Journée de formation oncologie
Saint Luc Bouge

25/05/2018

LE DEVELOPPEMENT DU MEDICAMENT

Frank ABOUBAKAR

DISCLOSURE

- AUCUN Conflit d’intérêt

CAST Coordinating Center
1107 NE 45th, Rm. 505
Seattle, WA 98105

THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL (CAST) INVESTIGATORS

Supported by contracts with the National Heart, Lung, and Blood Institute, Department of Health and Human Services.

Address reprint requests to the CAST Coordinating Center, 1107 NE 45th, Rm. 505, Seattle, WA 98105.

SPECIAL REPORT

PRELIMINARY REPORT: EFFECT OF ENCAINIDE AND FLECAINIDE ON MORTALITY IN A RANDOMIZED TRIAL OF ARRHYTHMIA SUPPRESSION AFTER MYOCARDIAL INFARCTION

Abstract The occurrence of ventricular premature depolarizations in survivors of myocardial infarction is a risk factor for subsequent sudden death, but whether antiarrhythmic therapy reduces the risk is not known.

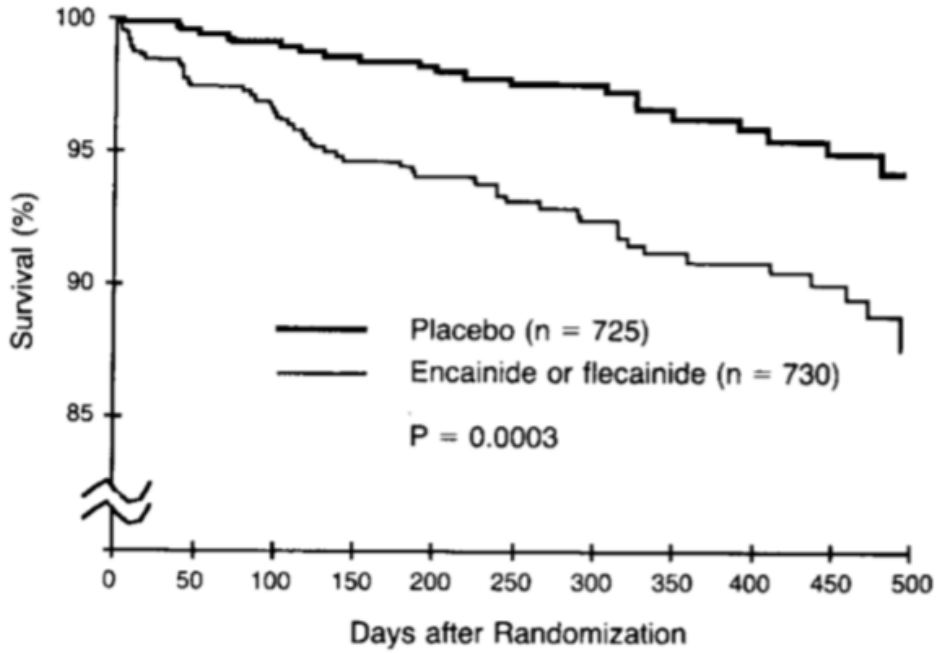


Figure 2. Survival among 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.

The calculations were based on all causes of death. The nominal P value was based on a traditional two-sided log-rank test adjusted for multiple groups.

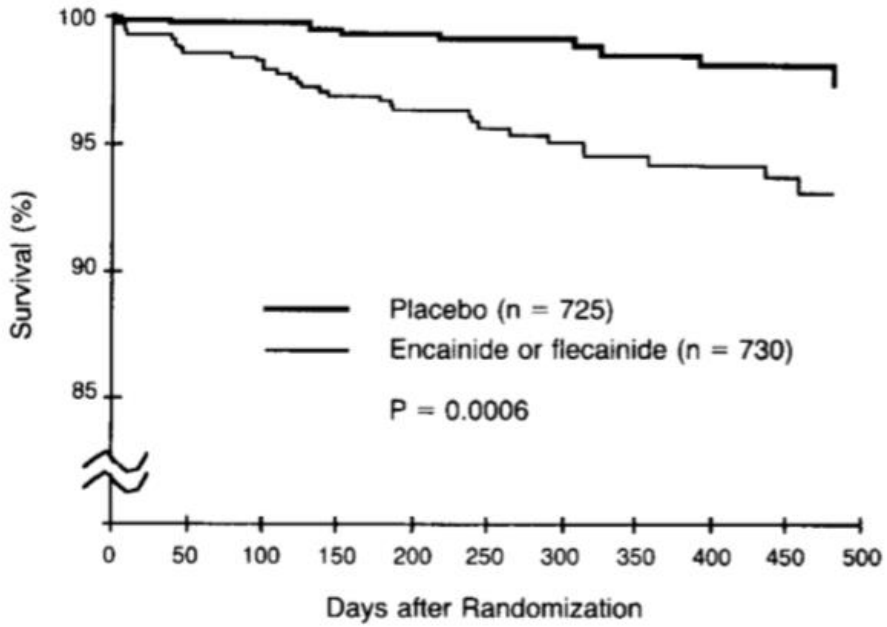
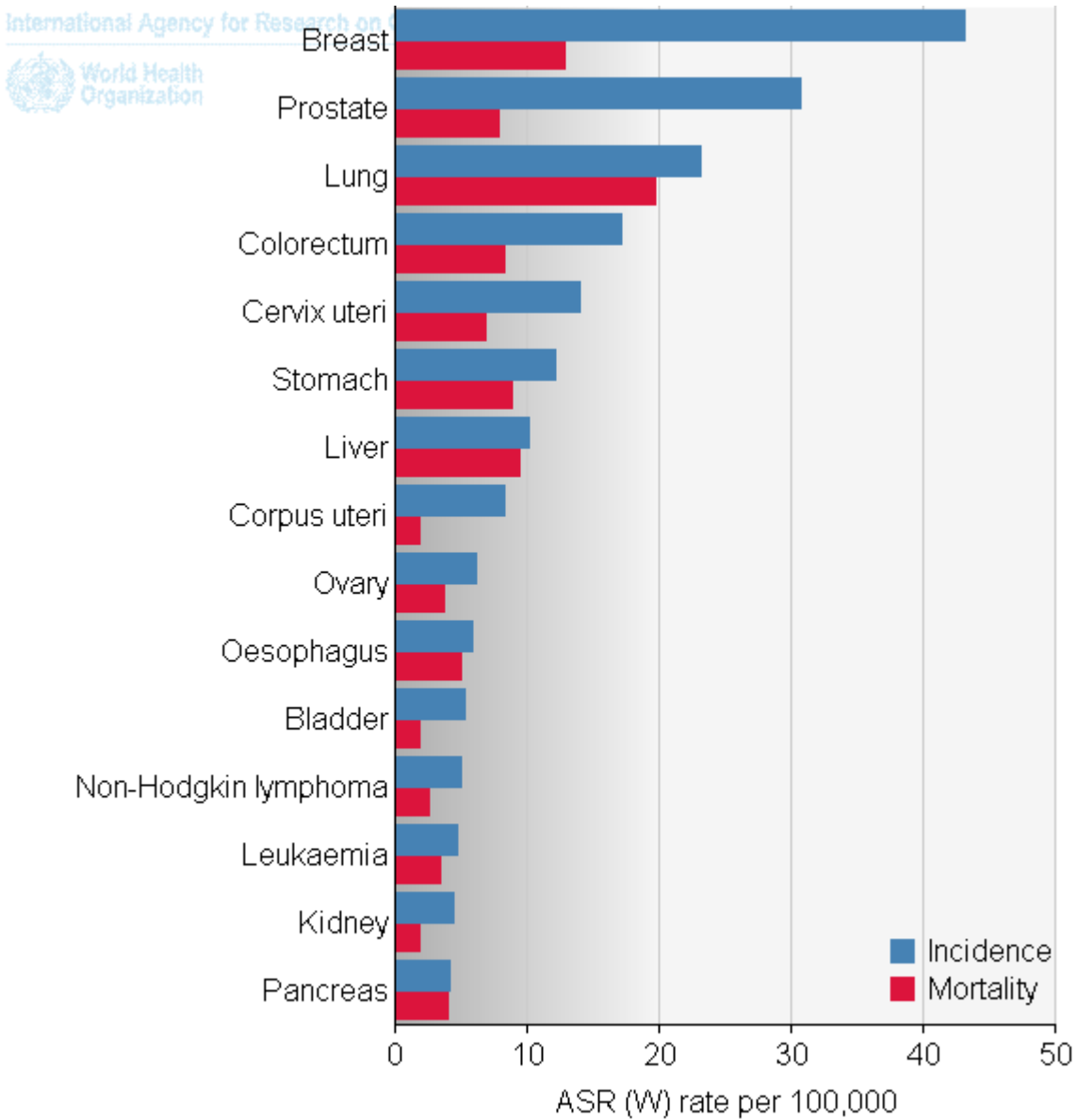


Figure 1. Survival among 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.

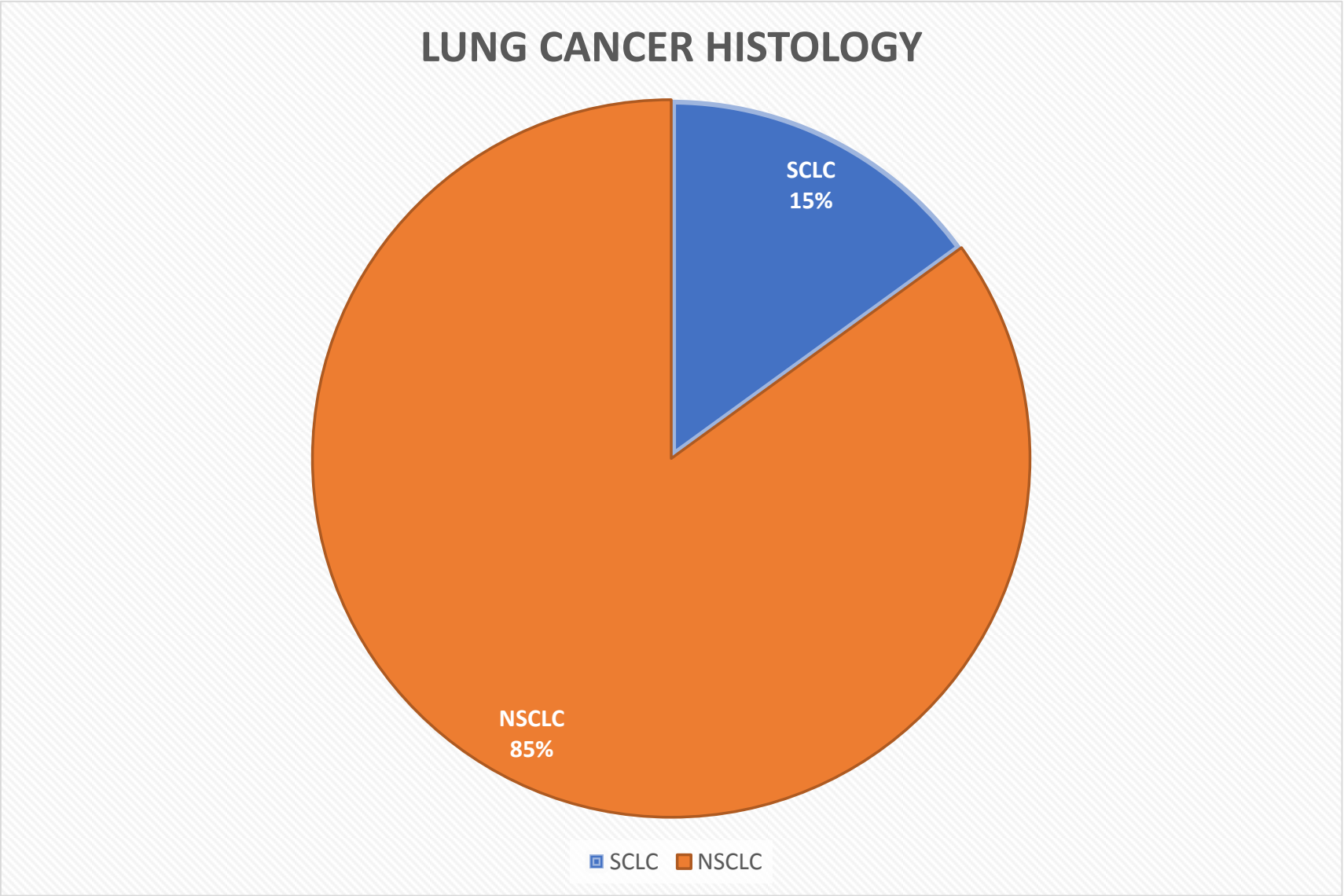
The cause of death was arrhythmia or cardiac arrest. The nominal P value was based on a traditional two-sided log-rank test adjusted for multiple groups.

STATE OF ART: LUNG CANCER



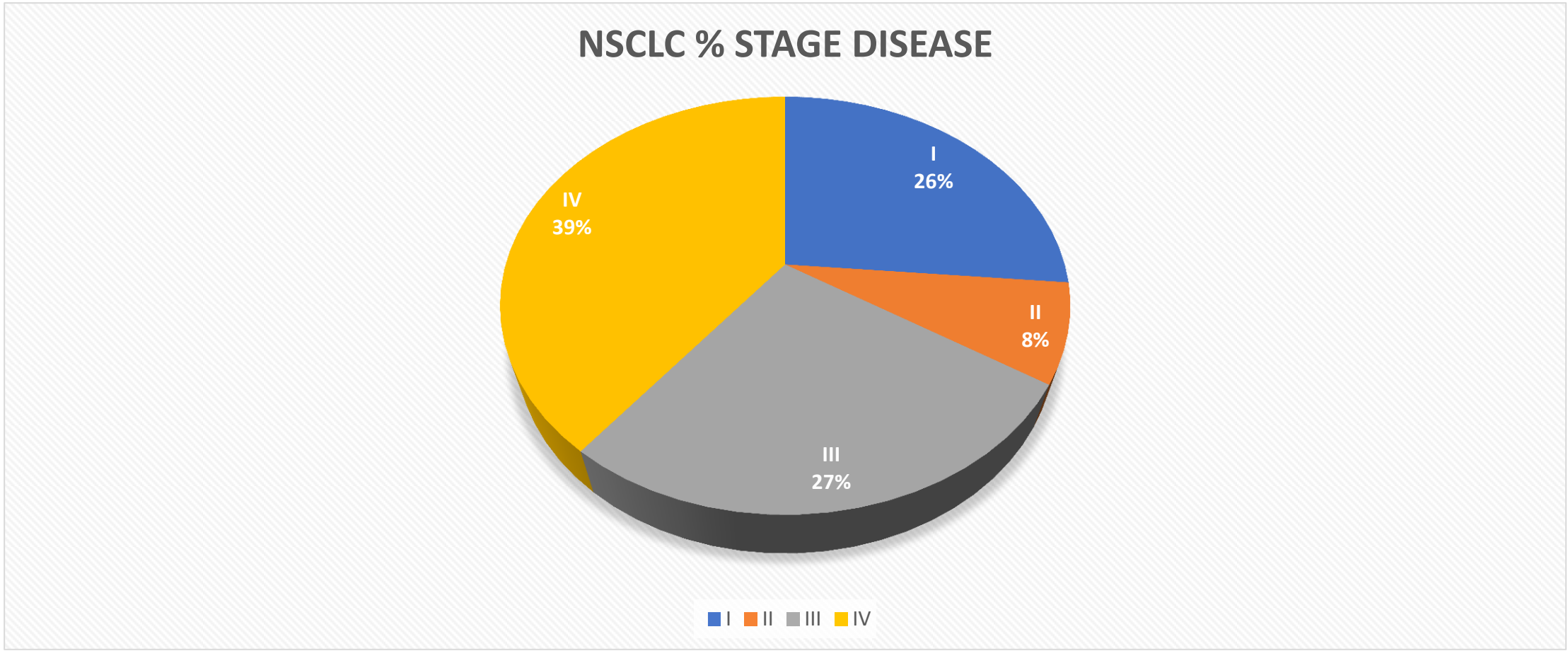
Age-standardised rate

STATE OF ART: LUNG CANCER



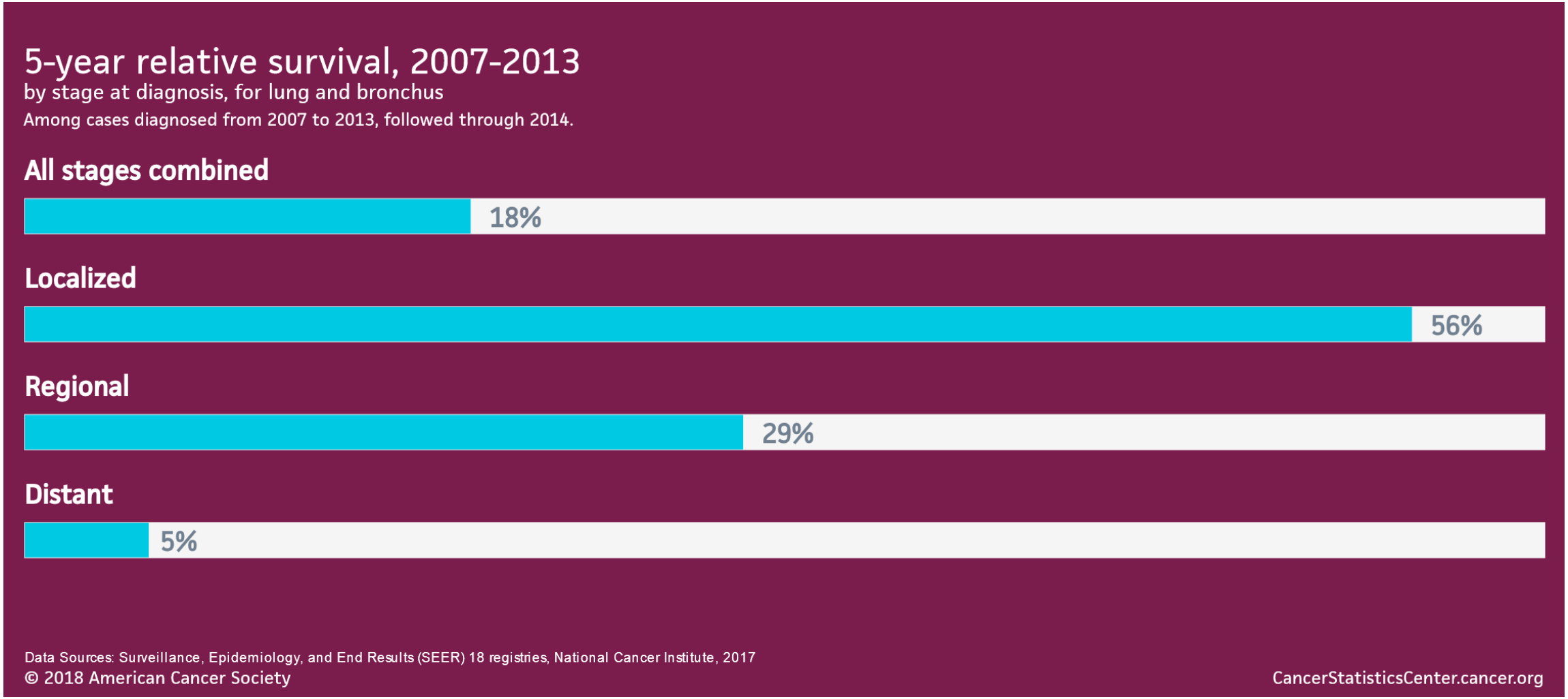
Morgensztern, D., et al. (2010).Journal of Thoracic Oncology 5(1): 29-33

STATE OF ART: LUNG CANCER

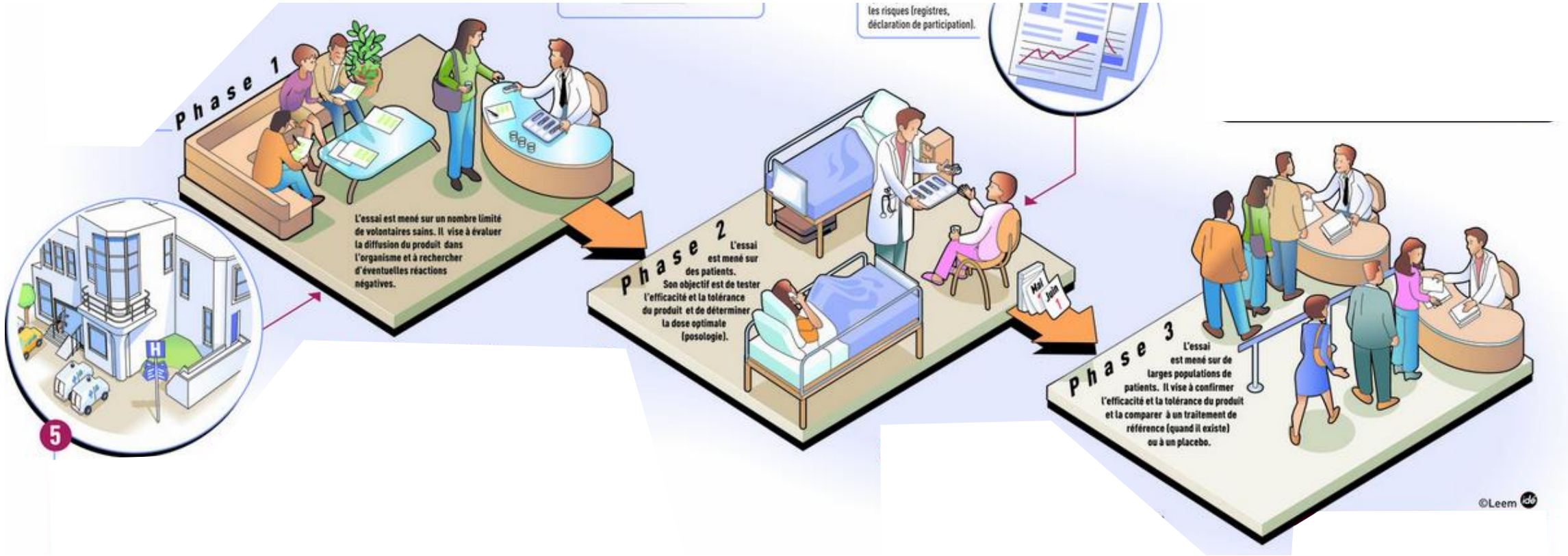


Morgensztern D, et al. Journal of Thoracic Oncology 2010;5(1):29-33

STATE OF ART: LUNG CANCER



ETAPES DES ESSAIS CLINIQUES



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13% infectiologie

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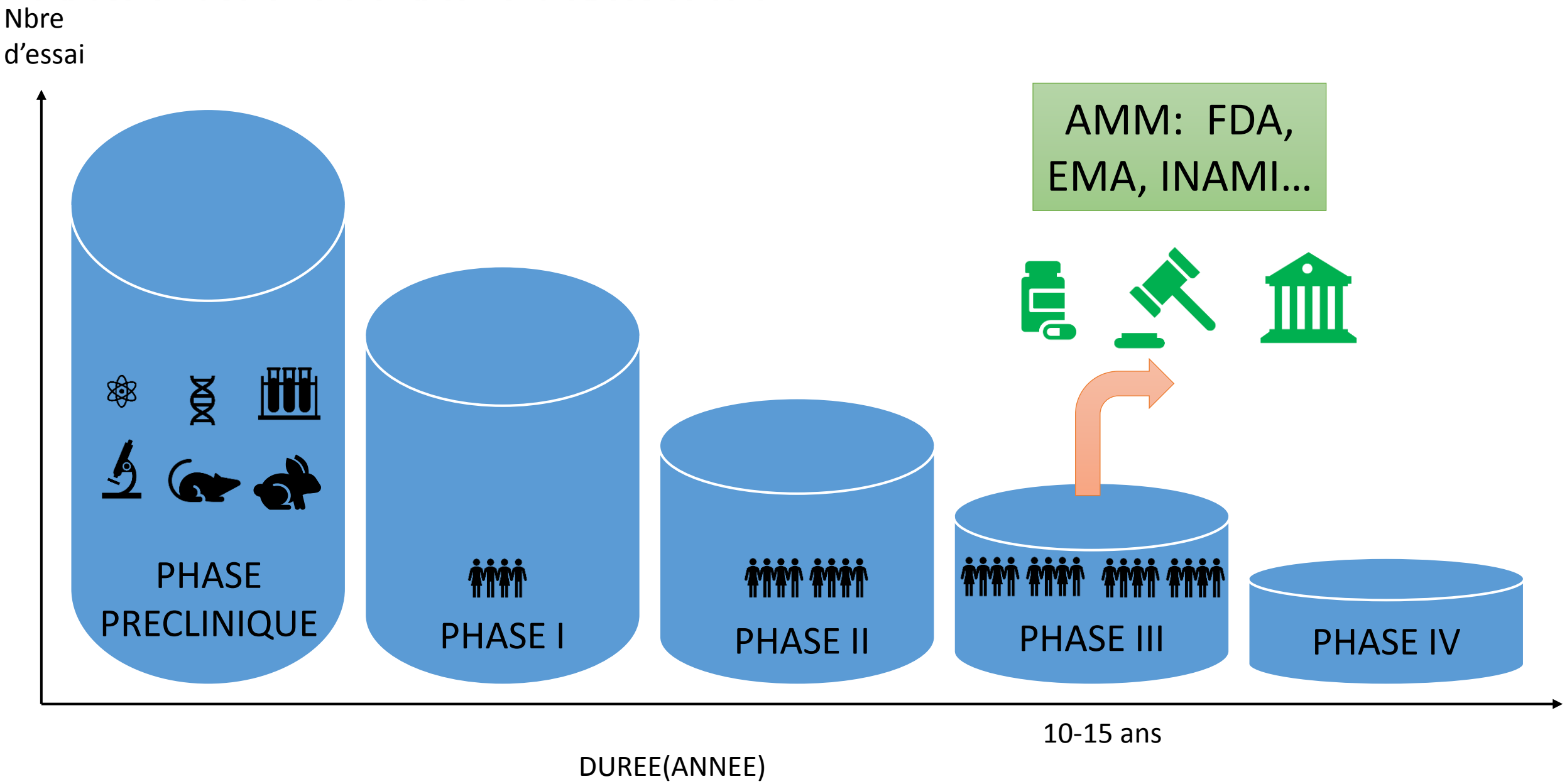
ETAPES DES ESSAIS CLINIQUES



STATE OF ART: NEW PARADIGM IN LUNG CANCER

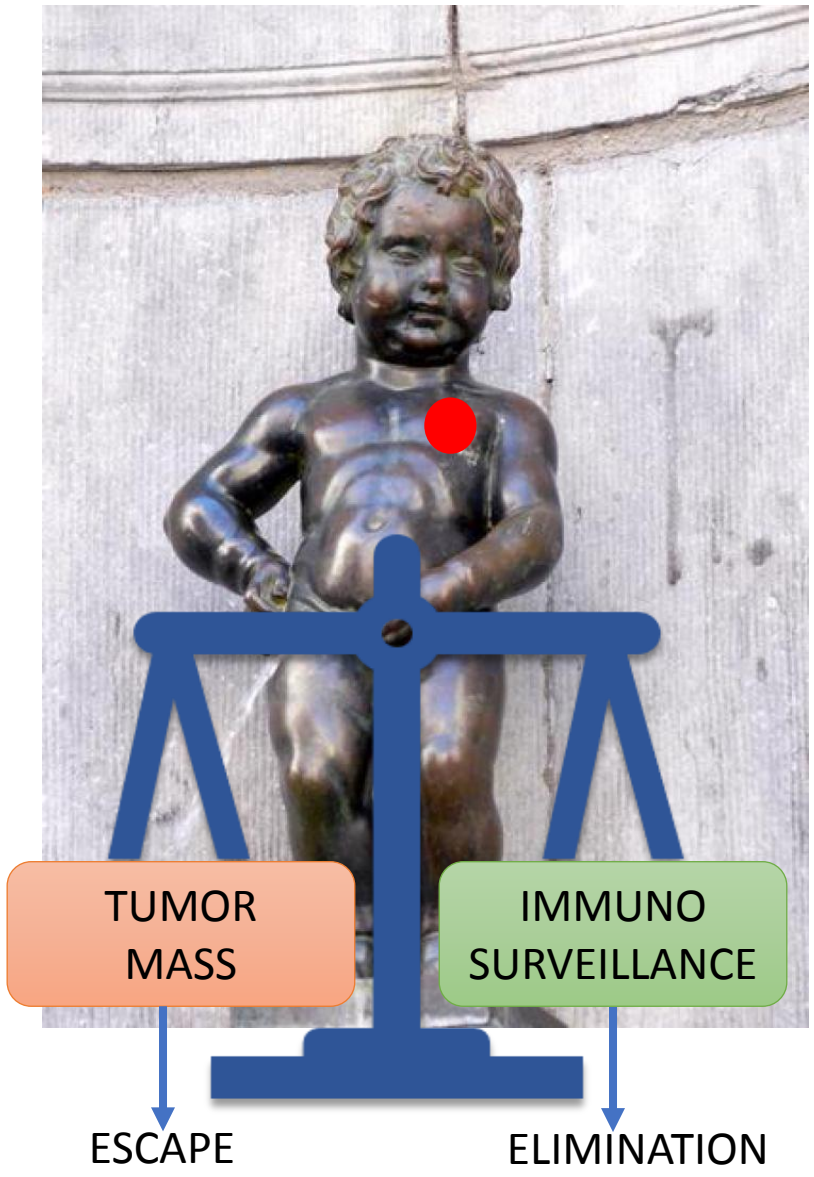
20 octobre 2013

3 avril 2015

STATE OF ART: NEW PARADIGM IN LUNG CANCER

ONCOLOGY VIEW

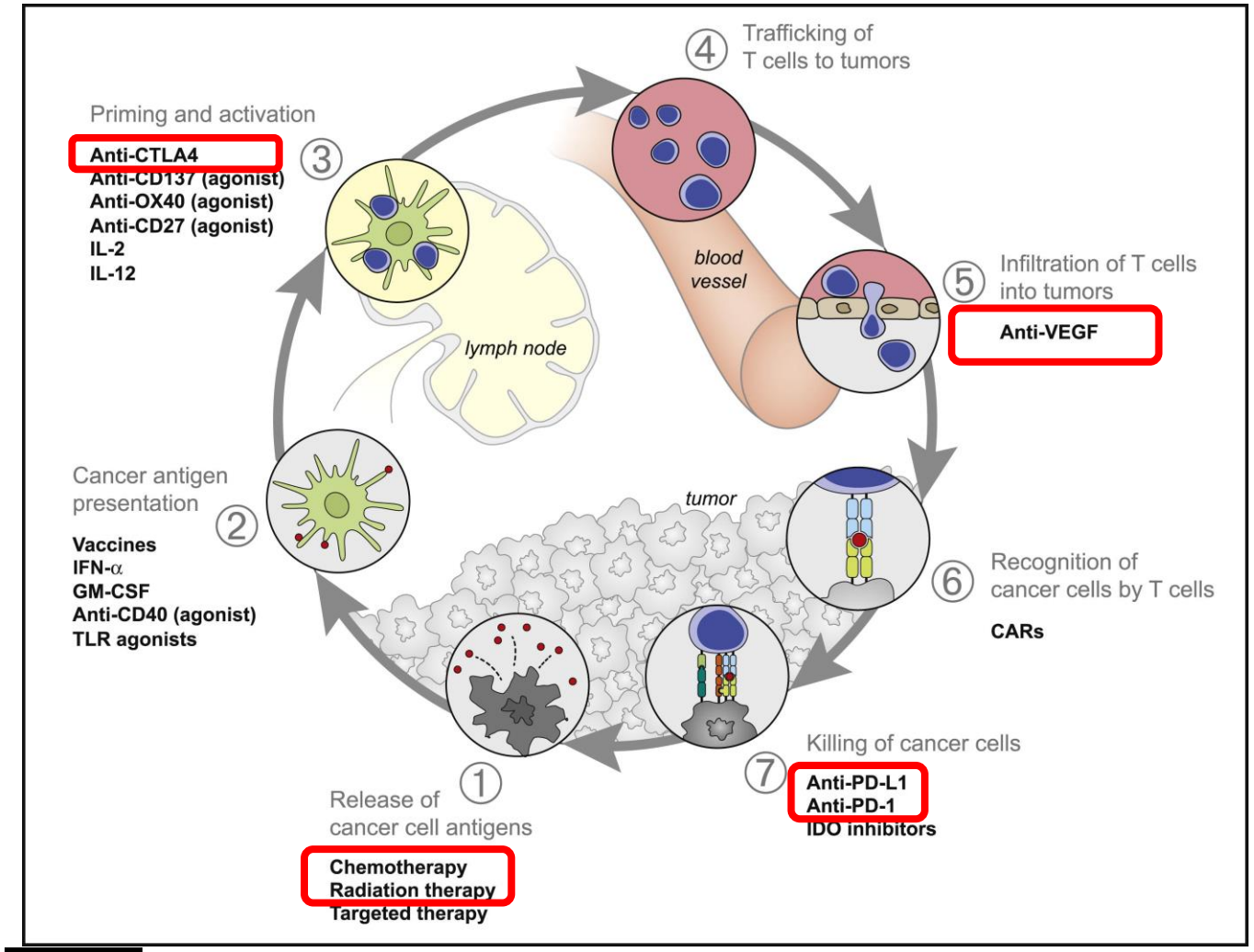
A CANCER THAT
GROW

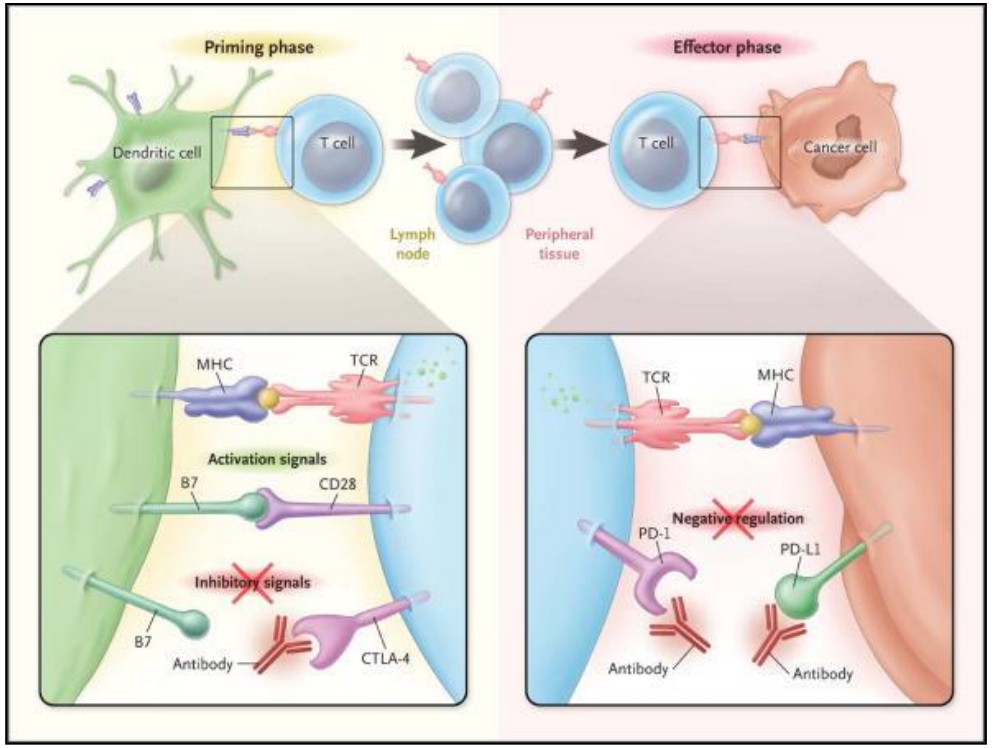


IMMUNO-ONCOLOGY VIEW

A BODY THAT
LET A CANCER GROW

STATE OF ART: NEW PARADIGM IN LUNG CANCER





Tumor Immunotherapy Directed at PD-1.
Ribas, Antoni

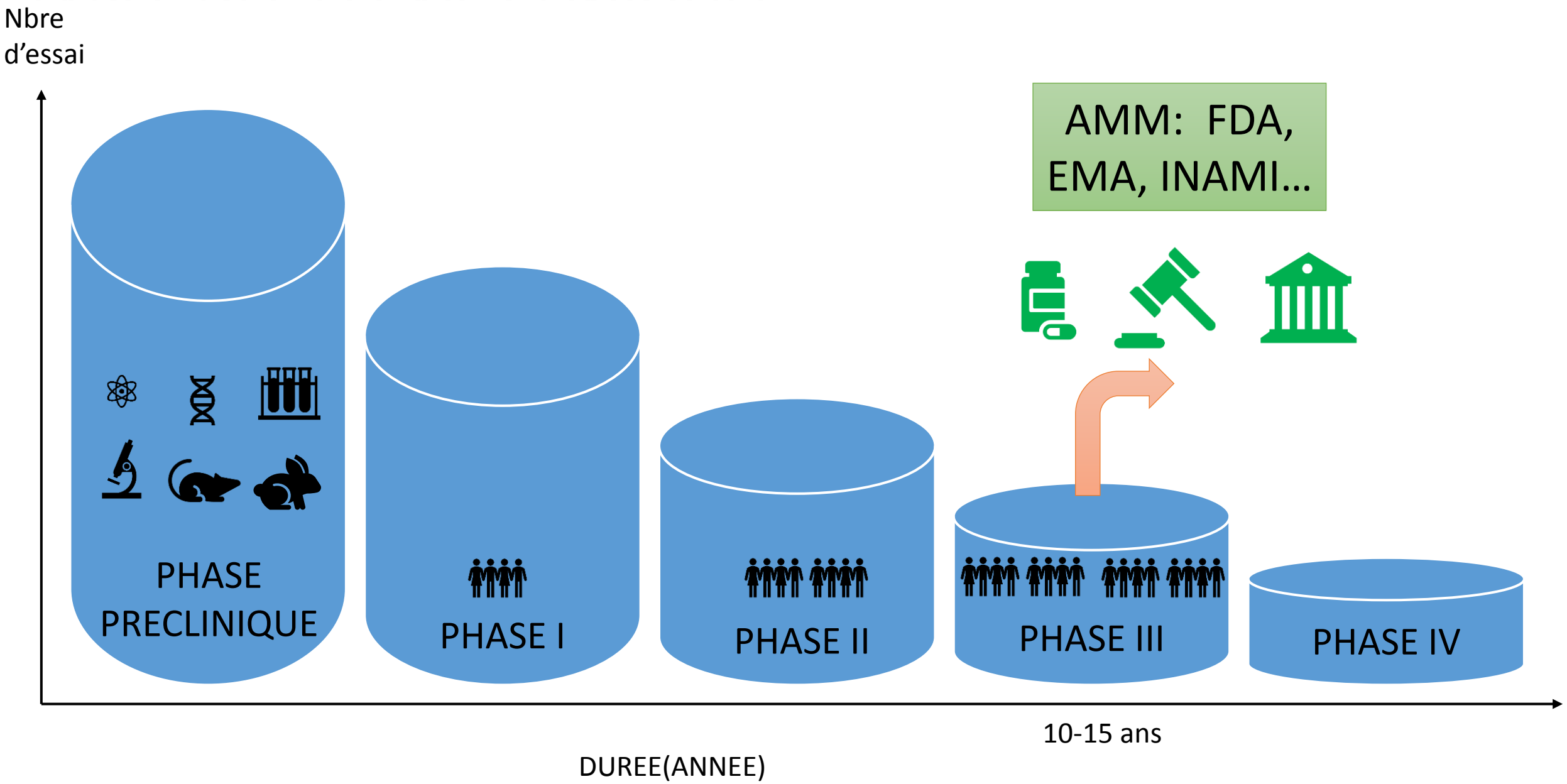
New England Journal of Medicine. 366(26):2517-2519, June 28, 2012.
DOI : 10.1056/NEJMe1205943

Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

AVAILABLE IMMUNOTHERAPIES

ANTI-CTLA-4	ANTI-PD-1	ANTI-PD-L1
IPILIMUMAB (BMS) TREMELIMUMAB (AZ)	NIVOLUMAB (BMS) PEMBROLIZUMAB (MSD)	ATEZOLIZUMAB (roche) DURVALUMAB (AZ) AVELUMAB (Merck,Pfizer)

ETAPES DES ESSAIS CLINIQUES



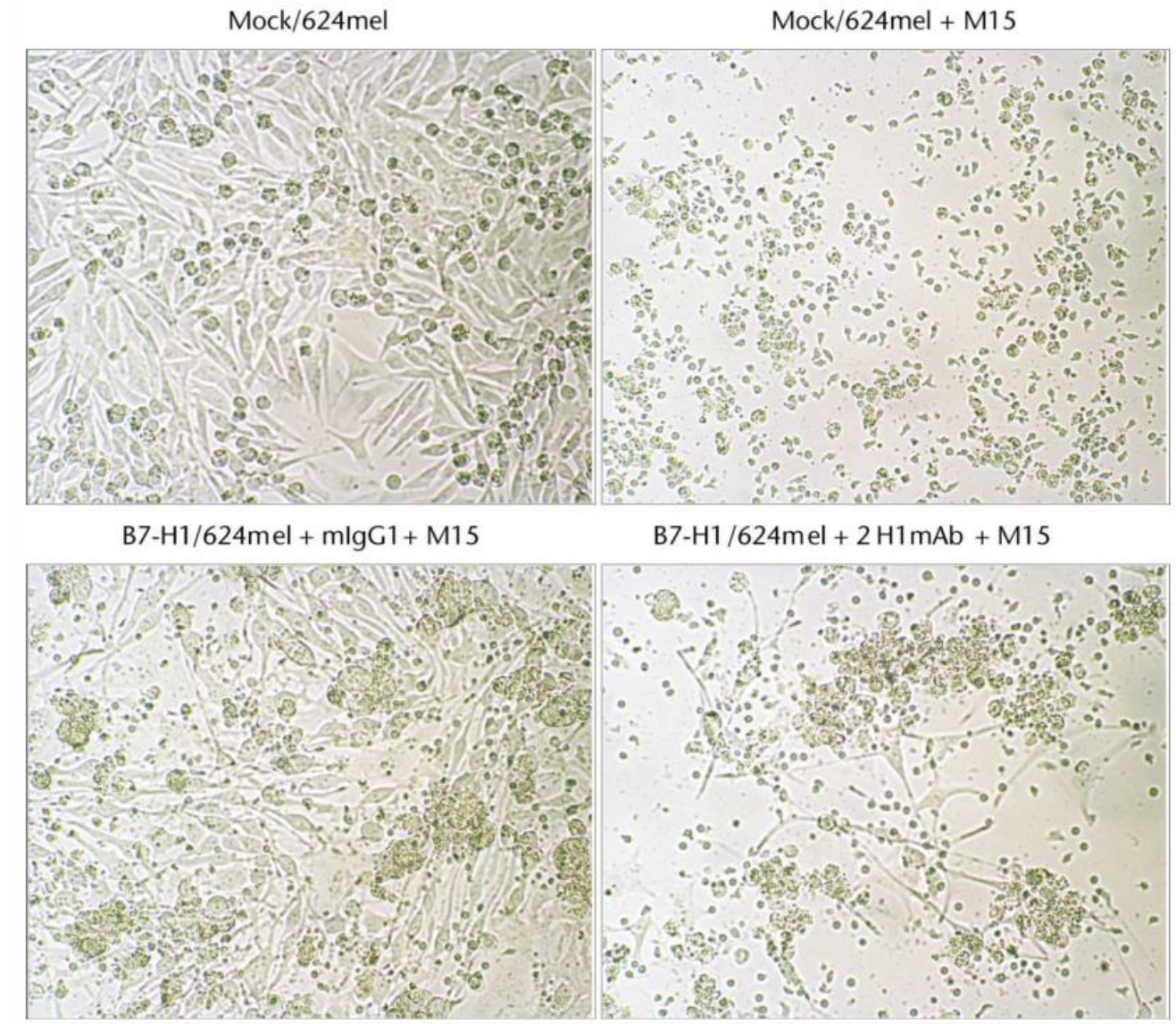
ANTI PD-1 & PDL-1: PHASE PRECLINIQUE

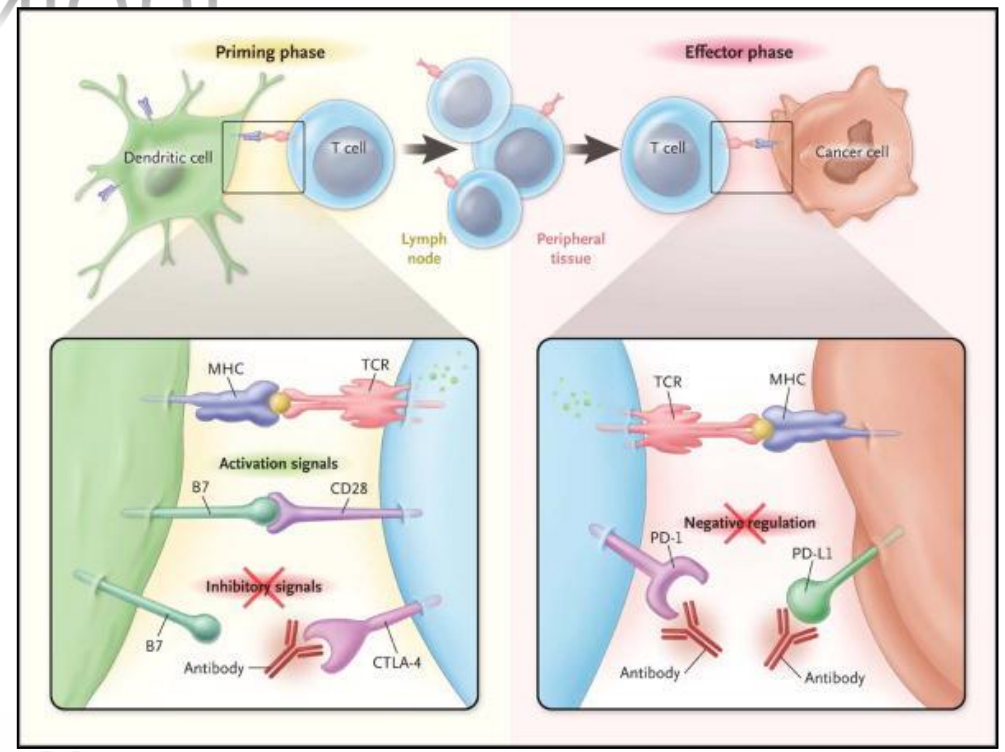
Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion

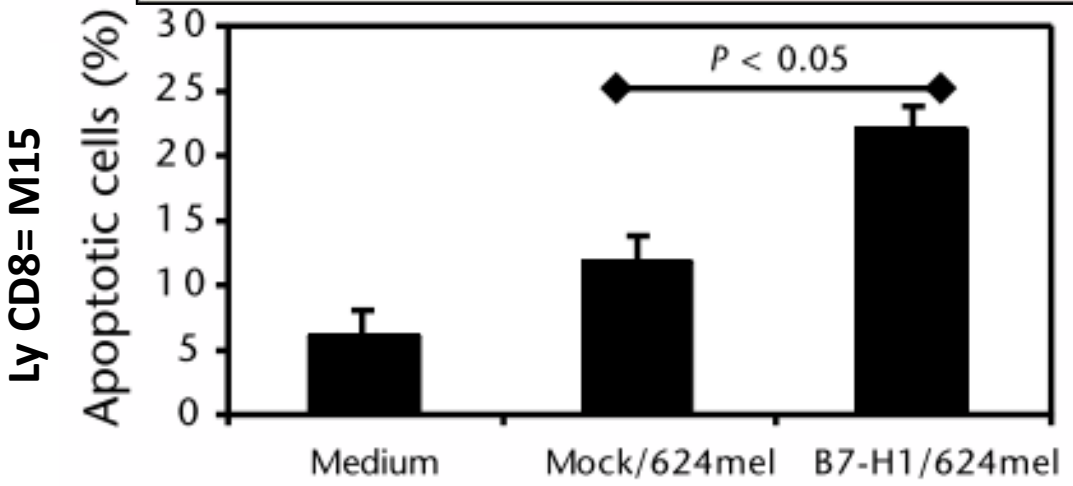
B7-H1= PDL-1

Dong H et al, Nature medicine **2002**;8:793

ANTI PD-1 & PDL-1: PHASE PRECLINIQUE





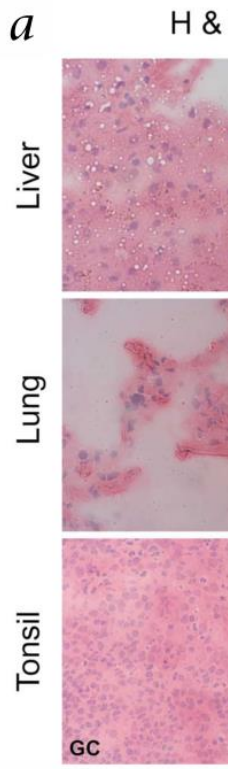


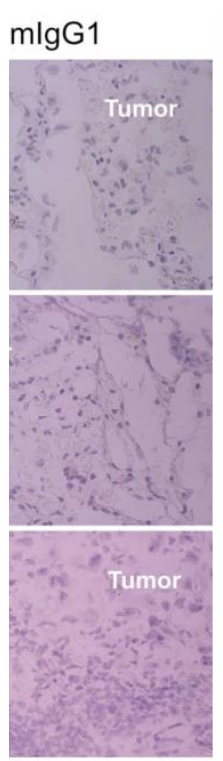
Dong H et al, Nature medicine **2002**;8:793

ANTI PD-1 & PDL-1: PHASE PRECLINIQUE

Table 1 Expression of B7-H1 in human cancer tissues

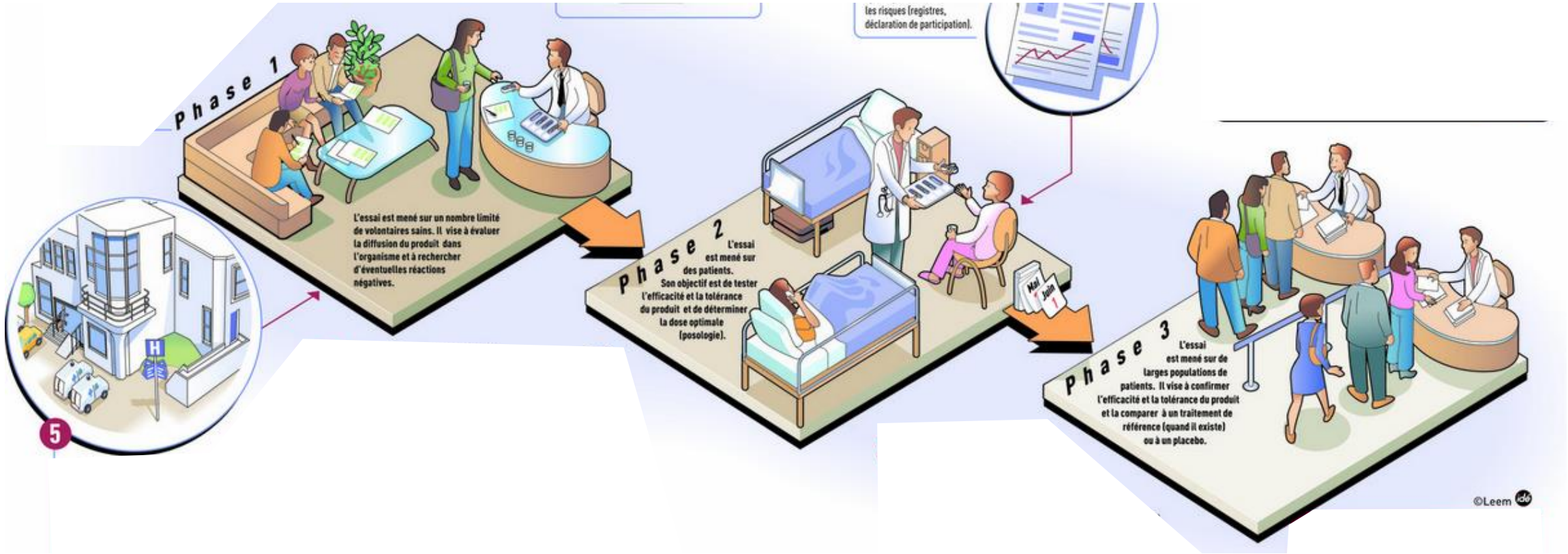
Diagnosis	Specimen numbers, positive/total (%)	Cases with staining intensity[a] –	+	++	+++
Lung cancer	20/21 (95)	1	9	10	1
Adenocarcinoma	10/10	0	5	5	0
Squamous cell carcinoma	8/8	0	2	5	1
Large cell carcinoma	1/2	1	1	0	0
Neuroendocrine carcinoma	1/1	0	1	0	0
Ovarian cancer	20/23 (87)	3	8	11	1
Adenocarcinoma	19/22	3	7	11	1
Carcinosarcoma	1/1	0	1	0	0
Melanoma	22/22 (100)	0	5	12	5
Skin	13/13	0	4	6	3
Lymph node metastasis	5/5	0	0	4	1
Brain metastasis	1/1	0	0	1	0
Axilla metastasis	2/2	0	1	0	1
Breast metastasis	1/1	0	0	1	0
Colon adenocarcinoma	10/19 (53)	9	6	2	2





Dong H et al, Nature medicine **2002**;8:793

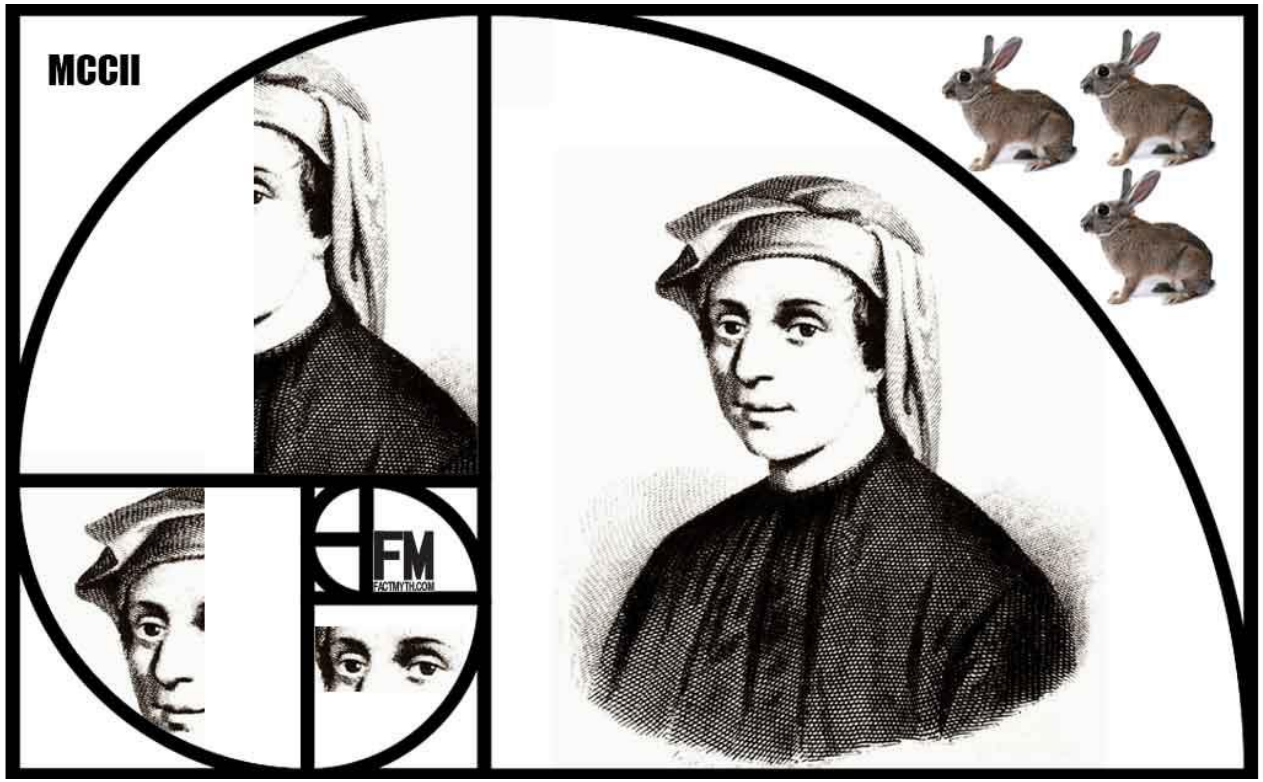
PHASE I


les risques (registres, déclaration de participation).
Phase 1
L'essai est mené sur un nombre limité de volontaires sains. Il vise à évaluer la diffusion du produit dans l'organisme et à rechercher d'éventuelles réactions négatives.
Phase 2
L'essai est mené sur des patients. Son objectif est de tester l'efficacité et la tolérance du produit et de déterminer la dose optimale (posologie).
Mai
Juin
Phase 3
L'essai est mené sur de larges populations de patients. Il vise à confirmer l'efficacité et la tolérance du produit et la comparer à un traitement de référence (quand il existe) ou à un placebo.
5
©Leem

ESSAI CLINIQUE: PHASE I ; OBJECTIFS

- Déterminer les profils de toxicité et de sécurité d'emploi d'un nouvel agent ou d'une nouvelle combinaison d'agents connus
- Décrire le profil pharmacocinétique du médicament après son administration
- Établir une dose optimale à administrer pour les études de phase II en découlant

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB



FIBONACCI

1200

ESSAI CLINIQUE: PHASE I ; OBJECTIFS

Tableau. Escalade de doses suivant la suite de Fibonacci, et la suite modifiée, compte tenu d'une dose de départ de 1 mg/m².

Palier	Série de Fibonacci		Série de Fibonacci modifiée	
	Dose (mg/m²)	Incrément (%)	Dose (mg/m²)	Incrément (%)
1	1	-	1	-
2	2	100	2	100
3	3	50	3,3	67
4	5	67	5	50
5	8	60	7	40
6	13	63	9	33
7	21	62	12	33
8	34	62	16	33

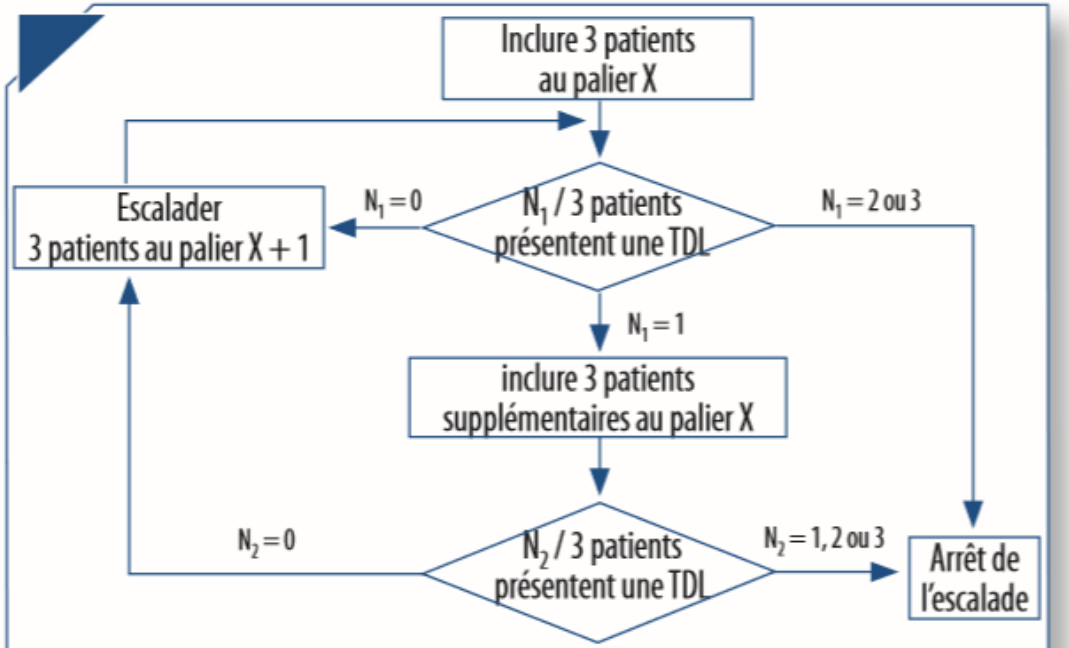


Figure 3. *Escalade de doses : méthode standard (schéma de Fibonacci modifié), affectation des patients et critère d'arrêt.*

La Lettre du Pharmacologue - vol. 22 - n° 3 - juillet-août-septembre 2008

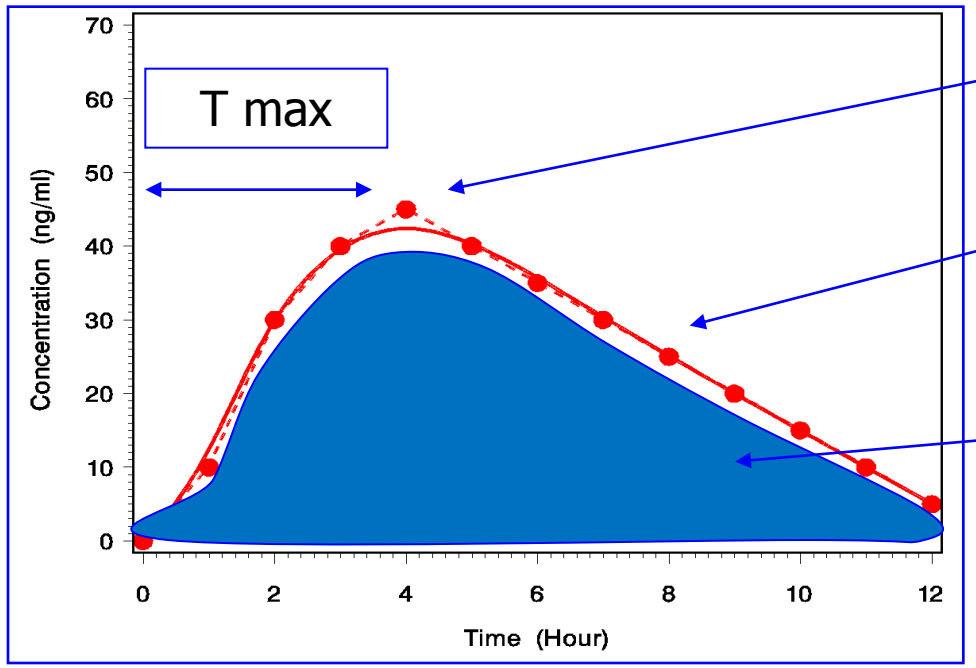
ESSAI CLINIQUE: PHASE I ; OBJECTIFS

Définitions

- La pharmacocinétique (PK) : étude quantitative de ce que l'organisme fait au médicament (ex. concentrations, AUC, clairances…).
- La pharmacodynamie (PD) : étude de ce que le médicament fait à l'organisme = effets chez le patient (ex. Toxicité, survie, réponse…)

ESSAI CLINIQUE: PHASE I ; OBJECTIFS

Pharmacocinétique (PK): paramètres

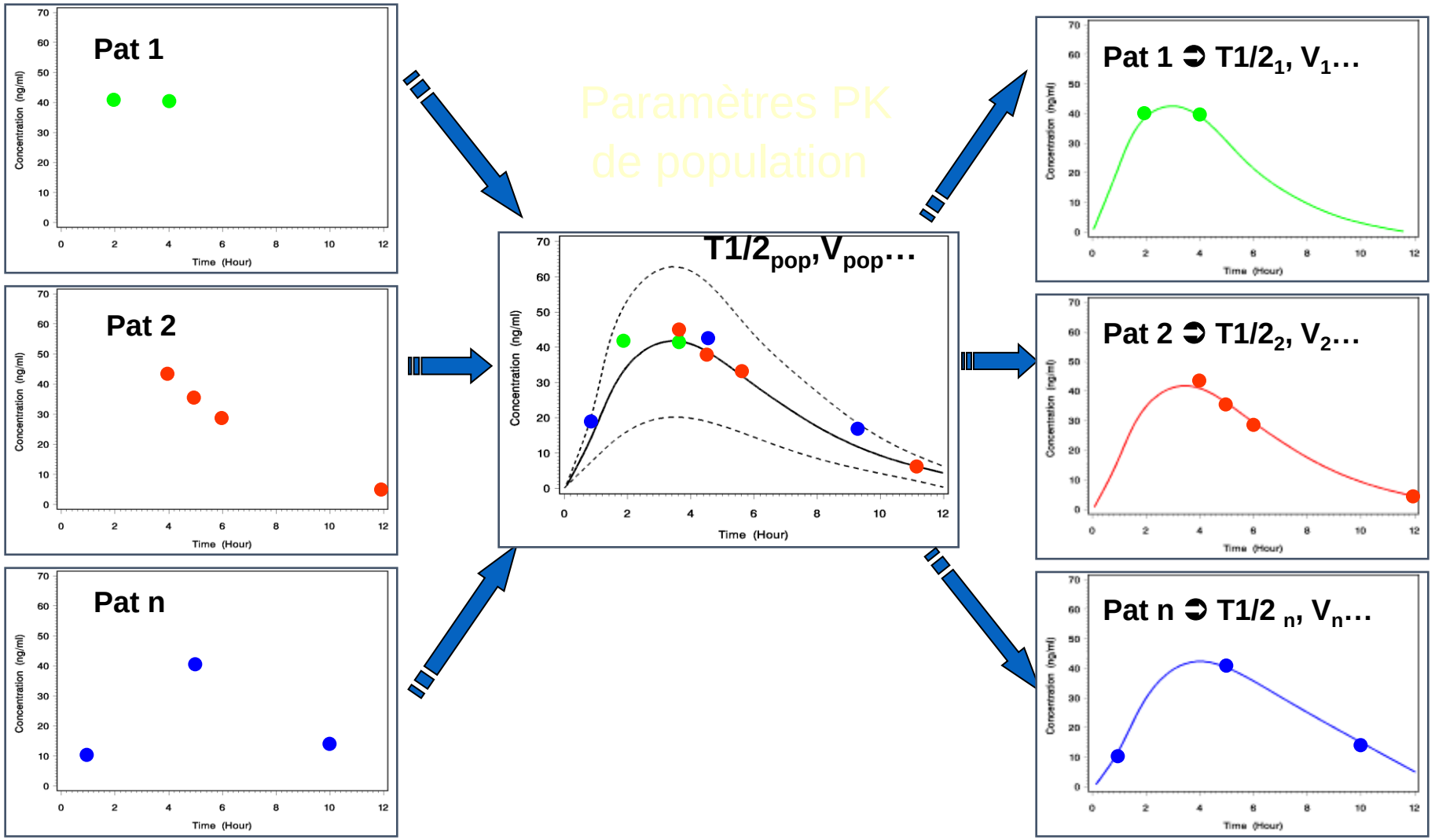


Autres: Concentration équilibre (Css), biodisponibilité…

=> Carte d'identité du médicament

ESSAI CLINIQUE: PHASE I ; OBJECTIFS

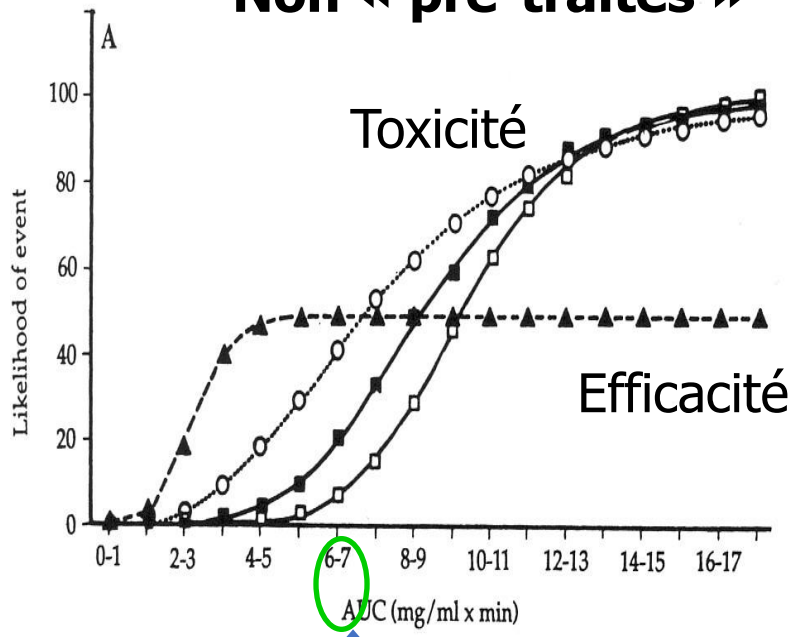
Analyse PK - PD :Approche de Population



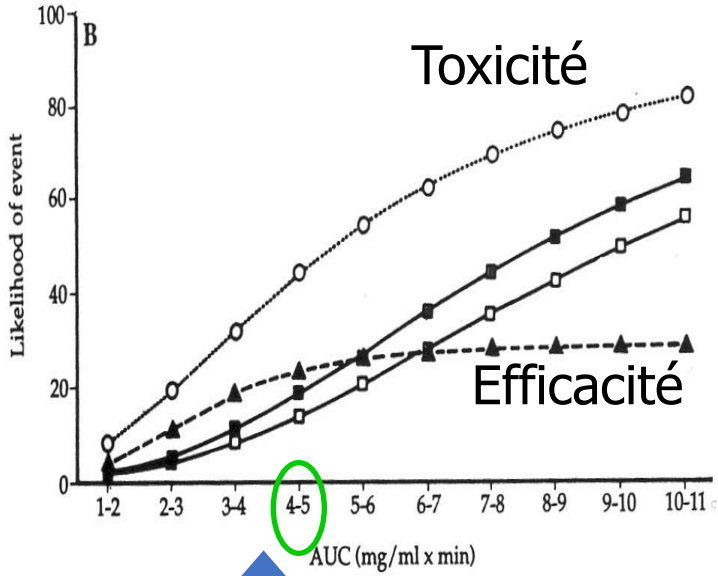
ESSAI CLINIQUE: PHASE I ; OBJECTIFS

Relation concentration-effet

Non « pré-traités »



« Pré-traités »



ASC Cible

Dose (mg) = CL (ml/min) x AUC cible (min.mg/ml)

Jodrell et al, J Clin Oncol 1992

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB

Published OnlineFirst May 14, 2015; DOI: 10.1158/1078-0432.CCR-14-2607

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Study of Pembrolizumab (MK-3475; Anti–PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors

Amita Patnaik[1], S. Peter Kang[2], Drew Rasco[1], Kyriakos P. Papadopoulos[1], Jeroen Elassaiss-Schaap[2], Muralidhar Beeram[1], Ronald Drengler[1], Cong Chen[2], Lon Smith[1], Guillermo Espino[1], Kevin Gergich[2], Liliana Delgado[2], Adil Daud[3], Jill A. Lindia[2], Xiaoyun Nicole Li[2], Robert H. Pierce[2], Jennifer H. Yearley[2], Dianna Wu[2], Omar Laterza[2], Manfred Lehnert[2], Robert Iannone[2], and Anthony W. Tolcher[1]

Patnaik A et al, Clinical Cancer Research **2015**;21(19):4286.

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB

Abstract

Purpose: This phase I study evaluated the safety, maximum tolerated dose, antitumor activity, and pharmacokinetics and pharmacodynamics of pembrolizumab in patients with advanced solid tumors.

Experimental Design: In a 3 + 3 dose escalation study, 10 patients received pembrolizumab 1, 3, or 10 mg/kg intravenously every 2 weeks until progression or intolerable toxicity. Seven additional patients received 10 mg/kg every 2 weeks. Thirteen patients participated in a 3-week intrapatient dose escalation (dose range, 0.005–10 mg/kg) followed by 2 or 10 mg/kg every 3 weeks. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Results: No dose-limiting toxicities were observed. Maximum administered dose was 10 mg/kg every 2 weeks. One patient with melanoma and one with Merkel cell carcinoma experienced complete responses of 57 and 56+ weeks' duration, respectively. Three patients with melanoma experienced partial responses. Fifteen patients with various malignancies experienced stable disease. One patient died of cryptococcal infection 92 days after pembrolizumab discontinuation, following prolonged corticosteroid use for grade 2 gastritis considered drug related. Pembrolizumab exhibited pharmacokinetic characteristics typical of humanized monoclonal antibodies. Maximum serum target engagement was reached with trough levels of doses greater than or equal to 1 mg/kg every 3 weeks. Mechanism-based translational models with a focus on intratumor exposure prediction suggested robust clinical activity would be observed at doses ≥2 mg/kg every 3 weeks.

Conclusions: Pembrolizumab was well tolerated and associated with durable antitumor activity in multiple solid tumors. The lowest dose with full potential for antitumor activity was 2 mg/kg every 3 weeks. *Clin Cancer Res; 21(19); 4286–93. ©2015 AACR.*

See related commentary by van Elsas et al., p. 4251

Patnaik A et al, Clinical Cancer Research **2015**;21(19):4286.

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB

Table 1. Baseline characteristics of treated patients

Characteristics	Parts A and A-1, *n* = 17	Part A-2, *n* = 13	All patients, *N* = 30
Age, years, median (range)	67.0 (35–87)	66.0 (33–82)	66.5 (33–87)
Sex, *n* (%)			
Male	10 (59)	13 (100)	23 (77)
Female	7 (41)	0 (0)	7 (23)
ECOG performance status, *n* (%)			
0	5 (29)	5 (38)	10 (33)
1	12 (71)	8 (62)	20 (67)
Tumor type, *n* (%)			
Adenocarcinoma	2 (12)	0 (0)	2 (7)
Carcinoid/neuroendocrine	2 (12)	1 (8)	3 (10)
Colorectal	3 (18)	0 (0)	3 (10)
Melanoma	2 (12)	5 (38)	7 (23)
Merkel cell carcinoma	0 (0)	1 (8)	1 (3)
Non–small cell lung cancer	5 (29)	1 (8)	6 (20)
Prostate	1 (6)	2 (15)	3 (10)
Kaposi sarcoma	1 (6)	0 (0)	1 (3)
Soft tissue sarcoma	1 (6)	0 (0)	1 (3)
Peripheral nerve sheath tumor	0 (0)	1 (8)	1 (3)
Pancreatic adenocarcinoma	0 (0)	1 (8)	1 (3)
Squamous cell lung cancer	0 (0)	1 (8)	1 (3)
Prior therapies, *n* (%)			
0	0 (0)	5 (38)	5 (17)
1	2 (12)	3 (23)	5 (17)
2	2 (12)	3 (23)	5 (17)
≥3	13 (76)	2 (15)	15 (50)

Table 2. Treatment-related adverse events of any grade observed in ≥1 patient

	Pembrolizumab every 2 weeks			Pembrolizumab every 3 weeks		
Adverse event, *n* (%)	1 mg/kg, *n* = 4	3 mg/kg, *n* = 3	10 mg/kg, *n* = 10	2 mg/kg, *n* = 7	10 mg/kg, *n* = 6	Total, *N* = 30
Any	3 (75)	3 (100)	4 (40)	7 (100)	4 (67)	21 (70)
Fatigue	0	1 (33)	4 (40)	3 (43)	2 (33)	10 (33)
Nausea	0	2 (67)	1 (10)	2 (29)	2 (33)	7 (23)
Pruritus	2 (50)	1 (33)	1 (10)	1 (14)	0	5 (17)
Decreased appetite	0	0	2 (20)	0	2 (33)	4 (13)
Diarrhea	0	1 (33)	1 (10)	0	0	2 (7)
Hypothyroidism	0	0	0	1 (14)	1 (17)	2 (7)
Asthenia	0	0	0	0	1 (17)	1 (3)
Blurred vision	0	0	0	1 (14)	0	1 (3)
Breast pain	0	1 (33)	0	0	0	1 (3)
Dizziness	0	0	0	1 (14)	0	1 (3)
Dysgeusia	1 (25)	0	0	0	0	1 (3)
Erythema	0	0	0	1 (14)	0	1 (3)
Exertional dyspnea	0	0	0	1 (14)	0	1 (3)
Gait disturbance	0	0	0	1 (14)	0	1 (3)
Gastritis[a]	0	0	1 (10)	0	0	1 (3)
Hypomagnesemia	0	0	1 (10)	0	0	1 (3)
Hypotension	0	0	1 (10)	0	0	1 (3)
Impaired healing	0	0	0	1 (14)	0	1 (3)
Insomnia	0	0	0	0	1 (17)	1 (3)
Muscular weakness	0	0	0	1 (14)	0	1 (3)
Night sweats	0	0	0	1 (14)	0	1 (3)
Nipple pain	0	0	0	1 (14)	0	1 (3)
Pain	0	0	0	1 (14)	0	1 (3)
Pain in extremity	0	0	0	0	1 (17)	1 (3)
Pleuritic pain	0	0	0	0	1 (17)	1 (3)
Pneumonitis	0	1 (33)	0	0	0	1 (3)
Skin hypopigmentation	0	0	1 (10)	0	0	1 (3)
Tumor pain	0	0	0	1 (14)	0	1 (3)
Vomiting	0	0	0	0	1 (17)	1 (3)
Weight decreased	0	0	1 (10)	0	0	1 (3)

NOTE: All treatment-related adverse events were of grade 1 or 2 severity. Individual patients could have experienced ≥1 event.

[a]One patient died of disseminated cryptococcal infection in the lungs and central nervous system 92 days after discontinuing pembrolizumab 10 mg/kg once every 2 weeks. The death was considered possibly related to study treatment based on the prolonged use of corticosteroids for grade 2 gastritis, which was considered treatment related.

Patnaik A et al, Clinical Cancer Research **2015**;21(19):4286.

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB

Table 3. Summary statistics for PK parameters, Parts A and A-1

Dose	*n*	C_{max}, μg/mL, geometric mean (CV%)	T_{max}, days, median (range)	AUC_{0-28}, μg·day/mL, geometric mean (CV%)	$AUC_{0-\infty}$, μg·day/mL, geometric mean (CV%)	$t_{1/2}$,[a] days, geometric mean (CV%)
1 mg/kg	4	16.4 (22)	0.05 (0.02–0.17)	158 (20)[b]	212 (36)[b]	14.1 (51)[b]
3 mg/kg	3	107 (26)	0.17 (0.17–0.17)	955 (23)	1,530 (28)	21.6 (10)
10 mg/kg	10[c]	256 (37)	0.17 (0.03–0.99)	2,150 (31)[d]	3,270 (44)[d]	17.7 (56)[d]

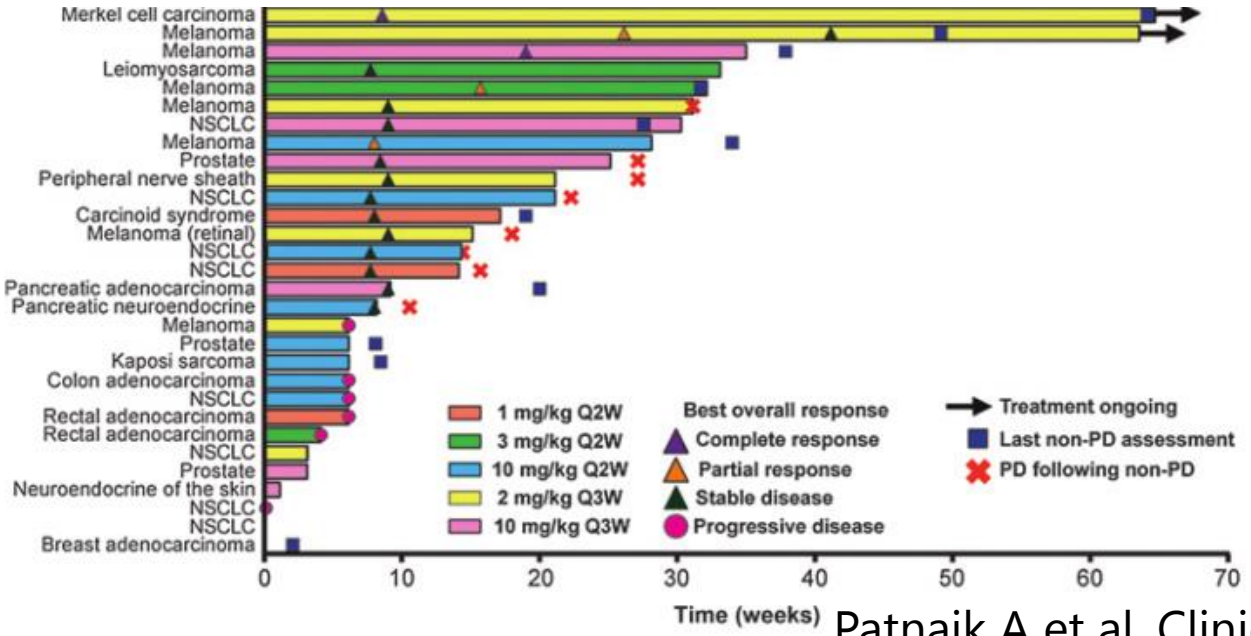
Abbreviations: AUC_{0-28}, area under the concentration–time curve from day 0 up to day 28; $AUC_{0-\infty}$, area under the concentration–time curve from day 0 to infinity; C_{max}, maximum observed serum concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; T_{max}, time of maximum observed serum concentration.

[a]Sampling up to 28 days following the first pembrolizumab administration.

[b]$n = 3$ (1 patient excluded because of treatment discontinuation).

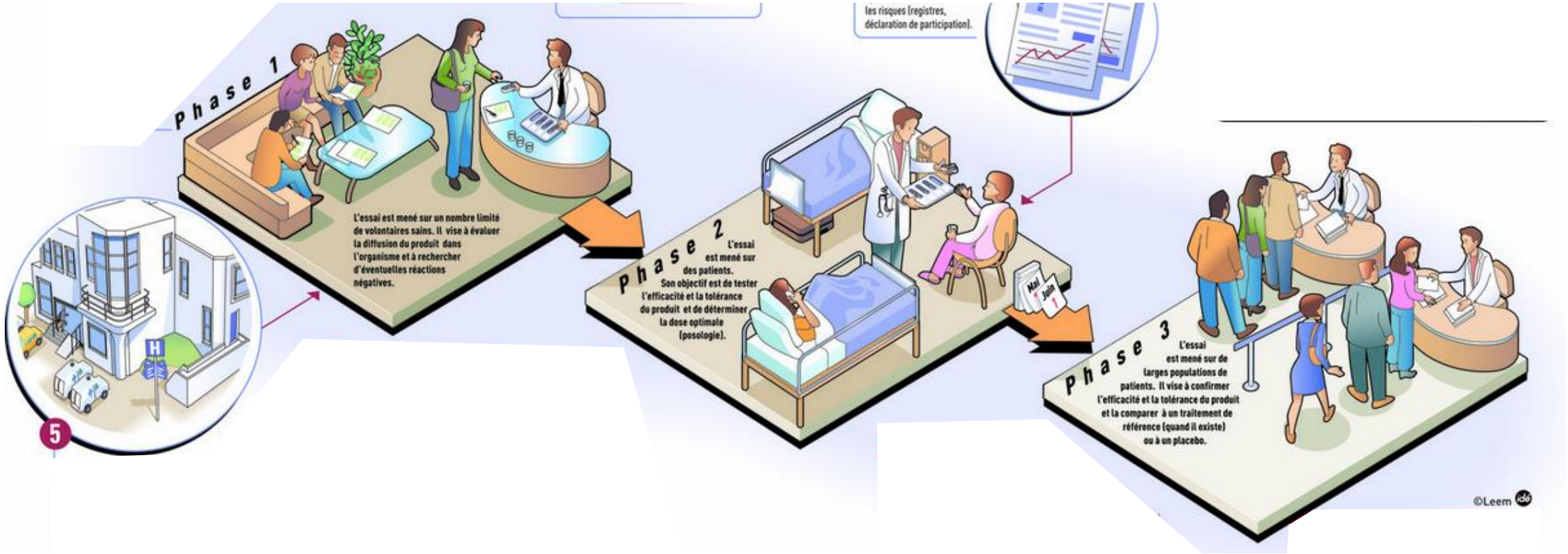
[c]$n = 3$ from Part A and $N = 7$ from Part A-1.

[d]$n = 9$ (1 patient excluded because of treatment discontinuation).



Patnaik A et al, Clinical Cancer Research **2015**;21(19):4286.

PHASE I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Mai
Juin
Phase 3
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ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB (NSCLC)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

Garon EB et al, The New England journal of medicine **2015**;

ESSAI CLINIQUE: PHASE I PEMBROLIZUMAB (NSCLC SEUL)

BACKGROUND

We assessed the efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced non–small-cell lung cancer enrolled in a phase 1 study. We also sought to define and validate an expression level of the PD-1 ligand 1 (PD-L1) that is associated with the likelihood of clinical benefit.

METHODS

We assigned 495 patients receiving pembrolizumab (at a dose of either 2 mg or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks) to either a training group (182 patients) or a validation group (313 patients). We assessed PD-L1 expression in tumor samples using immunohistochemical analysis, with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score). Response was assessed every 9 weeks by central review.

RESULTS

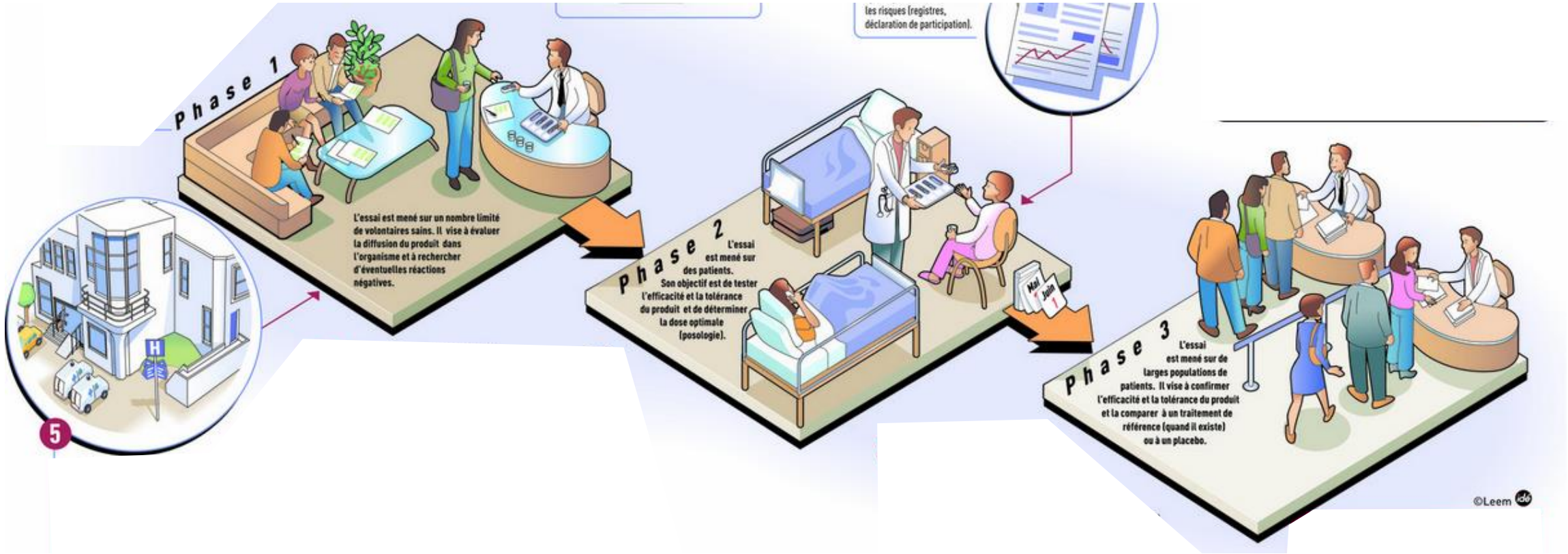
Common side effects that were attributed to pembrolizumab were fatigue, pruritus, and decreased appetite, with no clear difference according to dose or schedule. Among all the patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. PD-L1 expression in at least 50% of tumor cells was selected as the cutoff from the training group. Among patients with a proportion score of at least 50% in the validation group, the response rate was 45.2%. Among all the patients with a proportion score of at least 50%, median progression-free survival was 6.3 months; median overall survival was not reached.

CONCLUSIONS

Pembrolizumab had an acceptable side-effect profile and showed antitumor activity in patients with advanced non–small-cell lung cancer. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab. (Funded by Merck; KEYNOTE-001 ClinicalTrials.gov number, NCT01295827.)

Garon EB et al, The New England journal of medicine **2015**;

PHASE II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Juin 1
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PHASE II

- Seules les molécules ayant montré une efficacité antitumorale

suffisante à l'issue de cette phase justifieront la poursuite de leur développement dans des essais comparatifs de phase III, essais à beaucoup plus grande échelle nécessitant de gros moyens

ESSAI CLINIQUE: PHASE II PEMBROLIZUMAB

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Ralabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger

Goldberg SB et al. The Lancet Oncology **2016**

ESSAI CLINIQUE: PHASE II PEMBROLIZUMAB

Summary

Background Immunotherapy targeting the PD-1 axis has activity in several tumour types. We aimed to establish the activity and safety of the PD-1 inhibitor pembrolizumab in patients with untreated brain metastases from melanoma or non-small-cell lung cancer (NSCLC).

Methods In this non-randomised, open-label, phase 2 trial, we enrolled patients aged 18 years or older with melanoma or NSCLC with untreated brain metastases from the Yale Cancer Center. Patients had at least one untreated or progressive brain metastasis between 5 and 20 mm in diameter without associated neurological symptoms or the need for corticosteroids. Patients with NSCLC had tumour tissue positive for PD-L1 expression; this was not required for patients with melanoma. Patients were given 10 mg/kg pembrolizumab every 2 weeks until progression. The primary endpoint was brain metastasis response assessed in all treated patients. The trial is ongoing and here we present an early analysis. The study is registered with ClinicalTrials.gov, number NCT02085070.

Findings Between March 31, 2014, and May 31, 2015, we screened 52 patients with untreated or progressive brain metastases (18 with melanoma, 34 with NSCLC), and enrolled 36 (18 with melanoma, 18 with NSCLC). A brain metastasis response was achieved in four (22%; 95% CI 7–48) of 18 patients with melanoma and six (33%; 14–59) of 18 patients with NSCLC. Responses were durable, with all but one patient with NSCLC who responded showing an ongoing response at the time of data analysis on June 30, 2015. Treatment-related serious and grade 3–4 adverse events were grade 3 elevated aminotransferases (n=1 [6%]) in the melanoma cohort, and grade 3 colitis (n=1 [6%]), grade 3 pneumonitis (n=1 [6%]), grade 3 fatigue (n=1 [6%]), grade 4 hyperkalemia (n=1 [6%]), and grade 2 acute kidney injury (n=1 [6%]) in the NSCLC cohort. Clinically significant neurological adverse events included transient grade 3 cognitive dysfunction and grade 1–2 seizures (n=3 [17%]) in the melanoma cohort.

Interpretation Pembrolizumab shows activity in brain metastases in patients with melanoma or NSCLC with an acceptable safety profile, which suggests that there might be a role for systemic immunotherapy in patients with untreated or progressive brain metastases.

PEMBRO: 10mg/kg /2 semaines

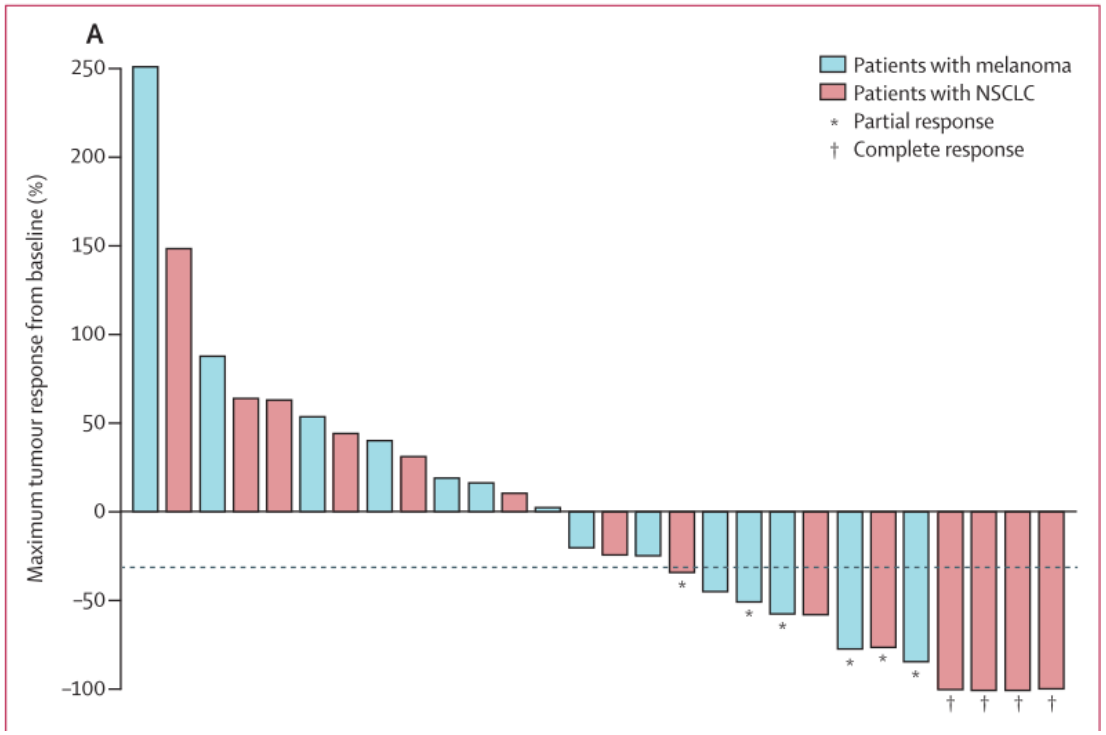
EFFICACITE META CEREB:
22% MELANONE
33% NSCLC

TOXICITE

Goldberg SB et al. The Lancet Oncology **2016**

ESSAI CLINIQUE: PHASE II PEMBROLIZUMAB

EFFICACITE



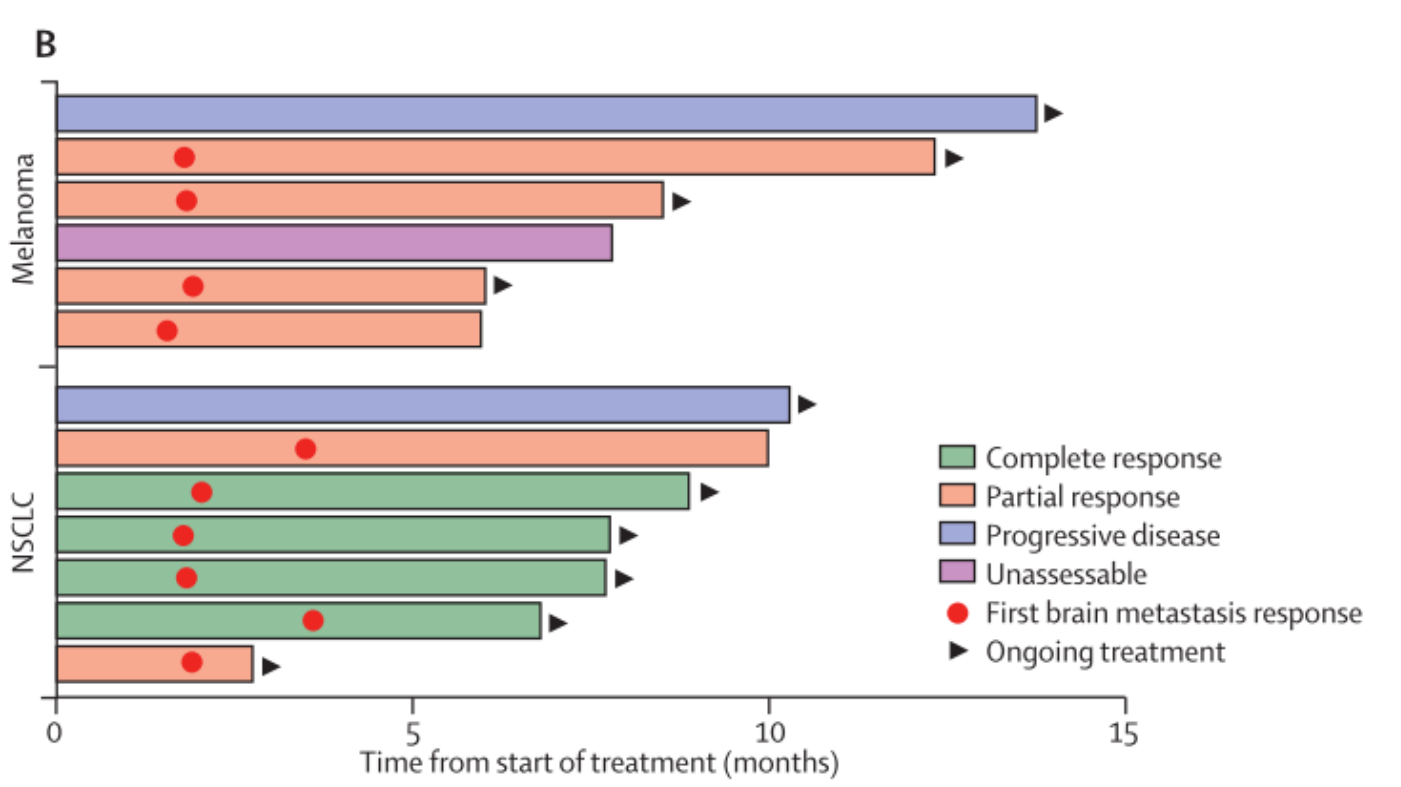


Figure: **Brain metastasis response in assessable patients with melanoma or NSCLC**

Goldberg SB et al. The Lancet Oncology **2016**

ESSAI CLINIQUE: PHASE II PEMBROLIZUMAB

TOXICITE

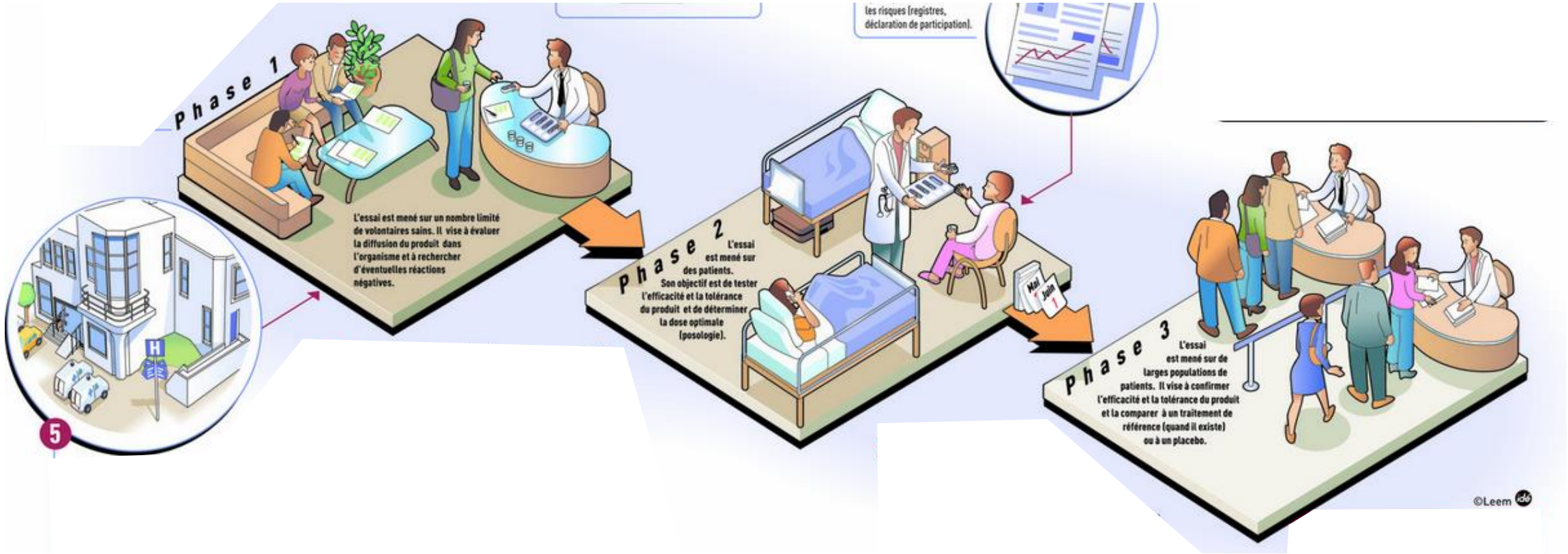
	Melanoma (n=18)			NSCLC (n=18)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neurological*						
Cognitive dysfunction	0	1 (6%)	0	1 (6%)	0	0
Headache	3 (17%)	0	0	4 (22%)	0	0
Dizziness	1 (6%)	0	0	2 (11%)	0	0
Stroke	0	0	0	1 (6%)	0	0
Seizure	3 (17%)	0	0	0	0	0
Treatment-related non-neurological						
Colitis or diarrhoea	0	0	0	3 (17%)	1 (6%)	0
Pneumonitis	0	0	0	0	1 (6%)	0
Acute kidney injury	0	0	0	1 (6%)	0	0
Fatigue	8 (44%)	0	0	5 (28%)	1 (6%)	0
Anorexia	1 (6%)	0	0	2 (11%)	0	0
Dermatological	6 (33%)	0	0	4 (22%)	0	0
Arthralgias	2 (11%)	0	0	1 (6%)	0	0
Endocrine	1 (6%)	0	0	5 (28%)	0	0
Hyperkalemia	0	0	0	0	0	1 (6%)
Haematological	0	0	0	2 (11%)	0	0
Elevated aminotransferases	0	1 (6%)	0	0	0	0

NSCLC=non-small-cell lung cancer. *Irrespective of attribution to study drug. There were no treatment-related deaths.

Table 3: **Neurological adverse events and treatment-related non-neurological adverse events in all treated patients with melanoma or NSCLC**

Goldberg SB et al. The Lancet Oncology **2016**

PHASE III


Phase 1
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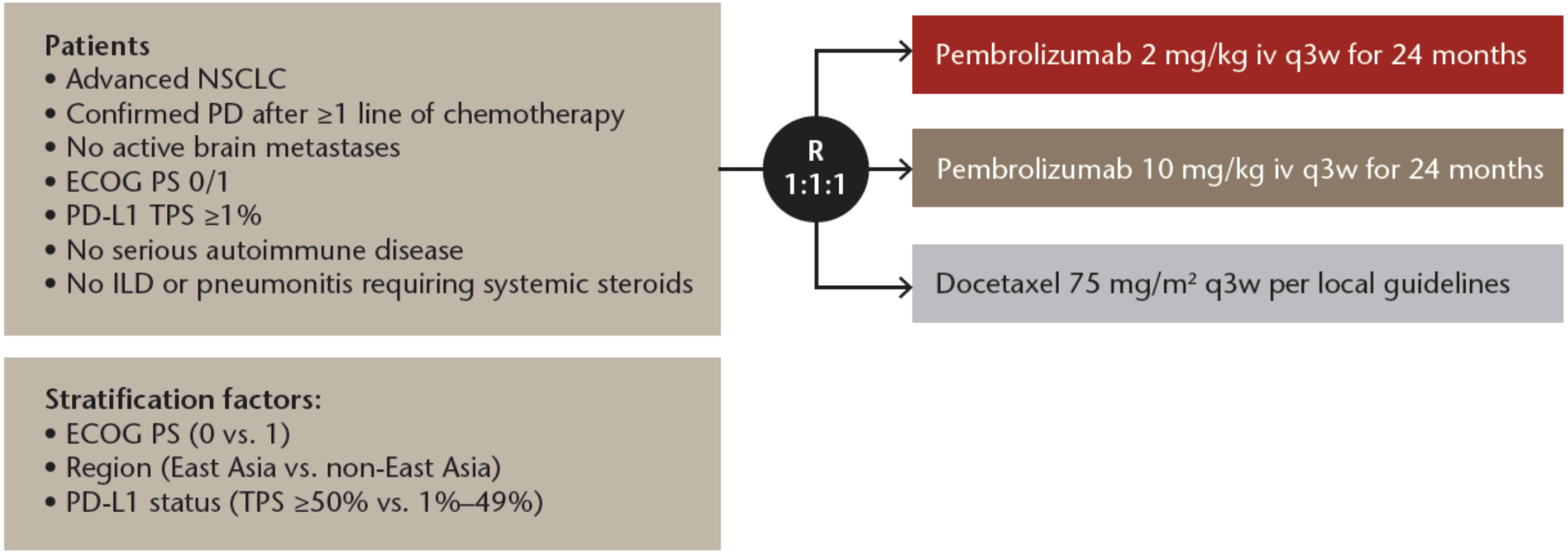
ESSAI CLINIQUE: PHASE III PEMBROLIZUMAB

Study design



ECOG PS = Eastern Cooperative Oncology Group performance status; ILD = interstitial lung disease; iv = intravenous; NSCLC = non-small cell lung cancer; PD = progressive disease; PD-L1 = programmed death-ligand 1; q3w = every three weeks; R = randomize; TPS = tumour proportion score

Herbst RS et al. The Lancet;387 **2015**

ESSAI CLINIQUE: PHASE III PEMBROLIZUMAB

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

Herbst RS et al. The Lancet;387 **2015**

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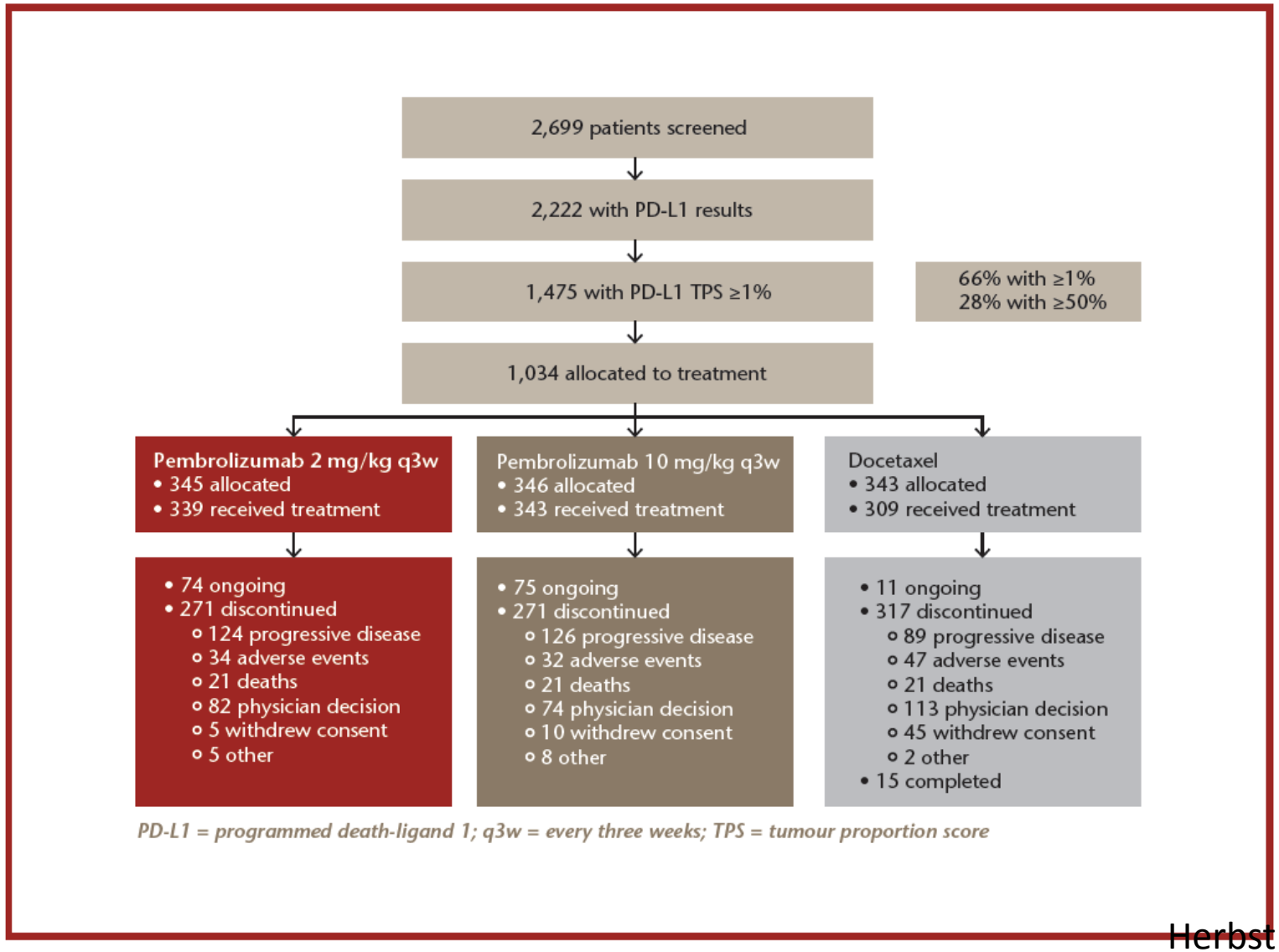
Figure 1. Patient disposition



Herbst RS et al. The Lancet;387 **2015**

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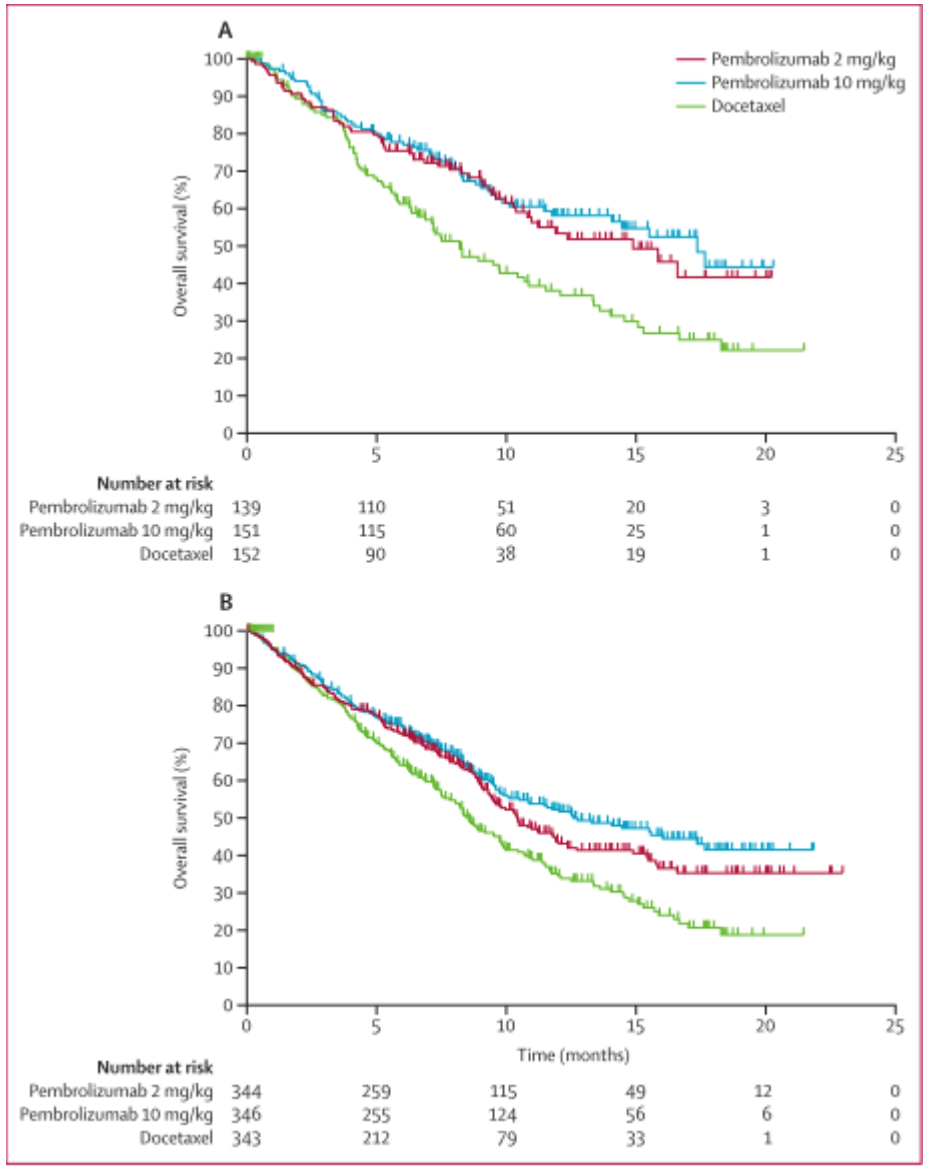


Figure 2: **Kaplan-Meier analysis of overall survival**

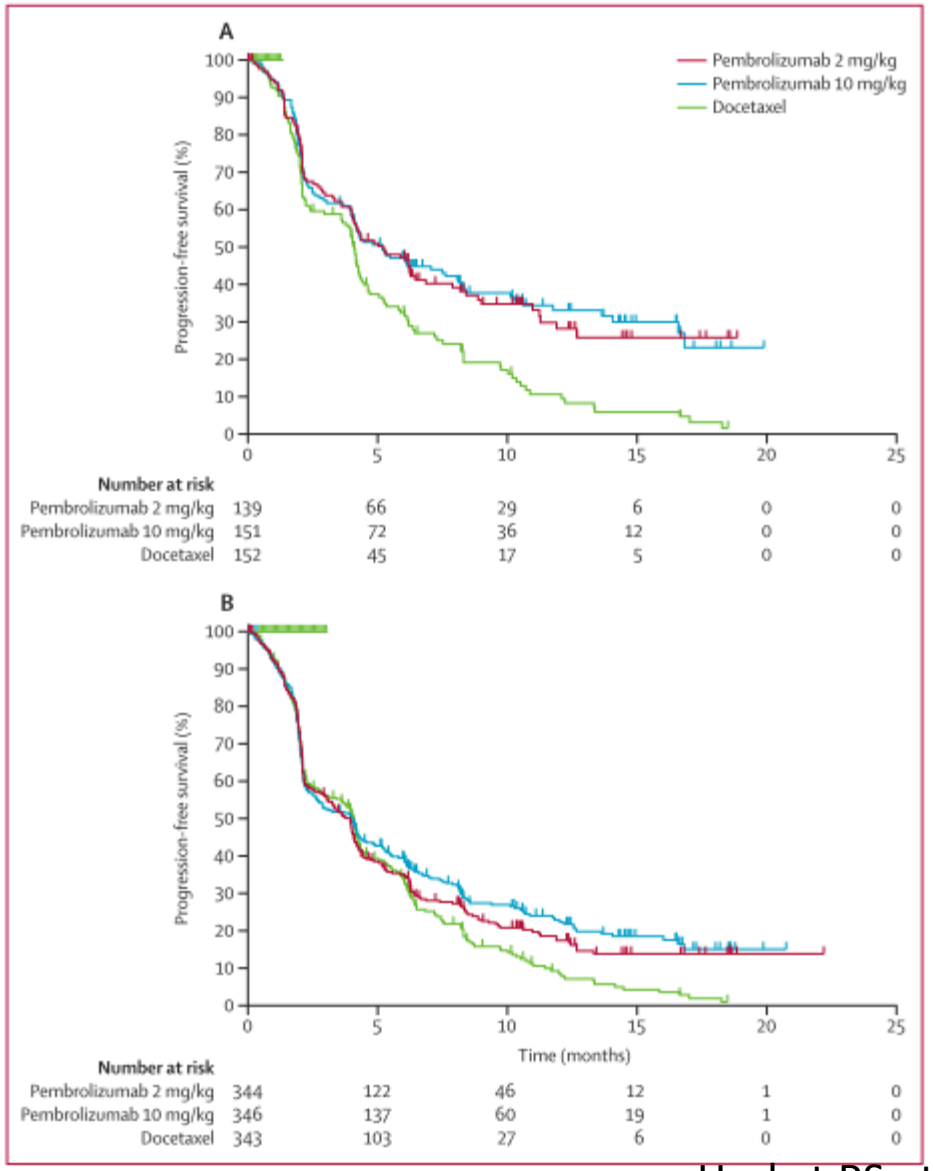
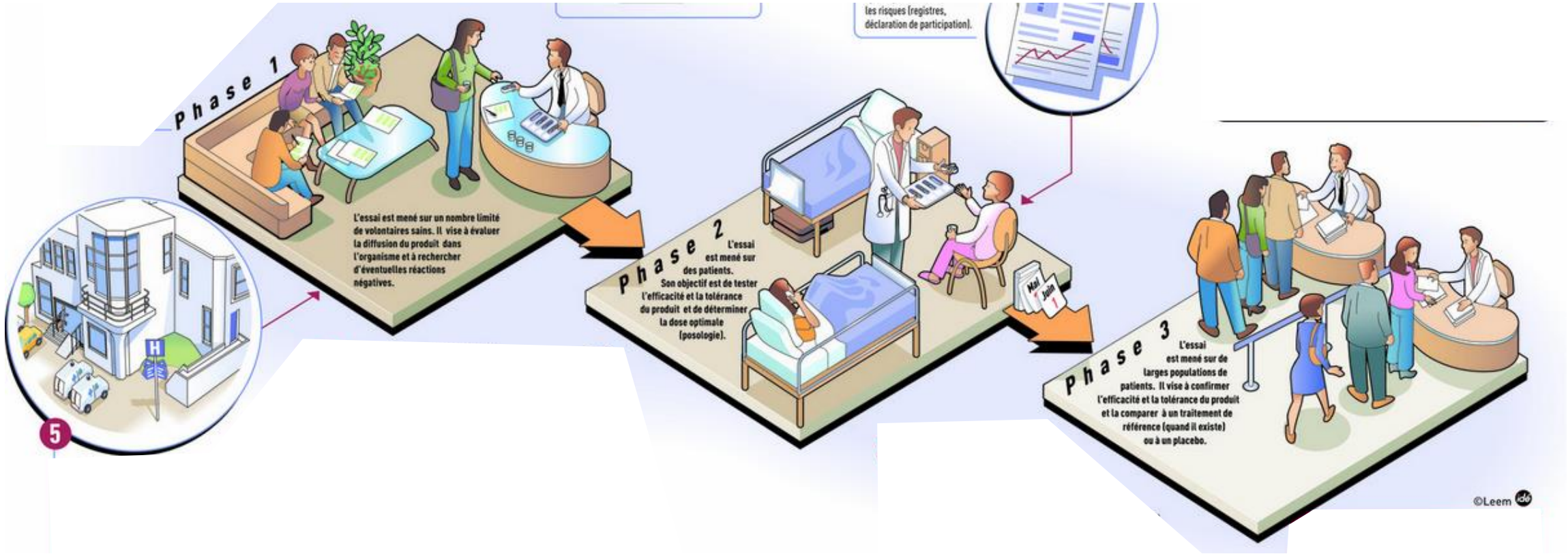


Figure 4: **Kaplan-Meier analysis of progression-free survival**
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

Herbst RS et al. The Lancet;387 **2015**

PHASE III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The NEW ENGLAND JOURNAL of MEDICINE

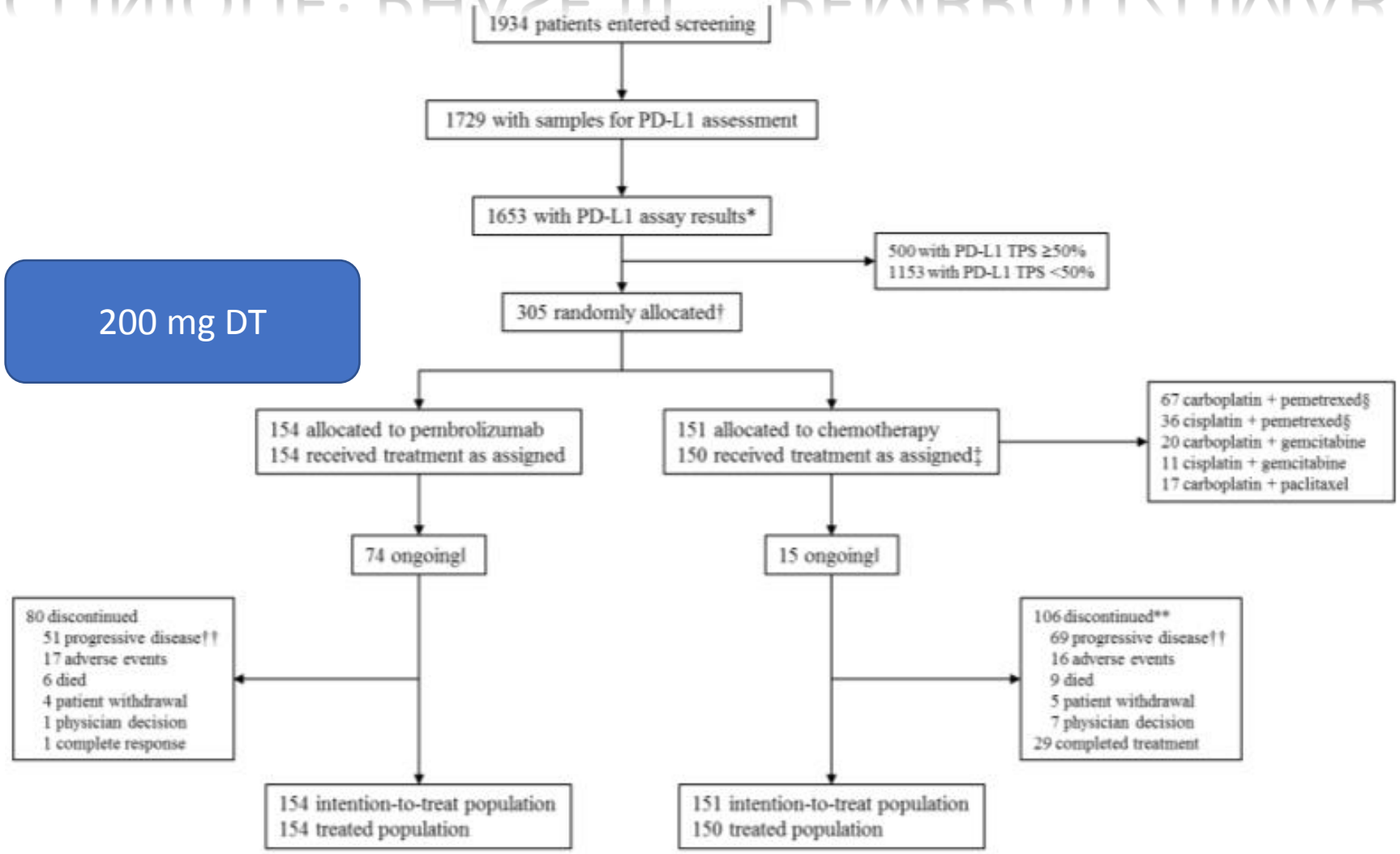
ORIGINAL ARTICLE

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

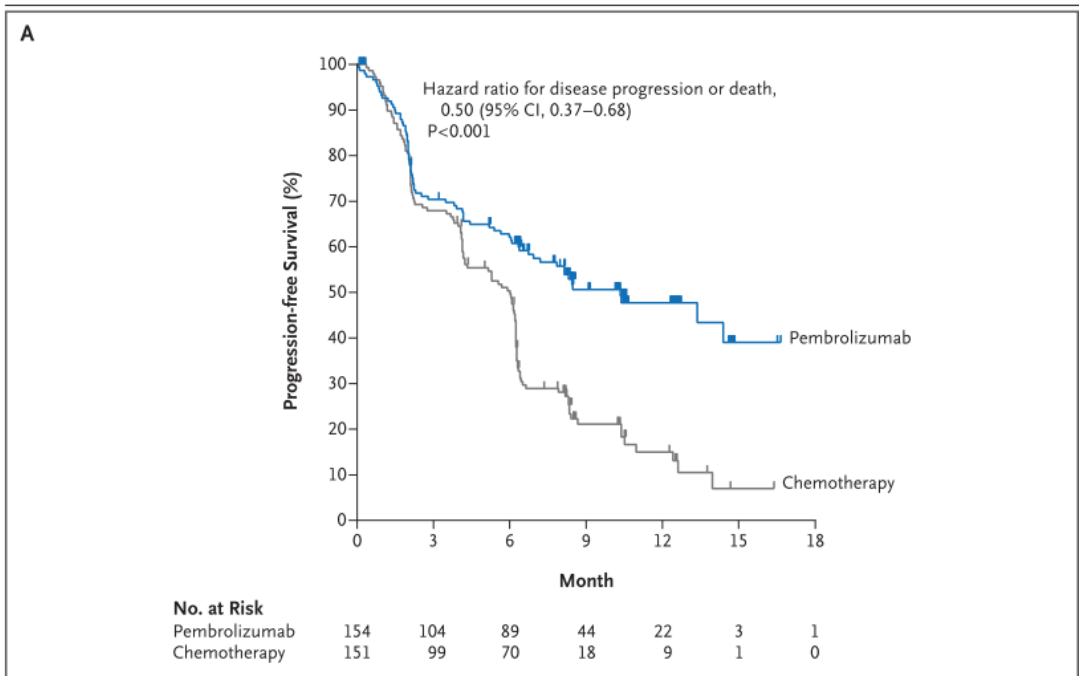
ESSAI CLINIQUE: PHASE III PEMBROLIZUMAB

200 mg DT

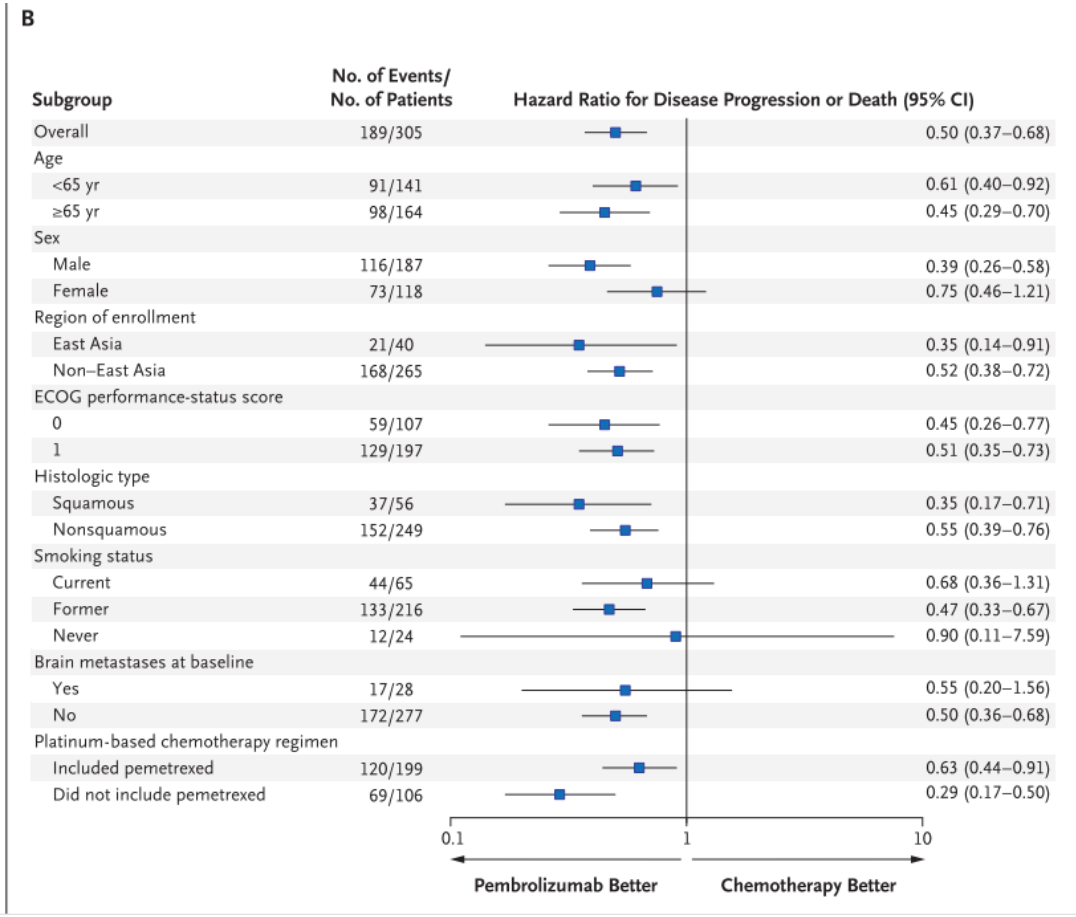


Reck M, et al. New England Journal of Medicine 2016

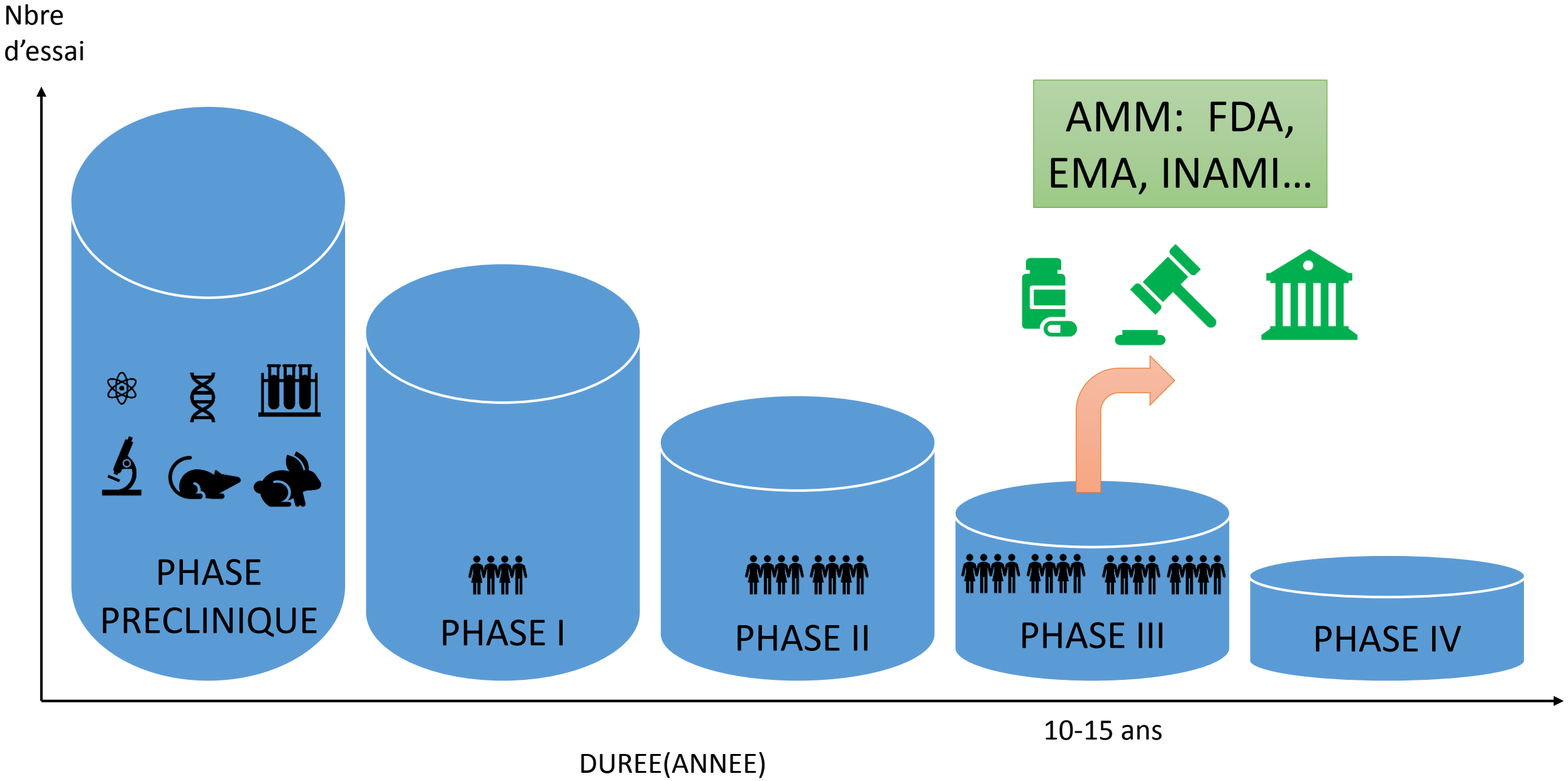
ESSAI CLINIQUE: PHASE III



PEMBROLIZUMAB



CONCLUSION : DVPT MEDICAMENT, LONG PROCESSUS



CONCLUSION : DVPT MEDICAMENT, LONG PROCESSUS

- REGLES BIEN CODIFIEES (administratif, éthique, scientifique)
- ETAPES A RESPECTER
- CENTRE EXPERTISE/CONTROL QUALITE
- PERMET DE COMPRENDRE UNE PATHOLOGIE

CONCLUSION : DVPT MEDICAMENT, LONG PROCESSUS

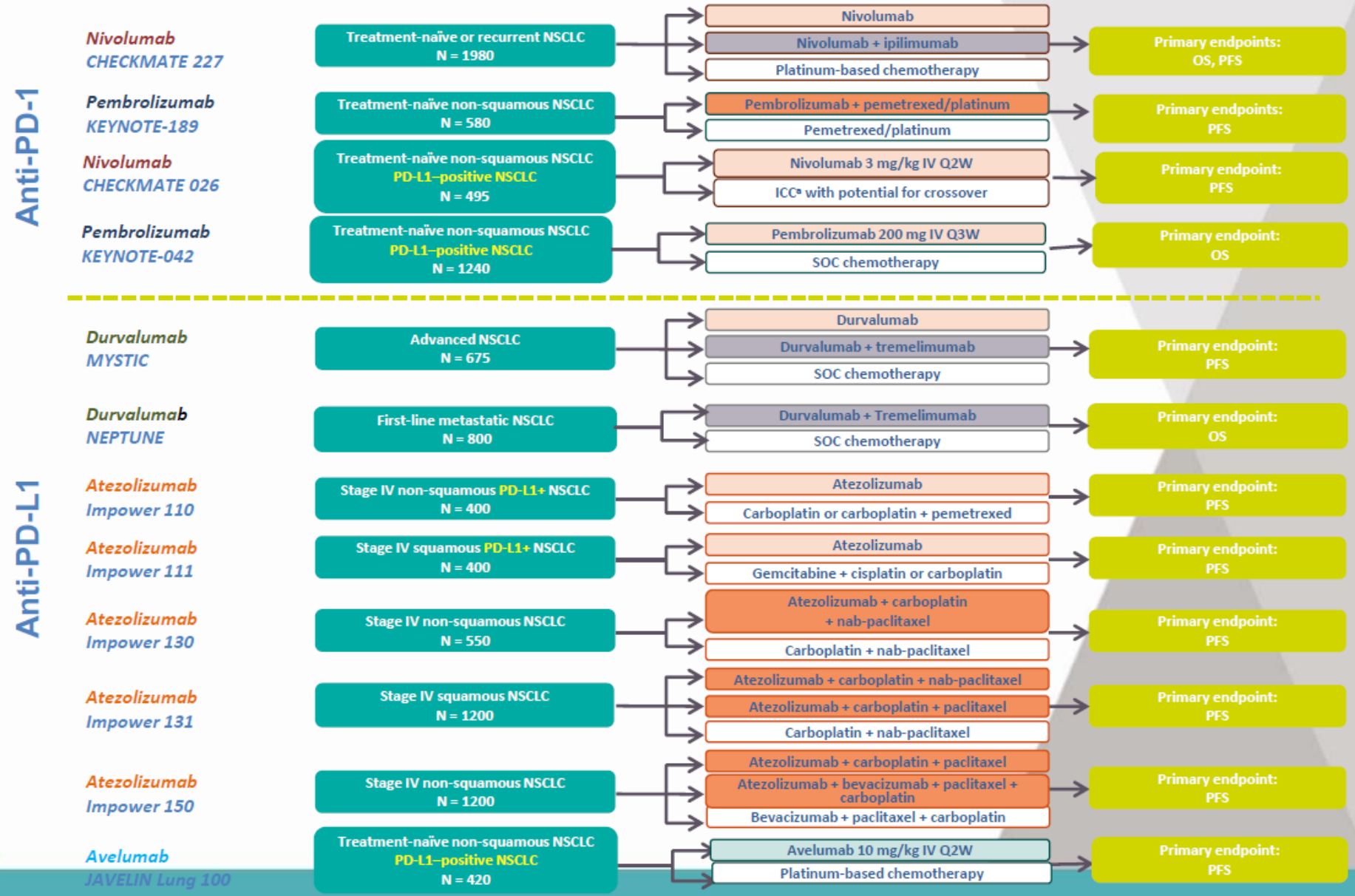
- EST UNE LIGNE THERAPEUTIQUE, INCLURE LES PATIENTS EN BON ETAT GENERAL

- AVOIR UNE OPTION THERAPEUTIQUE DANS LA POPULATION, DANS UNE INDICATION UNE FOIS LE TRAITEMENT VALIDE

- GENERER D'AUTRES HYPOTHESES DE RECHERCHE ET DE DEVELEPPOMENT THERAPEUTIQUE


RACE FOR 1st LINE APPROVAL

Phase III Trials in 1st line Advanced NSCLC (>10,000 Patients)



Courtesy of S.Peters