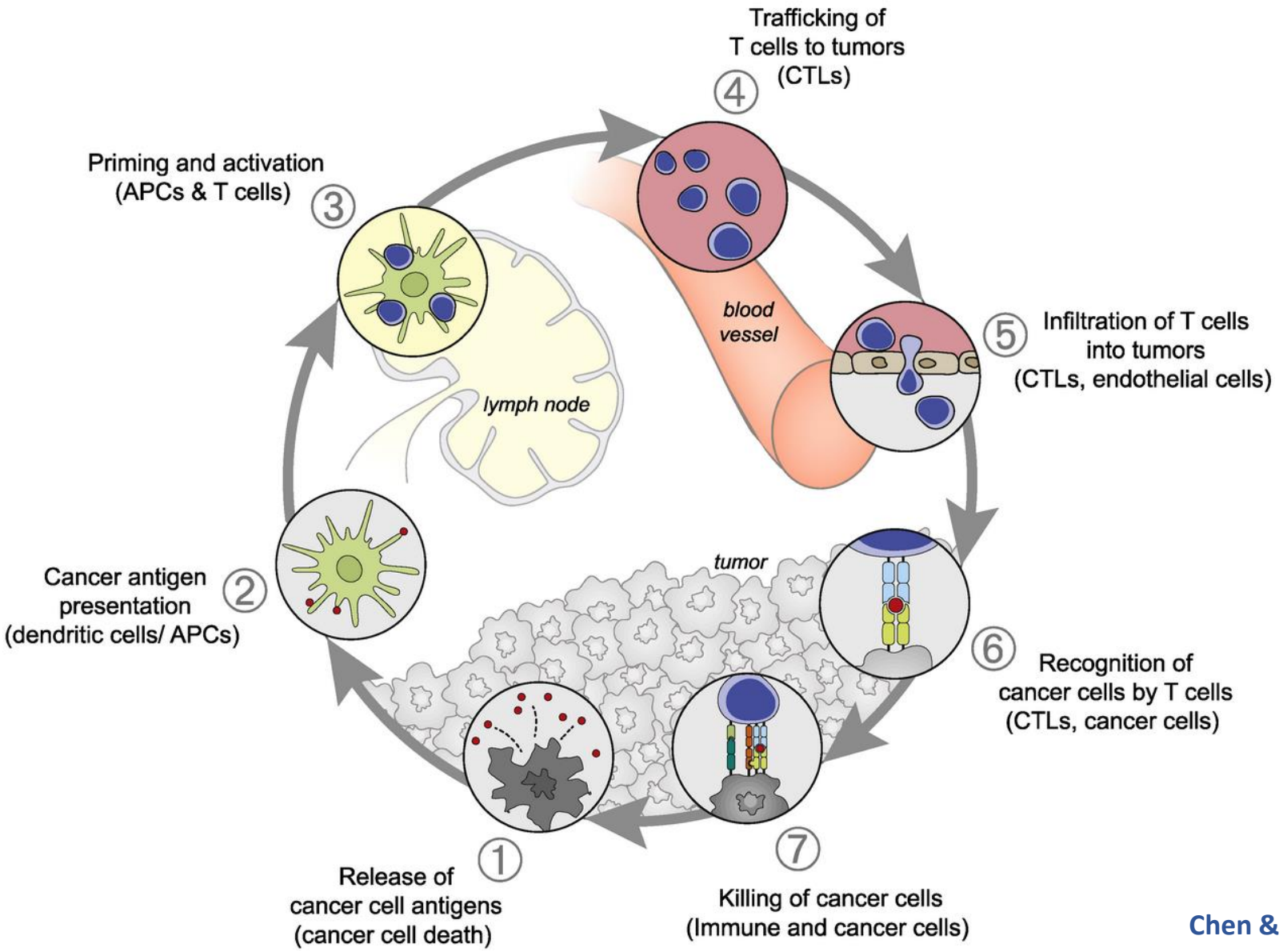
Vaccination en cancer – circonstances cliniques

Sélection des antigènes et production des vaccins

Objectifs des essais des vaccines en oncologie: exemples de la Ph3 a la Ph1

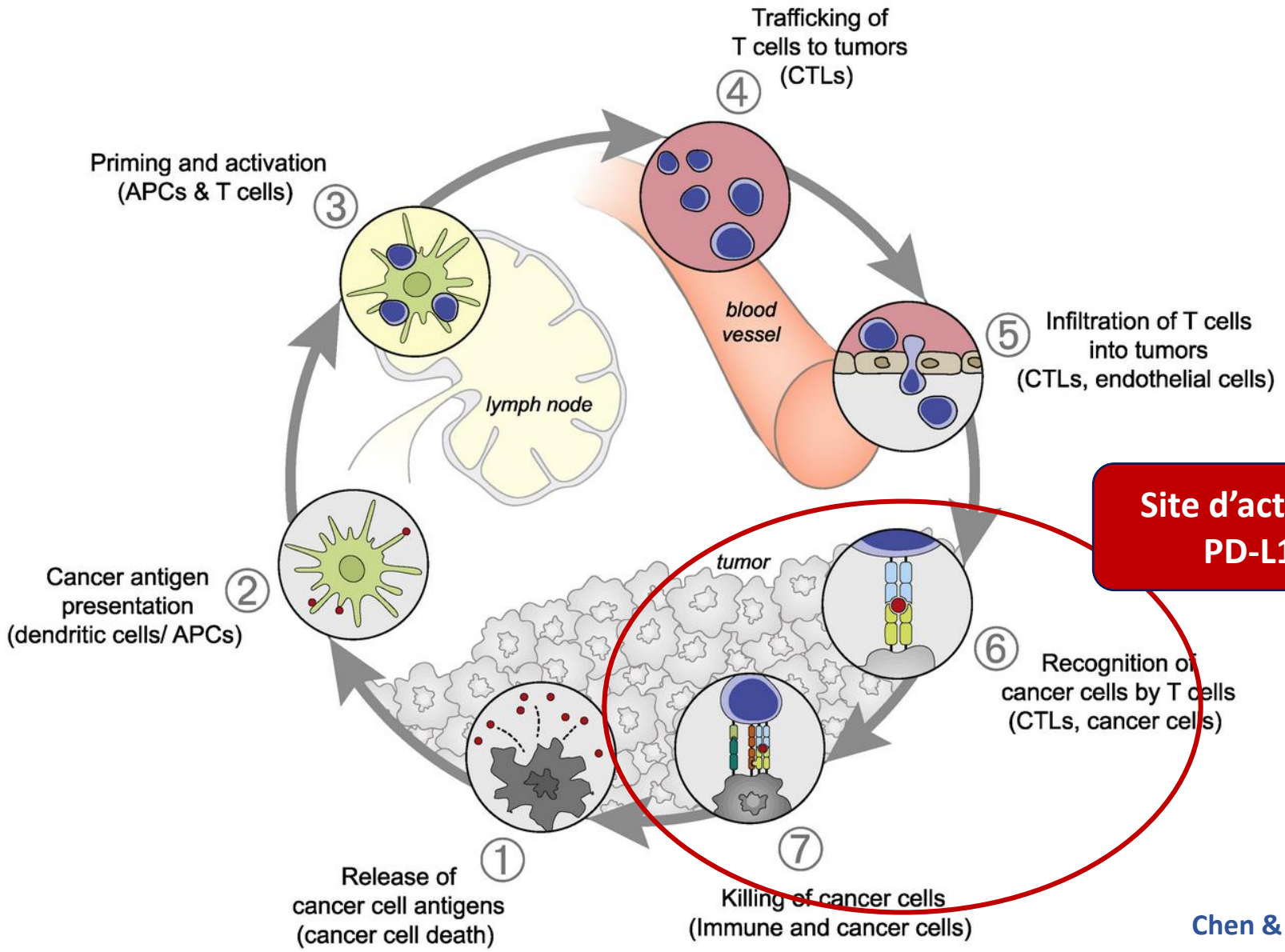
Réflexions: ce nous pouvons faire ensemble

Le cycle d'interaction entre le cancer et l'immunité



Chen & Mellman, Immunity 2013

Le cycle d'interaction entre le cancer et l'immunité

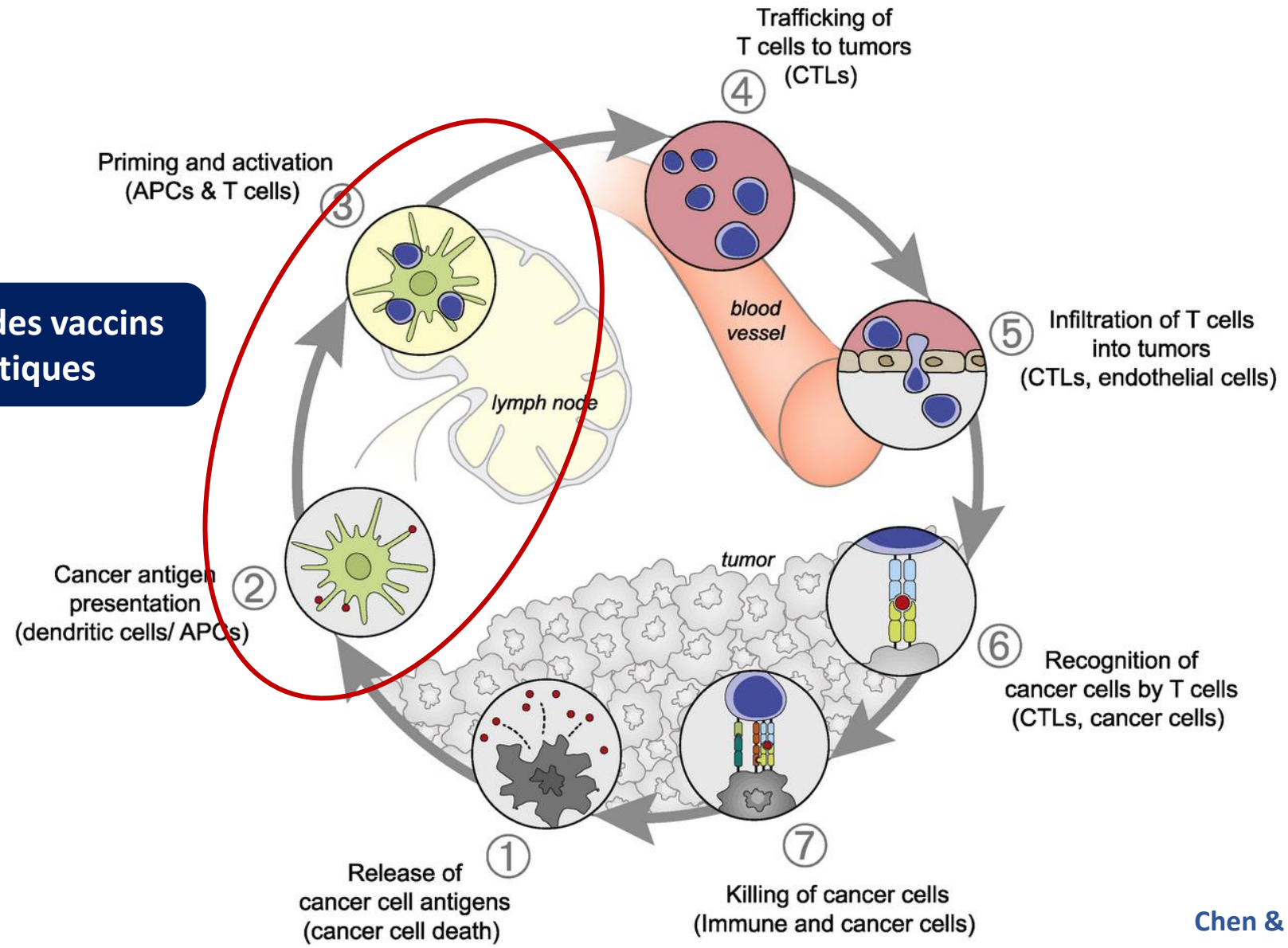


Site d'action des anti-PD-1 / PD-L1 et CAR-T cells

Chen & Mellman, Immunity 2013

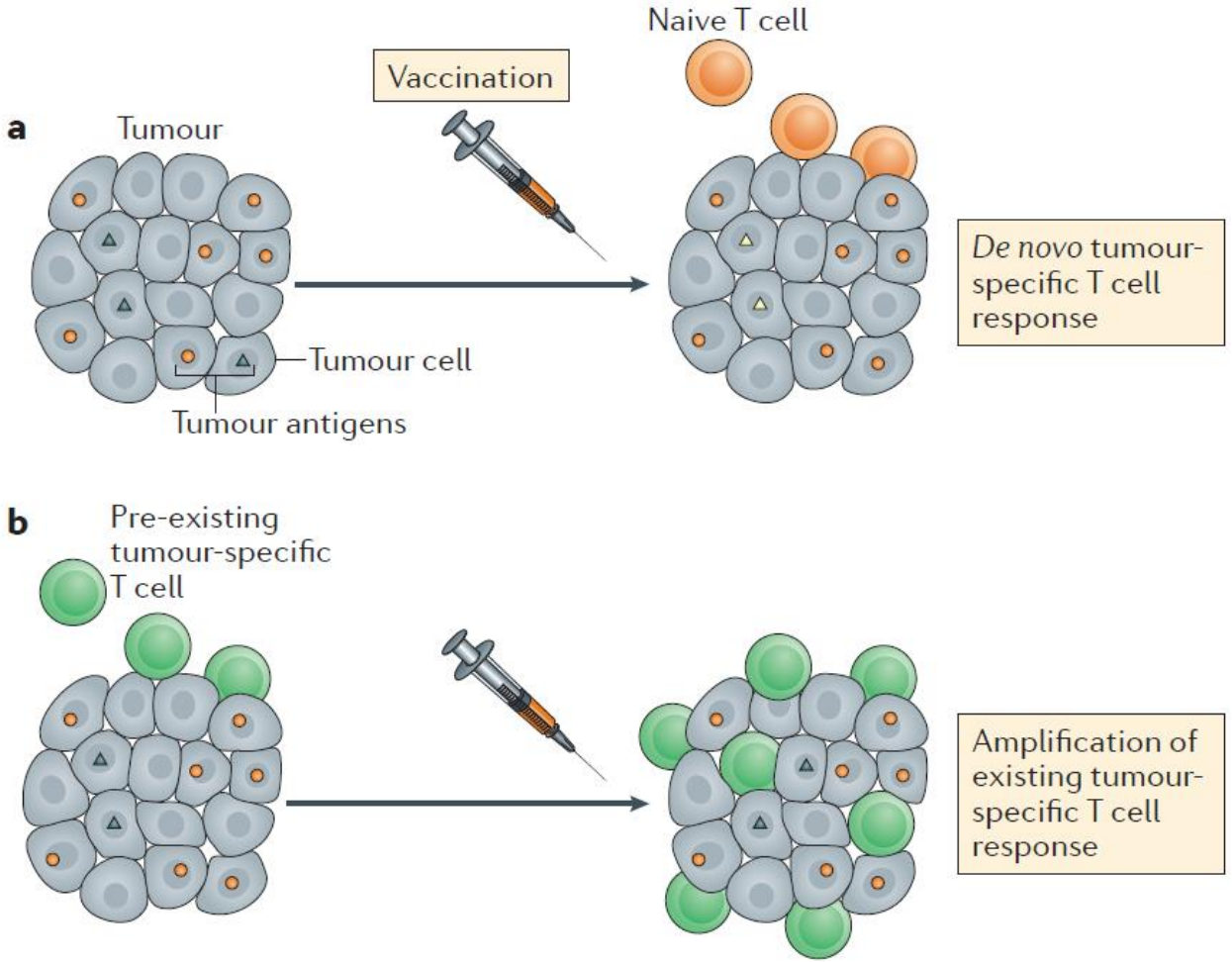
Le cycle d'interaction entre le cancer et l'immunité

Site d'action des vaccins thérapeutiques



Chen & Mellman, Immunity 2013

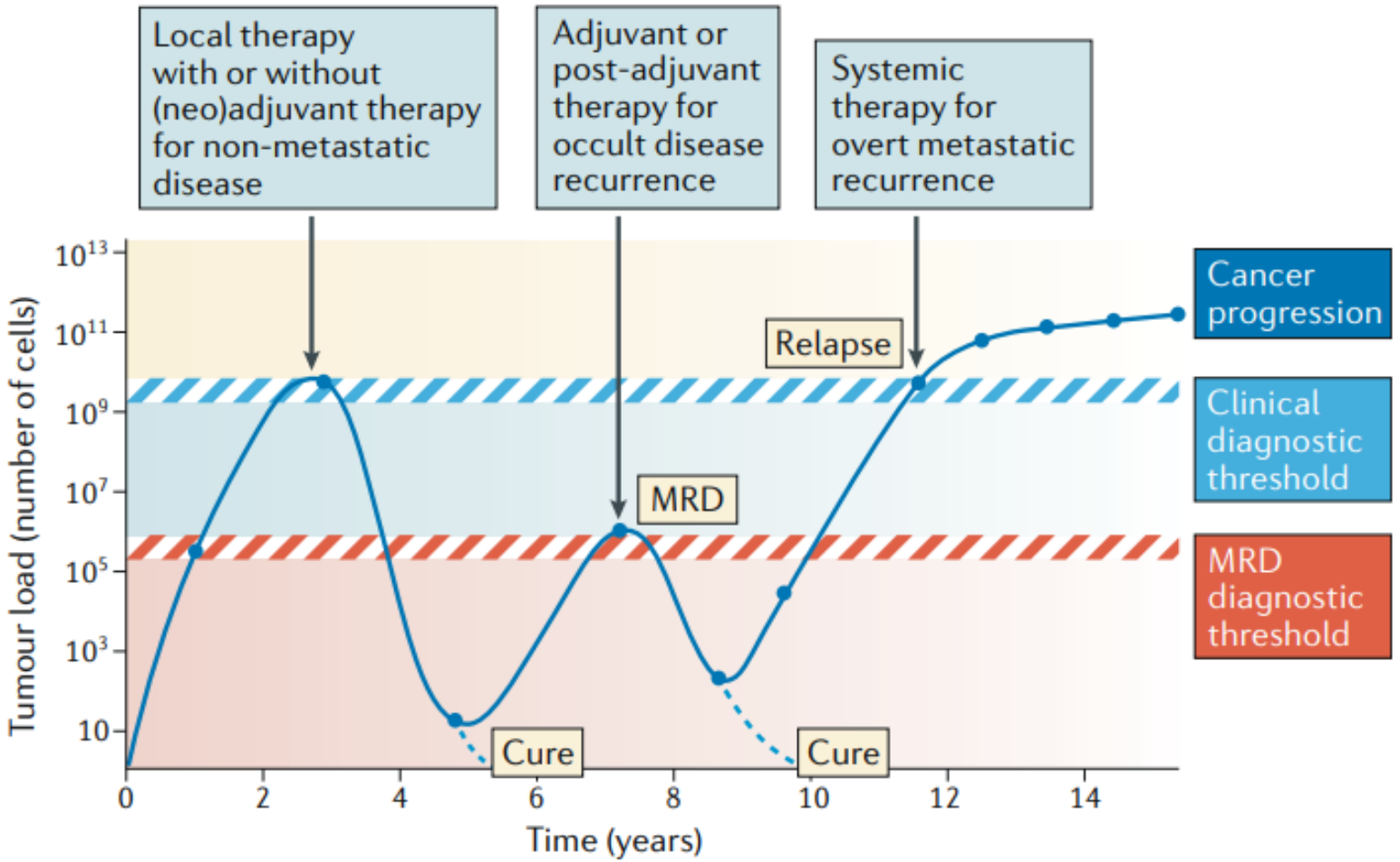
Attractivité de l'approche vaccinal en oncologie



- **Induction des réponses spécifiques**
- **Bonne tolérance**
- **Utilisation seul ou en association**

Wu HO, Nature Rev Immunol 2018

Rappel des situations du cancer



Pantel & Alix-Panabières, Nature Rev Clin Cancer2019

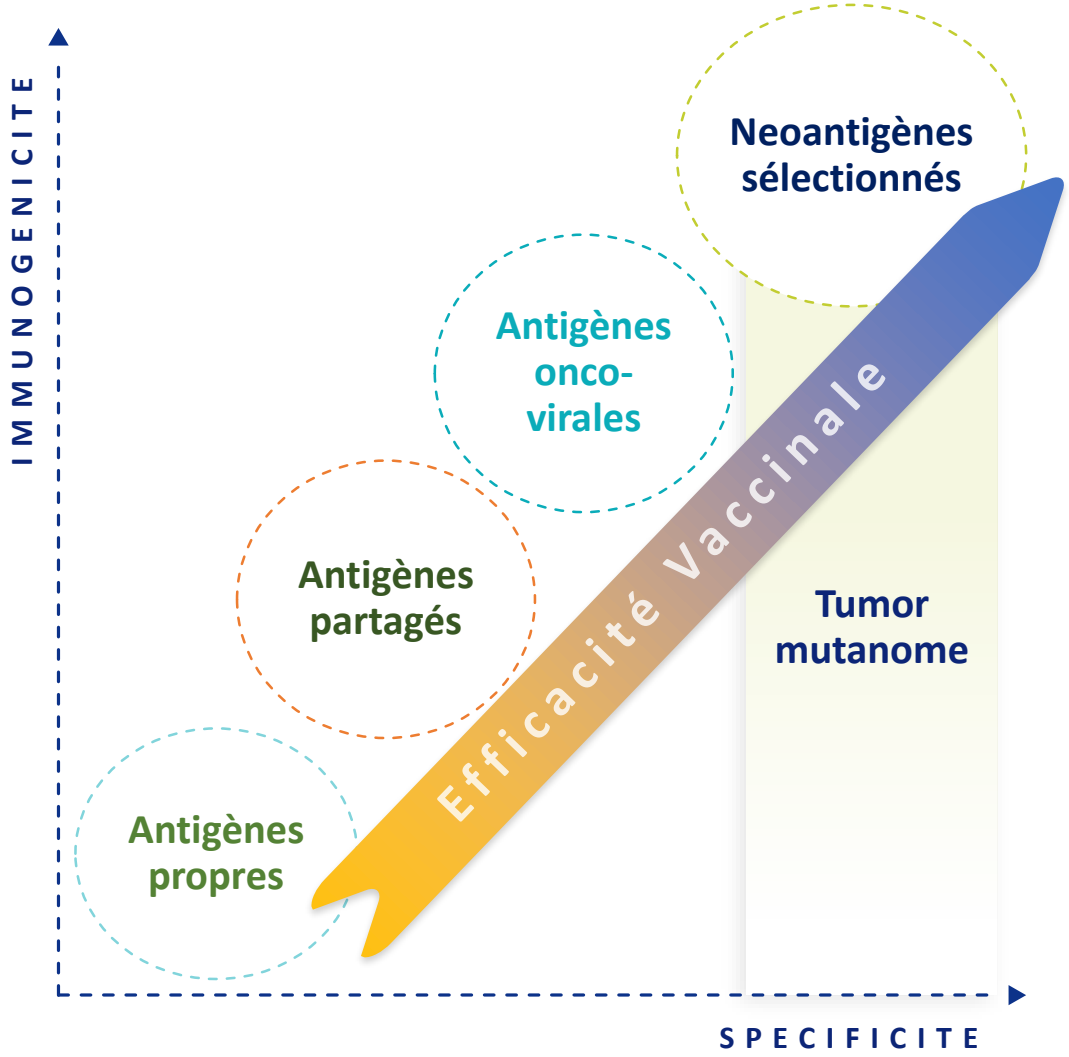
Vaccines en oncologie vs en infectiologie: différences

Cellule normale

Transformation

Cellule tumorale

Tous les antigènes ne sont pas pareils



Modifié de Von Witzleben, Front Imm 2020 et Transgene Septembre 2022

Types de cibles antigéniques en oncologie

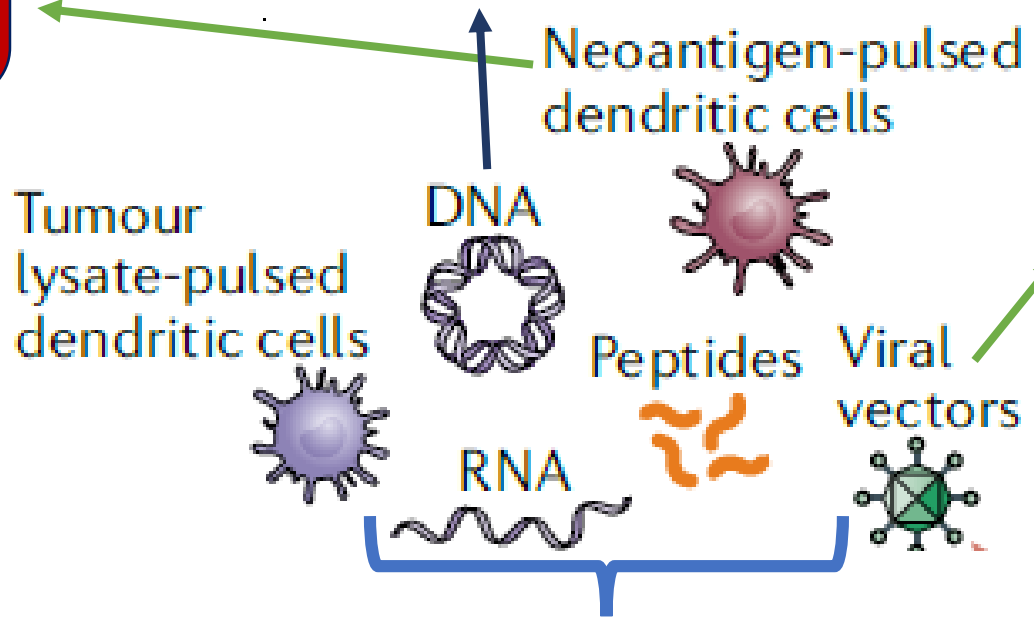
TYPE	EXPRESSION	PREVALENCE	EXEMPLES
Oncofetale	Physiologically expressed in fetal cells but re-expressed in cancer cells	Shared by a large number of patients in a specific histological indication or subtype	**CEA, PSA, WT1, MAGE**,
Surexprimé	Present in normal tissue but overexpressed by cancer cells		**Mesotheline, télomérase, HER2**
Modification post-translational	Present in healthy tissue but biochemical alteration in cancer tissue	Generally associated with a specific histology	**Muc1**
Oncovirale	Associated with infection by oncogenic viruses	Restricted to cancers with viral etiology	**HPV, EBV, HBV**
Neoantigène	**Specific to cancer cells, as the result of tumor-induced mutagenesis**	**Present in the majority of patients but different from one patient to another**	**Vaccins personnalisés**

Modifié de Von Witzleben, Front Imm 2020 et Transgene Septembre 2022

Technologies des vaccines en oncologie

- Activité immunitaire intense
- Vaccins approuvés aux USA (Sipuleucel – T)
- Plusieurs types des antigènes peuvent être utilisés

- Fabrication facile
- Tout épitope peut être encode
- Nécessité d'arriver au noyau
- Risque théorique des mutations par insertion

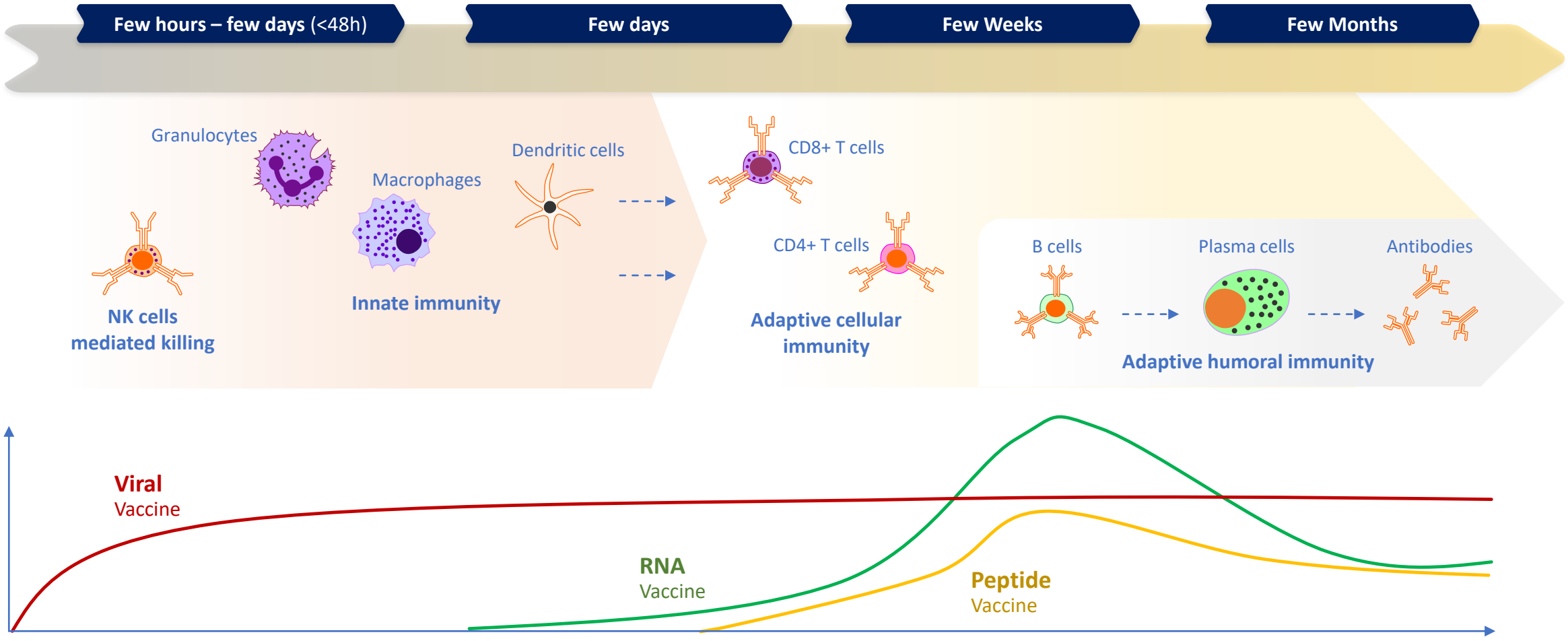


- Fabrication facile
- Expérience clinique en infectiologie
- Peut codifier tous les épitopes
- Forte réaction immunitaire au vecteur viral limitant son action

- Fabrication sans cellules
- Efficients pour activer les cellules dendritiques
- Plusieurs types de épitopes peuvent être fabriques
- Dégradation rapide

Wu HO, Nature Rev Immunol 2018
Sahin U, Science 2018

Durée des la réponse immunitaire innée et adaptative selon le type de vaccin

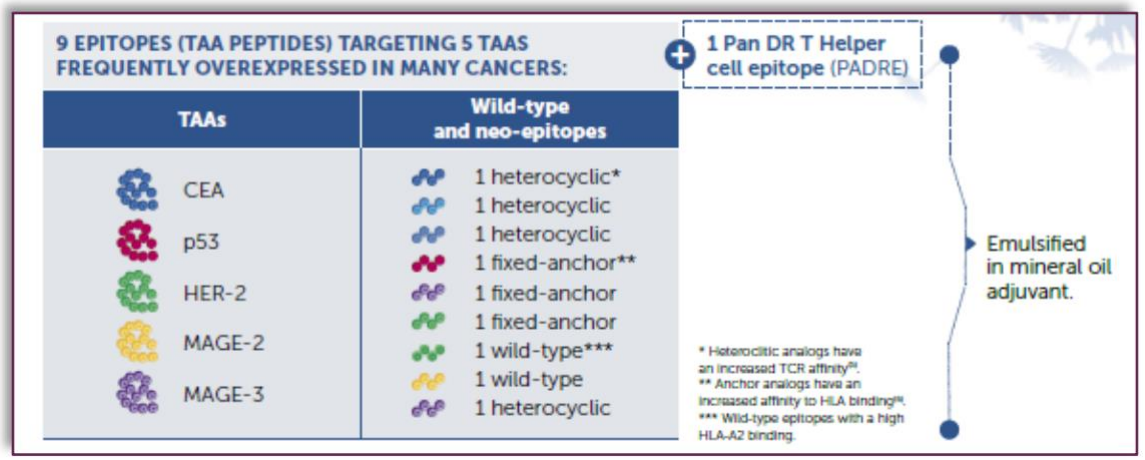


Karinko K et al, Immunity 2005, Collier A NEJM 2021, et Transgene Septembre 2022

Types de vaccins en clinique : exemple de phase 3

OSE2101 (Tedopi®) is an anticancer vaccine of neoepitopes restricted to HLA-A2+ targeting 5 TAAs frequently expressed in lung cancer[1]

Previous phase 2 study in pretreated NSCLC patients showed promising survival (OS) which correlated with T cell immune response[2,3,4]



Low 0-1 epitope: 406 ± 58 days of survival

Medium 2-3 epitopes: 778 ± 72 days of survival

High 4-6 epitopes: 875 ± 67 days of survival

Besse et al, ESMO 2021

Types de vaccins en clinique : exemple de phase 2

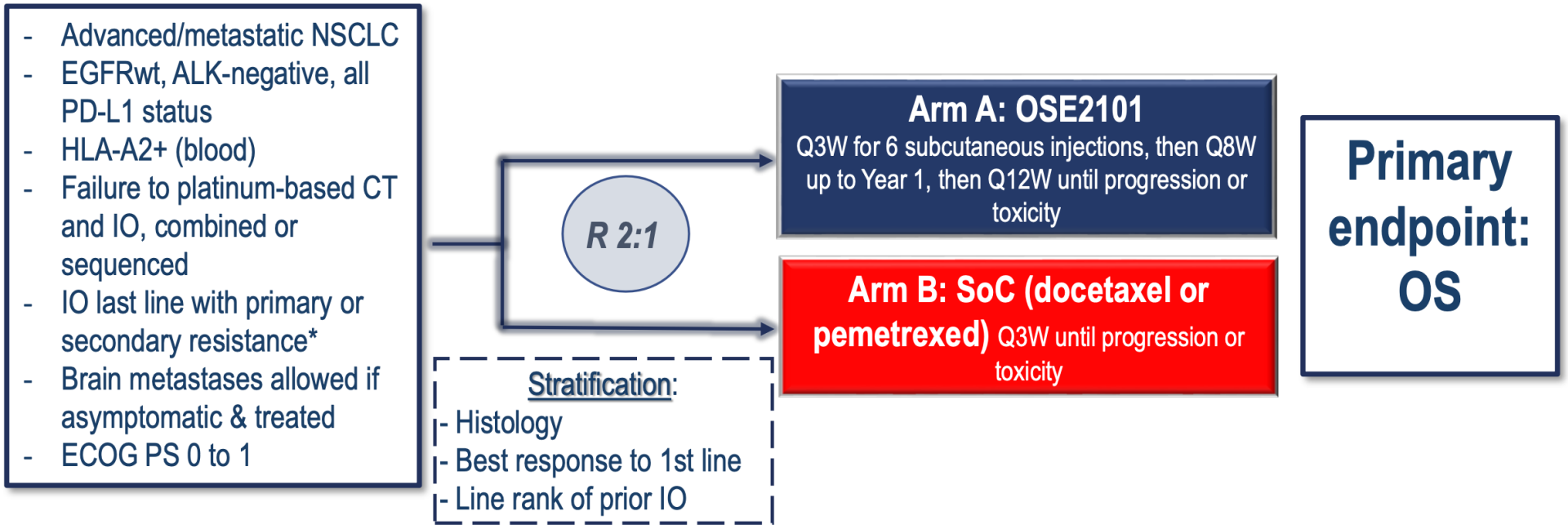
A Personalized Cancer Vaccine, mRNA-4157 (V940), Combined With Pembrolizumab Versus Pembrolizumab Alone in Patients With Resected High-risk Melanoma: Efficacy and Safety Results From the Randomized, Open-label Phase 2 mRNA-4157-P201/KEYNOTE-942 Trial

Adnan Khattak,[1,2] Matteo Carlino,[3] Tarek Meniawy,[4] George Ansstas,[5] Theresa Medina,[6] Matthew H. Taylor,[7] Kevin B. Kim,[8] Meredith McKean,[9] Georgina V. Long,[10] Ryan J. Sullivan,[11] Mark Faries,[12] Thuy Tran,[13] Charles Cowey,[14] Andrew Pecora,[15] Jennifer Segar,[16] Victoria Atkinson,[17] Geoffrey T. Gibney,[18] Jason Luke,[19] Sajeve Thomas,[20] Elizabeth Buchbinder,[21] Peijie Hou,[22] Lili Zhu,[22] Tal Zaks,[23] Michelle Brown,[22] Praveen Aanur,[22] Robert S. Meehan,[22] Jeffrey S. Weber[24,*]

Khattak et al, AACR 2023

Types de vaccins en clinique : Atalante 1

Atalante-1 Study Design: NSCLC After Failure to Chemo – IO



*Primary resistance: failure within 12 weeks of IO, secondary resistance: failure after minimum 12 weeks of IO; Kluger et al. 2020

Besse et al, ESMO 2021

Types de vaccins en clinique : Atalante 1

Atalante-1 Study Design: NSCLC After Failure to Chemo – IO

- Advanced/metastatic NSCLC
- EGFRwt, ALK-negative, all PD-L1 status
- HLA-A2+ (blood)
- Failure to platinum-based CT and IO, combined or sequenced
- IO last line with primary or secondary resistance*
- Brain metastases allowed if asymptomatic & treated
- ECOG PS 0 to 1

R 2:1

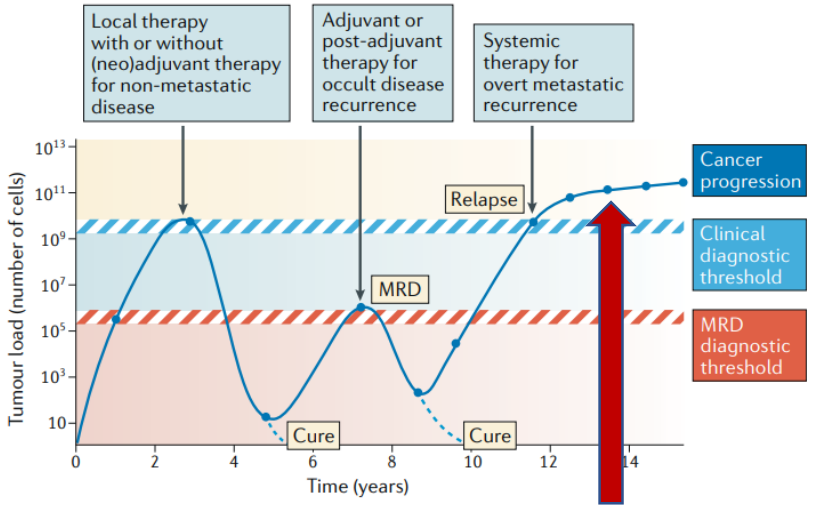
Arm A: OSE2101 Q3W for 6 subcutaneous injections, then Q8W up to Year 1, then Q12W until progression or toxicity

Arm B: SoC (docetaxel or pemetrexed) Q3W until progression or toxicity

Primary endpoint: OS

Stratification:
- Histology
- Best response to 1st line
- Line rank of prior IO

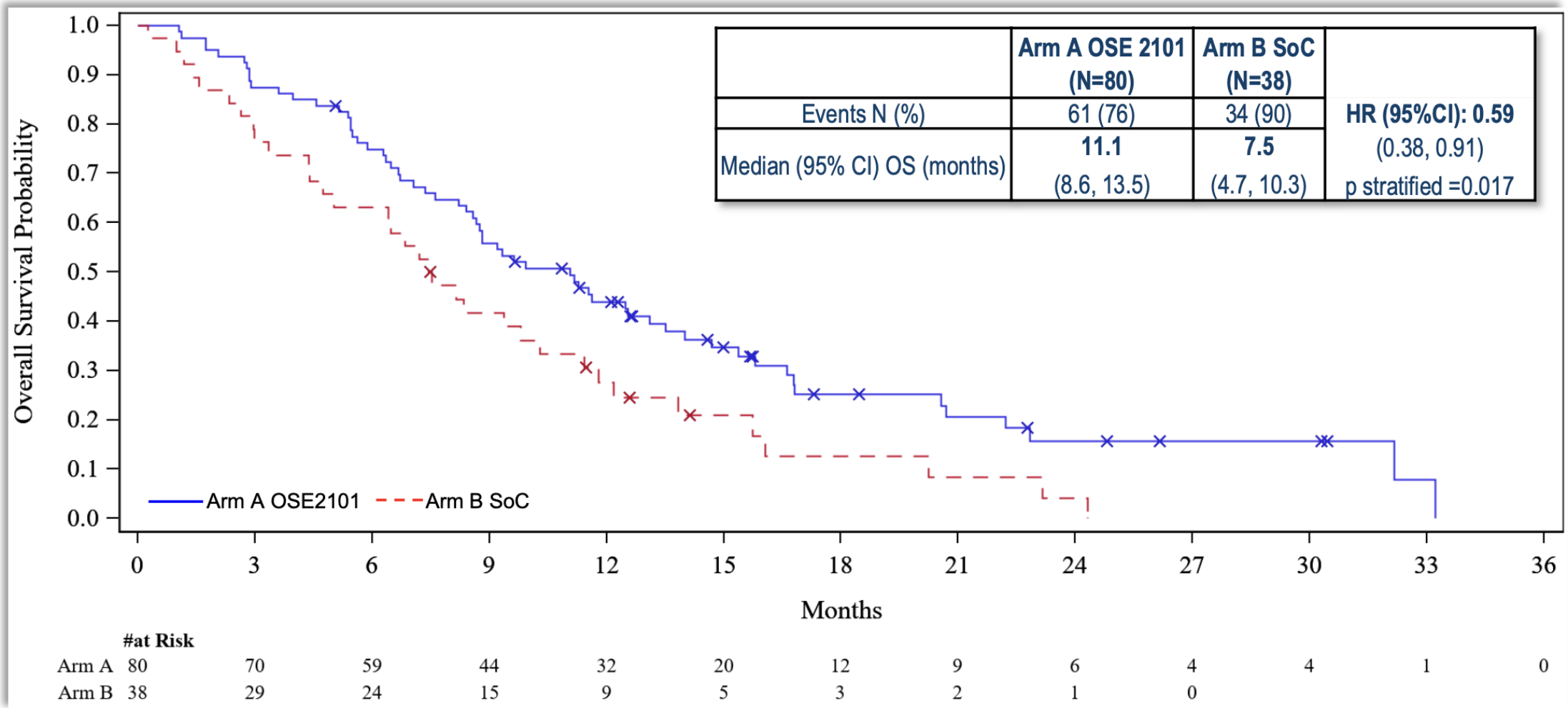
*Primary resistance: failure within 12 weeks of IO, secondary resistance: failure after minimum 12 weeks of IO; Kluger et al. 2020



Situation clinique métastatique en 2L+

Besse et al, ESMO 2021

Types de vaccins en clinique : objectif principal Survie Globale



	Arm A OSE 2101 (N=80)	Arm B SoC (N=38)	
Events N (%)	61 (76)	34 (90)	**HR (95%CI): 0.59** (0.38, 0.91) p stratified =0.017
Median (95% CI) OS (months)	**11.1** (8.6, 13.5)	**7.5** (4.7, 10.3)	

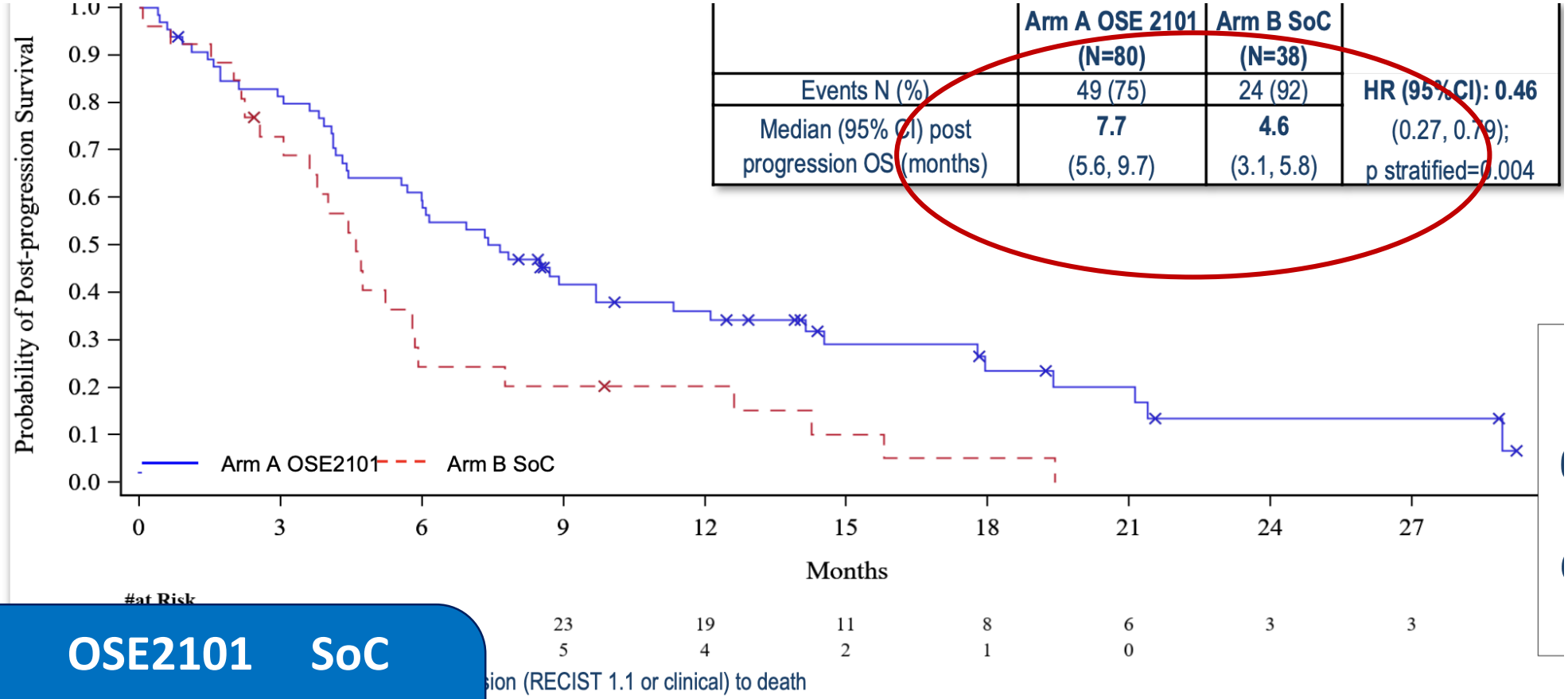
Cut-off 15JAN2021; median follow-up 25 months

PoI=Population of interest; SoC=Standard of care; OS=Overall survival; HR=Hazard ratio; CI=Confidence interval

Besse et al, ESMO 2021

Objectifs secondaires : survie après la progression

	Arm A OSE 2101 (N=80)	Arm B SoC (N=38)	
Events N (%)	49 (75)	24 (92)	**HR (95%CI): 0.46**
Median (95% CI) post progression OS (months)	**7.7** (5.6, 9.7)	**4.6** (3.1, 5.8)	(0.27, 0.79); p stratified=0.004

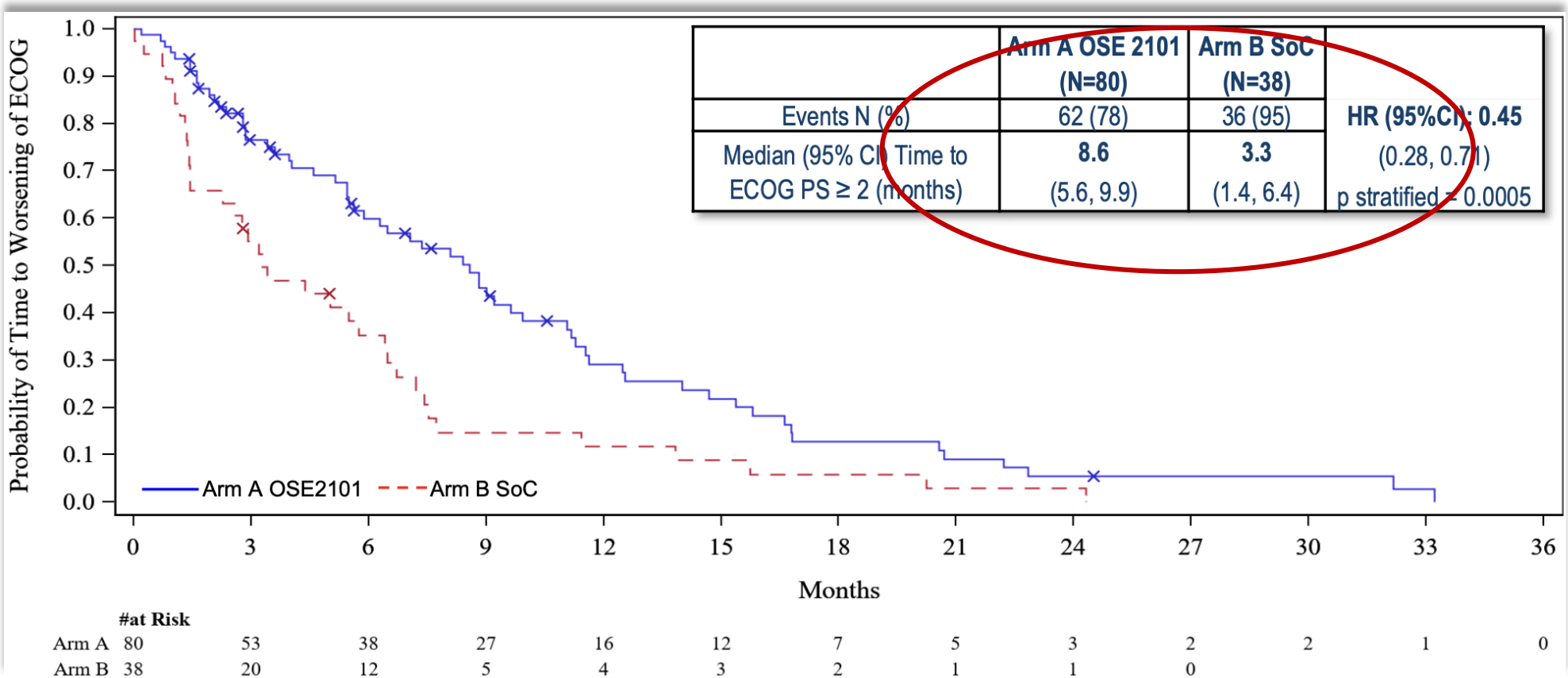


	OSE2101	SoC
PFS	2.7 mois	3.2 mois
DCR a 6M	25 %.	24%
Taux Réponse	8 %	18%

Besse et al, ESMO 2021

Types de vaccins en clinique : objectifs secondaires cliniquement importants?

Time to worsening ECOG PS ≥ 2 in Pol



	Arm A OSE 2101 (N=80)	Arm B SoC (N=38)	
Events N (%)	62 (78)	36 (95)	**HR (95%CI): 0.45** (0.28, 0.71) p stratified = 0.0005
Median (95% CI) Time to ECOG PS ≥ 2 (months)	**8.6** (5.6, 9.9)	**3.3** (1.4, 6.4)	

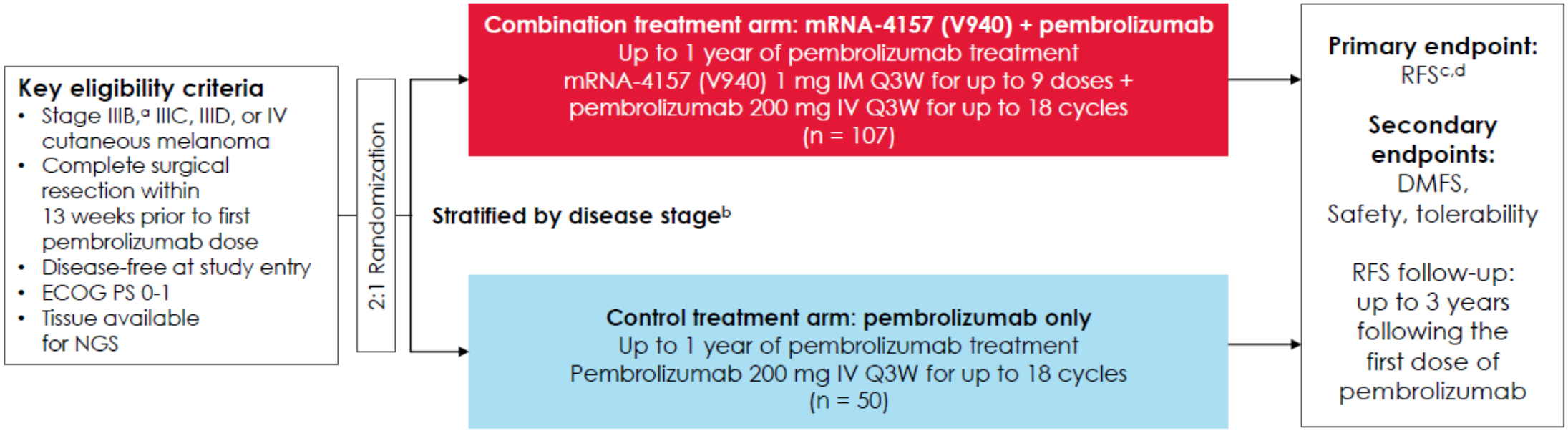
Time to worsening ECOG PS ≥2 =delay from randomization to earliest ECOG PS 2 or more

Besse et al, ESMO 2021

Types de vaccins en clinique : exemple de phase 2

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

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

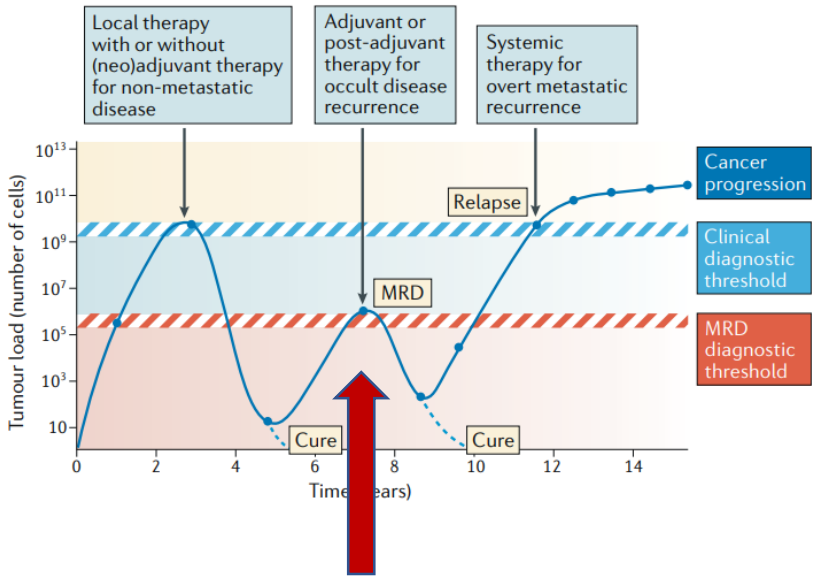


Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with 1-sided alpha of 0.1)

Median follow-up[e]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab only

Khattak et al, AACR 2023

Types de vaccins en clinique : exemple de phase 2



mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

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

Key eligibility criteria
- Stage IIIB,[a] IIIC, IIID, or IV cutaneous melanoma
- Complete surgical resection within 13 weeks prior to first pembrolizumab dose
- Disease-free at study entry
- ECOG PS 0-1
- Tissue available for NGS

2:1 Randomization

Stratified by disease stage[b]

Combination treatment arm: mRNA-4157 (V940) + pembrolizumab
Up to 1 year of pembrolizumab treatment
mRNA-4157 (V940) 1 mg IM Q3W for up to 9 doses +
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 107)

Control treatment arm: pembrolizumab only
Up to 1 year of pembrolizumab treatment
Pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 50)

Primary endpoint:
RFS[c,d]

Secondary endpoints:
DMFS,
Safety, tolerability

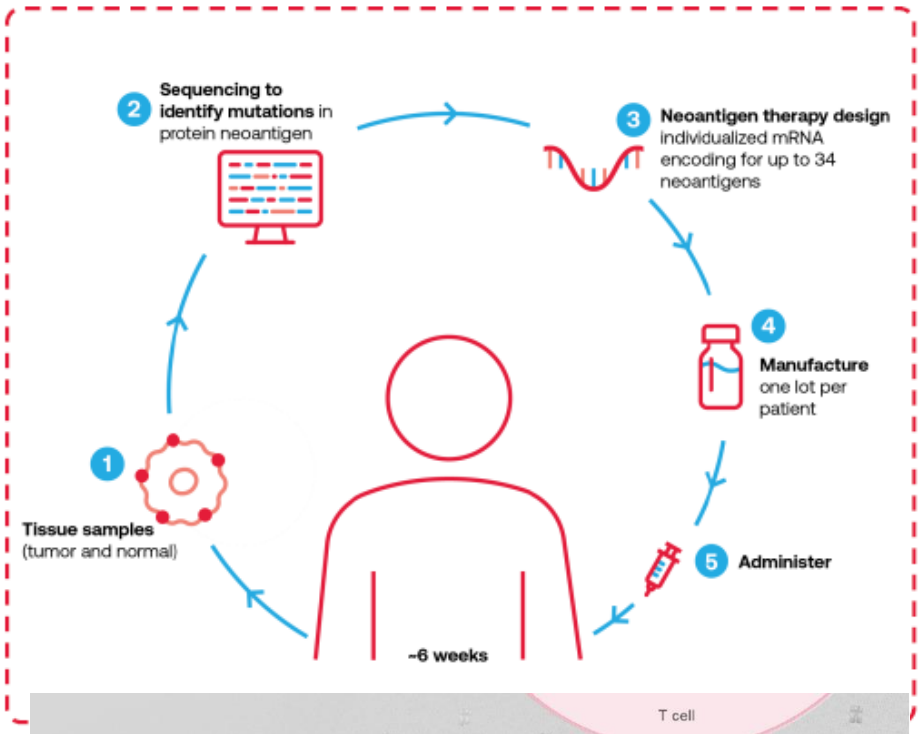
RFS follow-up:
up to 3 years following the first dose of pembrolizumab

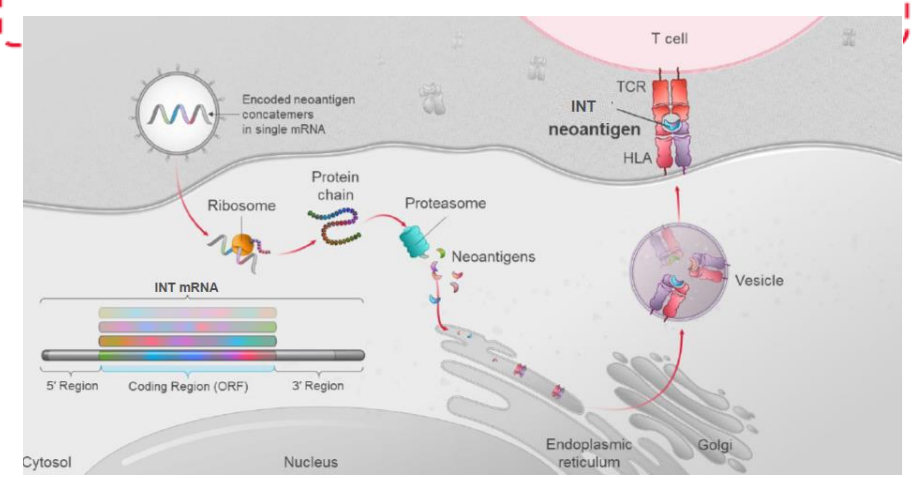
Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with 1-sided alpha of 0.1)

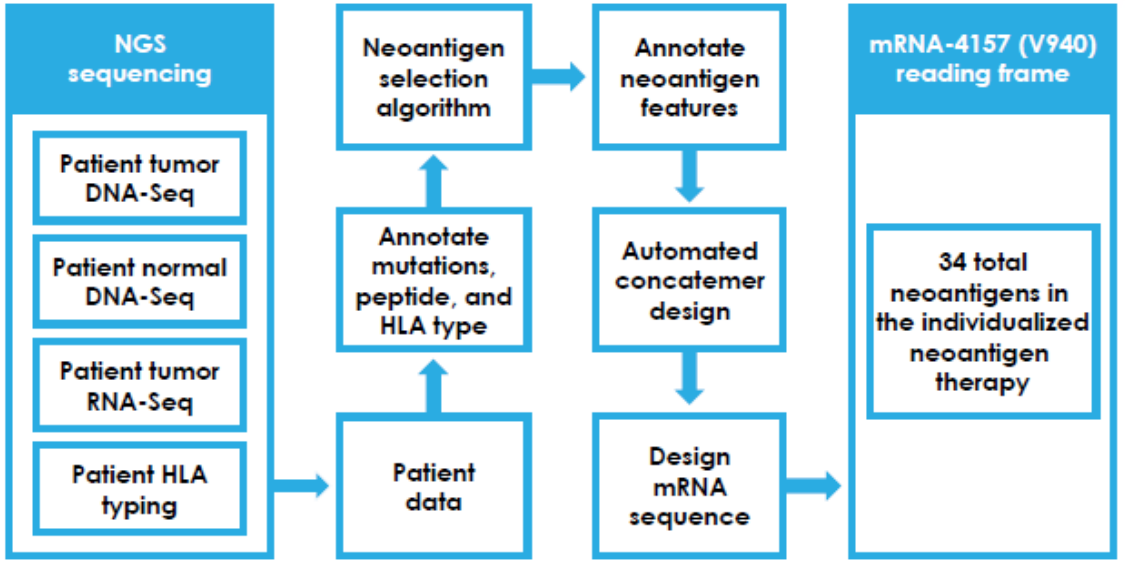
Median follow-up[e]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab only

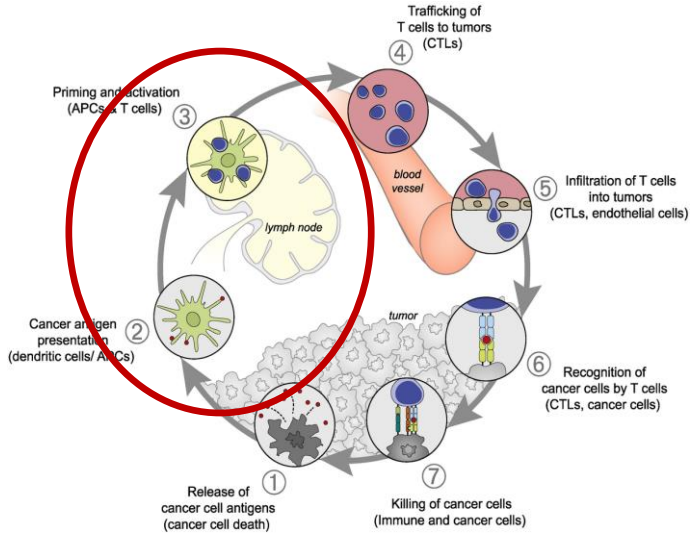
Khattak et al, AACR 2023

Types de vaccins en clinique : Phase 2 mRNA-4157





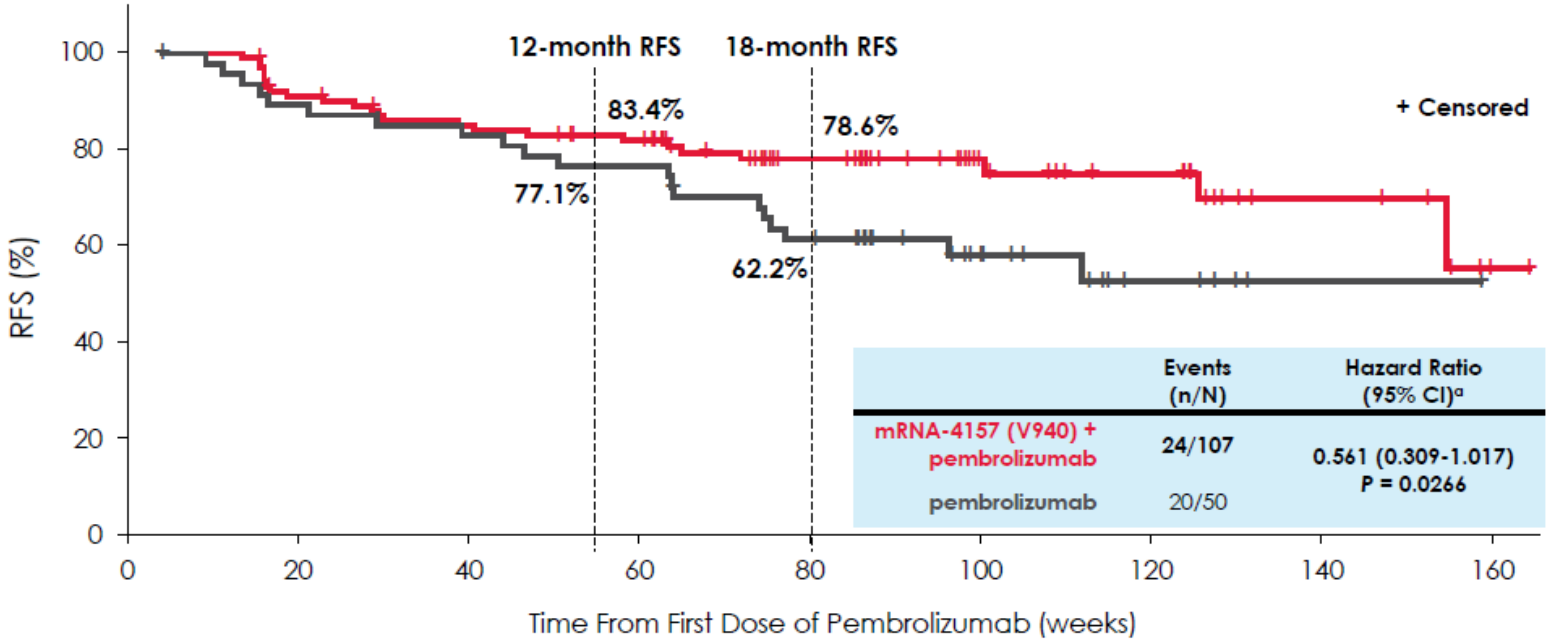




Khattak et al, AACR 2023

Types de vaccins en clinique : Phase 2 mRNA-4157

mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in recurrence-free survival (RFS) vs pembrolizumab

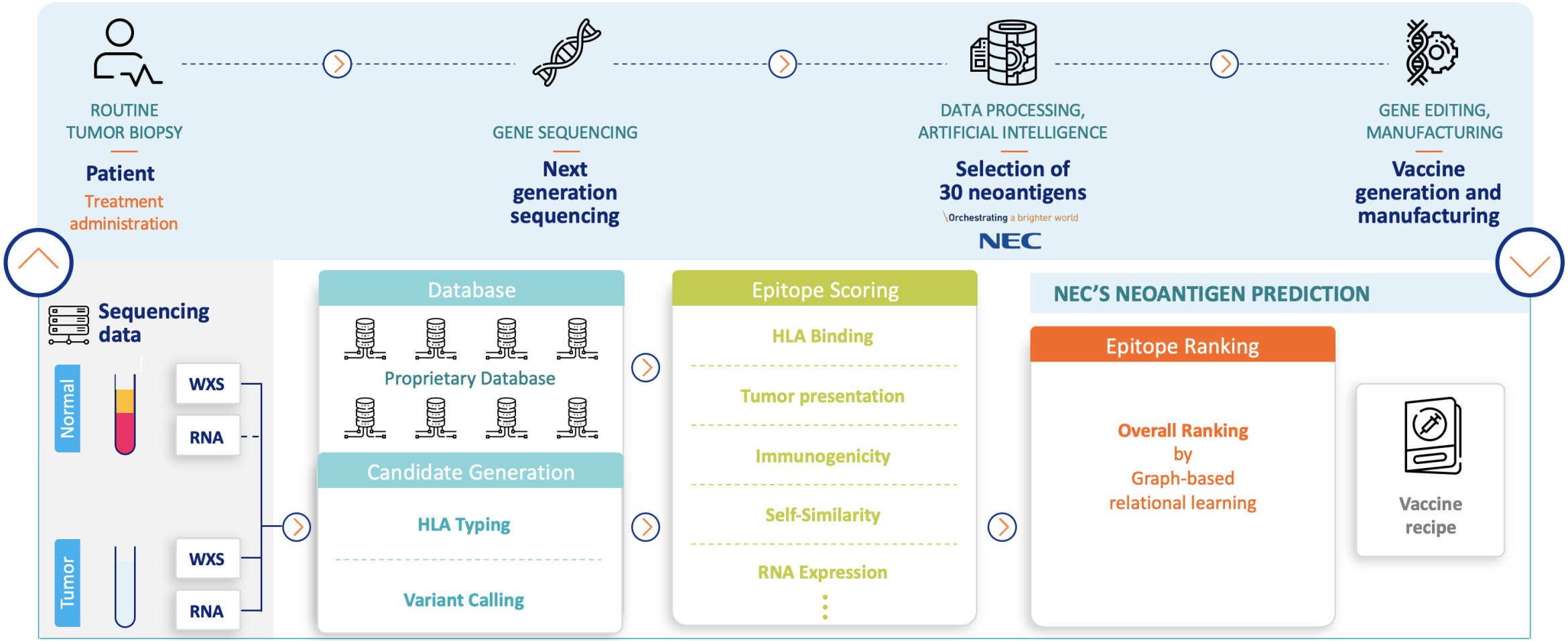


Number at Risk

mRNA-4157 (V940) + pembrolizumab	107	92	85	73	49	24	20	8	1
pembrolizumab	50	42	40	37	28	13	6	1	0

Khattak et al, AACR 2023

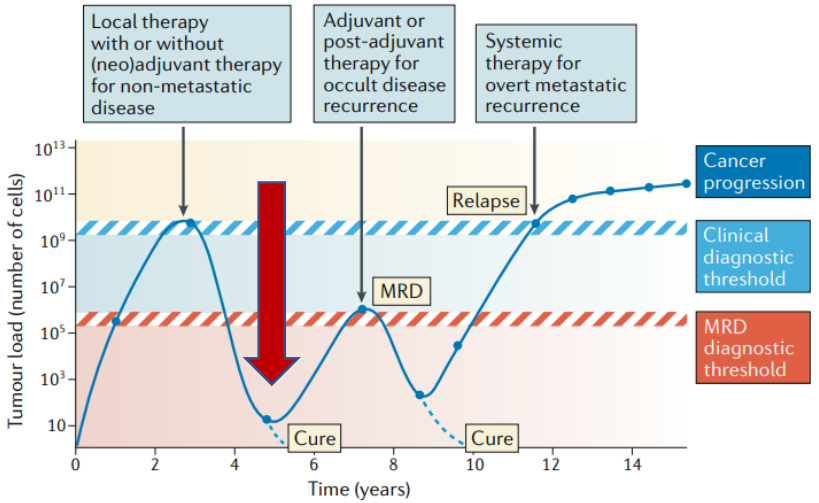
Types de vaccins en clinique : exemple de phase 1 « proof-of-concept »



Courtesy JP Delord

Types de vaccins en clinique : phase 1 TG4050

Cancer ORL localement avancé



Chirurgie

Réponse complète

Analyse des mutations et production du vaccin

Vaccination 10^8 pfu

Hebdomadaire

Toutes les 3 semaines

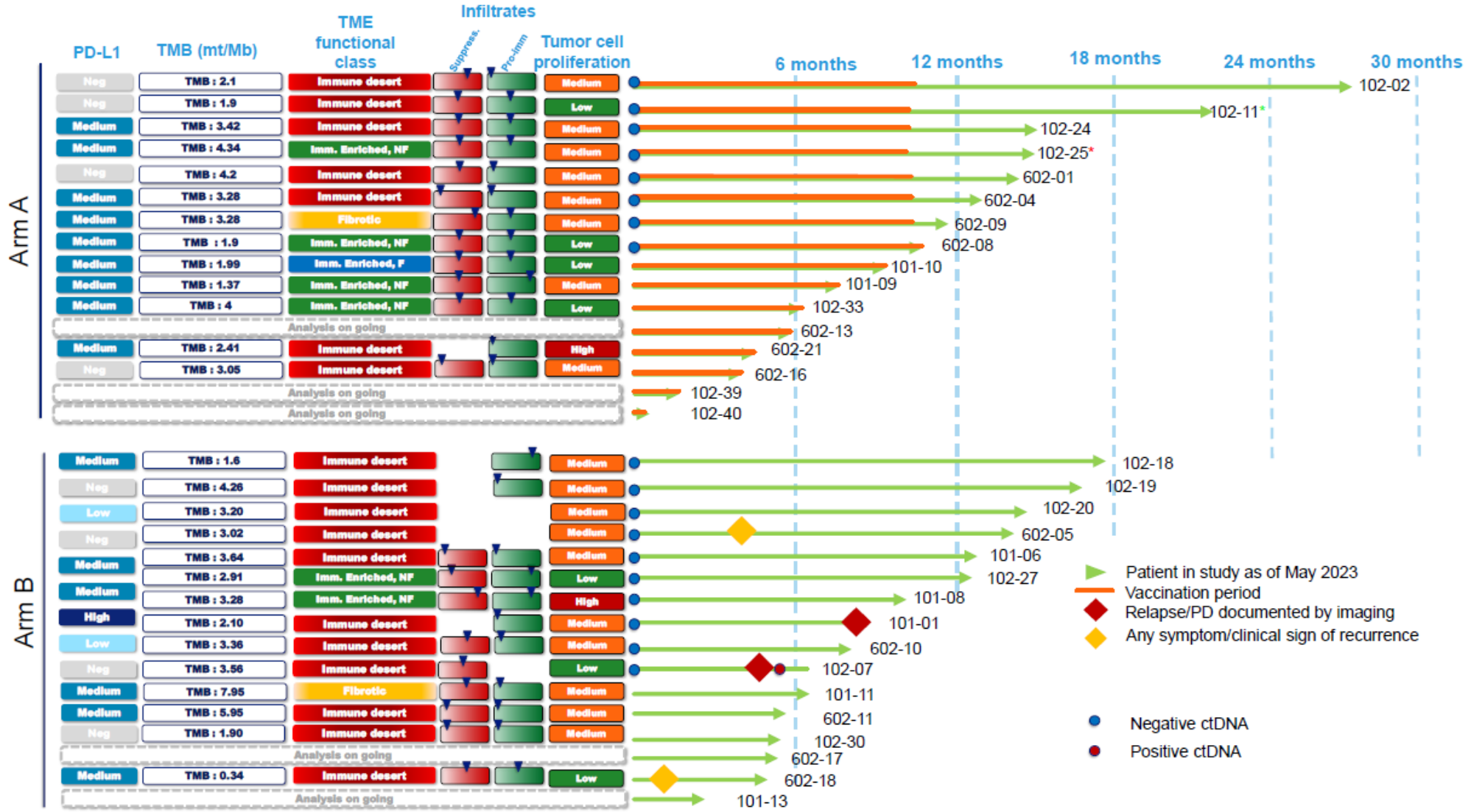
Suivi clinique

Radio-chimiothérapie 1ère ligne

3 mois

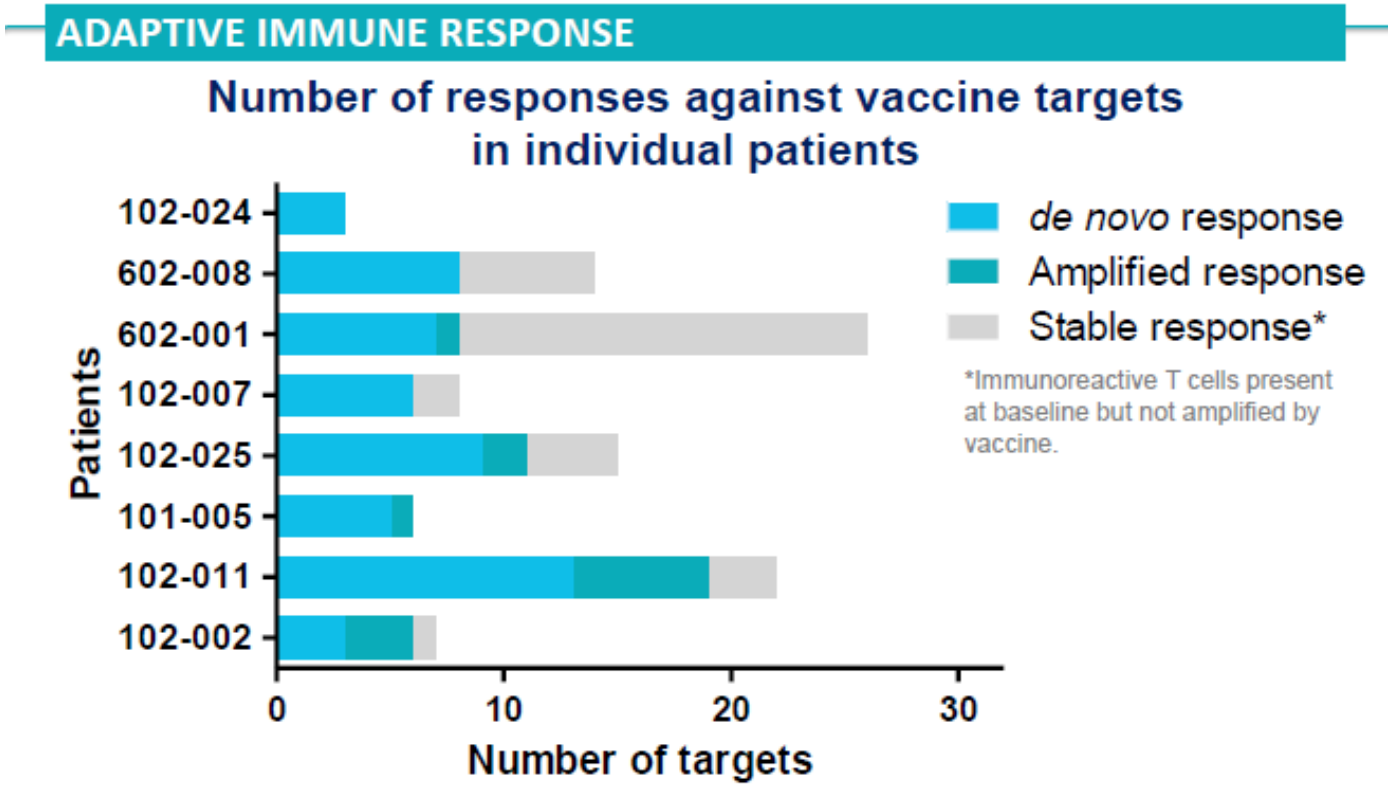
Traitement Immuno-monitorage

Types de vaccins en clinique : phase 1 TG4050

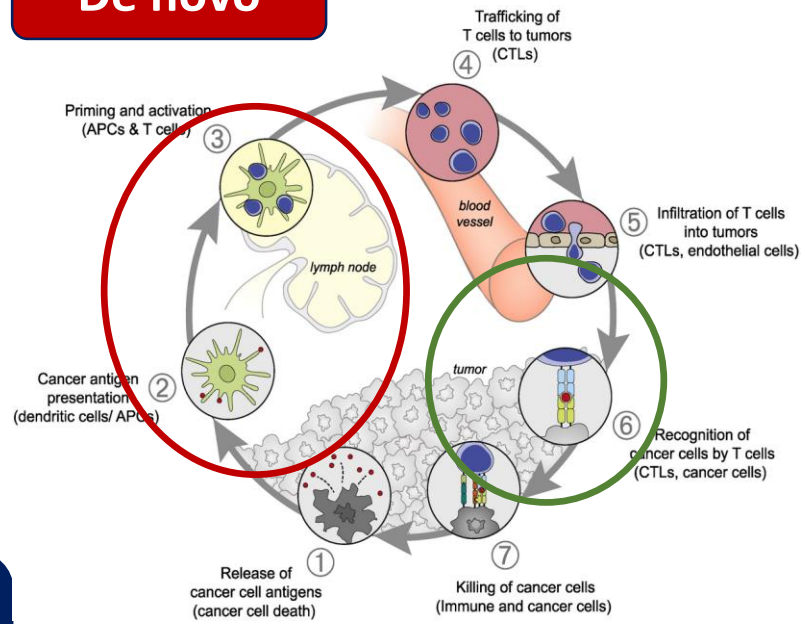


Ottensmeier et al, ASCO 2023

Types de vaccins en clinique : exemple de phase 1 TG4050



De novo



- Moyen de 9 épitopes « cibles » par patient
- 80% de réponses « de novo » cellules T réactives aux épitopes
- 20% amplification des réponses existantes

Amplification

Ottensmeier et al, ASCO 2023

Réflexions: ce nous pouvons faire ensemble

Respect de la protection du patient ⟷ Parcours du patient complexe

Bien-fondé et pertinence du projet de recherche ⟷ Circonstances cliniques et technologiques en constante évolution

Qualité méthodologique ⟷ Evolution des objectifs primaires et secondaires en évolution

Réflexions: ce nous pouvons faire ensemble

Evaluation d'un essai clinique en oncologie

CPP

Promoteur

Investigateur